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Re-evaluation of human-toxicological maximum permissible risk levels

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Abstract

Soil Intervention Values are generic soil quality standards based on potential risks to humans and ecosystems. They are used to determine whether or not contaminated soils meet the criteria for “serious soil contamination” of the Dutch Soil Protection Act.
Regarding the potential risks to humans, MPR values quantifying the human-toxicological risk limits (i.e., tolerable daily intake, tolerable concentration in air, oral cancer risk and/or inhalation cancer risk) for some 50 chemicals and chemical classes were derived in the period 1991-1993. These MPRs have now been updated. Together the compounds comprise 12 metals (including cadmium, lead and mercury), 10 aromatic compounds (including the polycyclic aromatics), 13 chlorinated hydrocarbons (including dioxins and polychlorinated biphenyls), 6 pesticides (including DDT and the drins) and 7 other compounds including cyanides and total petroleum hydrocarbons. For each compound or compound class a toxicity profile has been compiled, consisting of a concise summary of the available toxicity data, information on background exposure, and a survey of existing limit values derived by other organisations. Each profile leads to an updated MPR for the compound (or class of compounds) in question.

Preface

This investigation has been performed as part of RIVM project 711701, “Risk in relation to Soil Quality”, by account of The Ministry of Housing Physical Planning and the Environment, Directorate General for the Environment (DGM), Directorate of Soil Protection, and comprises the full revision of human-toxicological Maximum Permissible Risk levels as was summarised in Chapter 4 of RIVM report 711701 023: “Technical evaluation of the Intervention Values for soil/sediment and groundwater” (December 2000).

Contents

Samenvatting

Dit rapport geeft een overzicht van de opnieuw geëvalueerde humaan-toxicologische MTR waarden zoals in 1991-1993 afgeleid in het kader van het RIVM project betreffende interventiewaarden ten behoeve van bodemsanering. De voorliggende evaluaties werden uitgevoerd door het Centrum voor Stoffen en Risicobeoordeling van het RIVM. Tevens wordt een overzicht gegeven van de wetenschappelijke uitgangspunten waarop de evaluaties zijn gebaseerd.
Voor elke beoordeelde stof werden Maximum Toelaatbare Risico's afgeleid voor de orale blootstellingsroute, en indien relevant tevens voor de inhalatoire blootstellingsroute.
Voor sommige stoffen kon geen MTR worden afgeleid wegens het ontbreken van toxicologische gegevens, terwijl voor enkele stoffen slechts voorlopige (“provisional”) waarden konden worden afgeleid omdat het toxicologische informatiepakket voor de desbetreffende stoffen incompleet was.

Summary

This report contains an update of the human health-based MPR values for compounds and compound classes evaluated in the period 1991-1993, in the scope of the RIVM project on soil intervention values for soil clean-up. These updates have been performed by the Centre for Substances and Risk Assessment of the RIVM, in the years 1999 and 2000. Also the scientific basis for the evaluations is presented.
For each substance evaluated, Maximum Permissible Risk levels are derived for the oral route of exposure and, if relevant, also for the inhalation route of exposure.
In some instances the previously derived MPR values have been maintained due to lack of new and relevant data. For some substances only provisional values could be derived because of limitations in the available toxicological information.

1. Introduction

The Intervention Values for soil and groundwater are one of the instruments of the Dutch Soil Protection Act: based on these values decisions are made regarding the clean-up of contaminated soils.
In 1991 proposals have been derived for the first series of Intervention Values for about 70 (groups of) compounds. Since the promulgation of this first series of Intervention Values in 1994 more data, exposure models and calculation methods have become available. Also a large group of users of the Intervention Values (public and private environmental experts) have asked questions and elucidations on specific (groups of) compounds.
In 1997 Intervention Values for the second and third series of compounds were established, followed by the fourth series of compounds in 2000.
The Directorate General of Environment of the Ministry of Housing, Spacial Planning and the Environment commissioned RIVM to evaluate the existing Intervention Values, in order to have an up-to-date scientific basis for these values. This has led to the project 'Evaluation of Intervention Values Soil' which is carried out in the framework of the overall-project "Risk in relation to soil quality". The main purpose of the evaluation is to obtain an adjusted systematic tool for deriving Intervention Values according to the most recent views on exposure assessment to soil contaminants.
One of the building blocks for Intervention Values is the human-toxicological Maximum Permissible Risk (MPR_{human}) value. The present study comprises the revision of the MPRs of the first series of compounds, which was reported by Vermeire et al. (1991) and Vermeire (1993).

2. General procedure

2.1. Definitions

The MPR_{human} is defined as the amount of a substance (usually a chemical substance) that any human individual can be exposed to daily during full lifetime without significant health risk (see paragraph 2.3 for the more specific definition of cancer risks). It covers both oral and inhalation exposure (and if necessary also dermal exposure), and classical toxic risks as well as carcinogenic risks. The MPR_{human} is generally expressed as either a tolerable daily intake (TDI) or an excess carcinogenic risk via intake (CR_{oral}), both covering exposure by oral ingestion, or a tolerable concentration in air (TCA) or an excess carcinogenic risk via air (CR_{inhal}), both covering exposure by inhalation.
The procedure to derive $MPRs_{human}$ is outlined in detail by Janssen and Speijers (1997). In agreement with this report the approach of the present re-evaluation is a pragmatic one in that use has been made of existing toxicological evaluations by national and international bodies, in an attempt to avoid unwanted duplication of work. Existing evaluations were used in a critical fashion: on a case-by-case basis their adequacy for use in the present scope was judged, and from that the need to search additional and/or primary literature was determined.
In the following the abbreviation "MPR" is used throughout to indicate the MPR_{human}.

2.2. Threshold versus non-threshold approach

In evaluating the toxicity of chemical substances, distinction must be made between two fundamentally different approaches. Genotoxic carcinogens are assumed to exert their activity also at the smallest dose, i.e., by definition a threshold for genotoxic activity does not exist. Toxic effects other than genotoxic carcinogenicity, however, are assumed to occur via receptor interaction, which implies that a certain threshold needs to be exceeded before a toxic effect will occur.

2.3. Excess lifetime cancer risk

For genotoxic carcinogens a cancer risk estimate is made based on known tumour incidences for the compound in question. This procedure results in an *excess lifetime cancer risk*. This approach assumes a linear relationship (also at very low doses) between dose and cancer incidence, which implies that the cancer incidence due to exposure to a particular genotoxic chemical is zero only if the dose is zero.
In the framework of the Intervention Values the MPR is the criterion used for health based risk assessments; for genotoxic carcinogens the MPR has been defined as the excess lifetime cancer risk of 1 in 10,000 ($1:10^4$).

2.4. Tolerable daily intake (oral and inhalation)

Applying the threshold approach for all other toxic chemicals, a *tolerable daily intake (TDI)* is derived, representing the estimated amount of the chemical that humans can ingest daily during their entire lifetime without resultant adverse health effects. Analogously, a *tolerable concentration in air (TCA)* is derived for the inhalation route of exposure, representing the air concentration of the chemical that humans can inhale during their entire lifetime without resultant adverse health effects.

2.5. Deriving a MPR

Basically, the derivation of the MPR for a particular compound starts with examining the existing toxicology reviews of this compound, i.e., reviews by (inter)national organisations such as RIVM, WHO, EU, US-EPA, IARC, ATSDR [1]), etc. These are evaluations that are carried out by (inter)national committees of experts, and generally they can be taken as critical and well-validated data sources. If a data-set is more or less complete, these reviews report studies on the effects of the compound in humans, a variety of toxicological endpoints examined in animal experiments, and include information regarding the dose-effect relationship as well as information regarding the mechanism(s) of the toxic effect(s) observed. This information is critically evaluated, the pivotal toxicological endpoint is defined, and an overall *no observed adverse effect level (NOAEL)* is selected. The NOAEL is the highest dose in a study at which no substance-related adverse health effects were observed, i.e., the first dose below the one at which such effects did occur (which is defined as the *lowest observed adverse effect level - LOAEL*). In case of a non-genotoxic compound uncertainty factors are applied to extrapolate from the NOAEL to the MPR (see paragraph 2.6), while for a genotoxic compound a linear extrapolation is applied to arrive at the MPR for cancer risk.
Sometimes a MPR is characterised as *provisional* or *temporary*. *Provisional* is used if data for a particular route of exposure are not available, and other data had to be used to arrive at the MPR. *Temporary* is used if a particular substance is being evaluated internationally, but the evaluation process has not yet resulted in a final report.

2.6. Uncertainty factors

In agreement with the international procedures for toxicological risk assessments (Faustman and Omenn, 1996; Woodward, 1996), *uncertainty factors* (UFs, formerly called *safety factors*) are used to derive the MPR from the NOAEL. These UFs allow for interspecies (animal to human) variation and for intraspecies variation (variations in susceptibility in the human population). By default, these two types of variation are covered by UFs of 10 (Faustman and Omenn, 1996; Woodward, 1996; Vermeire et al., 1999). However, when there are flaws or omissions in the data package from which the NOAEL is taken, addional UFs or *modifying factors* (MFs) have to be applied. Thus:

$$MPR = NOAEL/UF_1 \times UF_2 \times \ldots$$

It must be emphasised that the UFs are applied to ensure that the limit value derived is safe for humans, even for sensitive subpopulations within the general population. The size of the UF is not to be interpreted as a simple measure of the reliability of the resulting MPR; it is the factor which by expert judgement is considered necessary to extrapolate from the available toxicological data (mostly animal NOAELs) to a MPR, i.e., the daily intake of a chemical which during entire lifetime appears is without appreciable risk on the basis of all currently known facts. Thus, the size of the total UF is not a simple uncertainty score. This does not mean that there is no relation whatsoever between the reliability of the MPR and the size of the UF. Using a higher UF means: making a larger-sized extrapolation (extrapolation further outside the experimentally observed dose-response range). Consequently, MPRs derived using a UF of 1000 (used when no adequate chronic animal NOAEL is available) will be less

[1]) WHO: World Health Organization (e.g., the International Programme on Chemical Safety, and the Joint FAO/WHO Meeting on Pesticide Residues); EU: various Scientific Committees of the European Union; US-EPA: US Environmental Protection Agency; IARC: International Agency for Research on Cancer; ATSDR: US Agency for Toxic Substances and Disease Registry.

accurate than MPRs derived using a UF of 10 (used when an adequate human NOAEL is available). Lower UFs are possible if more detailed information is available on the toxic repsonse of the chemical in humans. Only in this sense does the total UF reflect the quality of the data-set (see also paragraph 2.8).

2.7. Route-to-route extrapolation

In the human-toxicological evaluation aimed at deriving MPRs, toxicity data for all routes of interest for a particular compound (i.e., oral, inhalation, and if applicable also dermal) are considered. This full dataset is needed to obtain a complete picture of the toxicological properties of the compound. In practice, however, the available datasets are often limited. Consequently, when oral data are insufficient for deriving a TDI, *route-to-route extrapolation* is done, based on inhalation data. Vice versa, if inhalation data are lacking, route-to-route extrapolation can be applied using oral data. It must be emphasised, however, that route-to-route extrapolation is a rather unreliable method to derive any limit value.

2.8. Reliability

Depending on the size and quality of the database from which a MPR is derived, the resulting limit value has a certain reliability. In the current re-evaluation the reliability of the resulting MPRs is qualified as *high, medium* or *low*.
Basically these reliability scores are the result of expert judgement of the database from which the limit value is derived. This judgement involves:

- A MPR represents a limit value for lifetime exposure. Accordingly, toxicity studies from which a MPR is derived should thus preferably be chronic studies (exposure of experimental animals during their full or almost full lifetime). Consequently, if chronic studies, and even semi-chronic studies are not available, the resulting MPR will be of low or at best medium reliability. It should be noted, however, that some pivotal effects can only be observed in specific studies regarding, e.g., reproduction or teratogenicity. Moreover, chronic studies are not by definition of better quality than other studies.
- The size of the database. Any specific toxicity of a particular substance is better characterised if observed in different studies, by different investigators, in different animals, with different study designs. Thus, if only studies in one experimental animal species are available, or if only a very small number of studies is available, the resulting MPR will at best be of medium reliability. In this framework it should be noted that more recent studies may be expected to have involved modern research methods and good laboratory practice, but that studies of older date are not by definition less reliable.
- The design of a particular study. It should allow establishing the significance of a particular toxic effect, and its dose-effect relationship. If possible a toxic effect should be supported by histopathological data, microscopic observations, research (*in vivo* or *in vitro*) regarding the molecular mechanism of the effect, etc. Thus, poorly designed studies will result in a MPR with low reliability (if the database does not contain other, better designed and more extensive studies).
- In general a MPR is qualified as highly reliable if resulting from the evaluation by an internationally renown committee of experts, particularly because these committees only derive an MPR if a rather complete database is available (cf. paragraph 2.5).
- In addition, the extent of international consensus regarding the nature and the severity of a specific toxic effect of a particular compound indicates the trust (or distrust) of the international expert community in the toxicological characterisation of this substance.

It should be noted that in the present re-evaluation of MPRs the reliability qualification is only of a rough nature, due to the rather pragmatical way by which the MPRs were derived (cf. paragraph 2.1).

3. Results and discussion

3.1. MPRs

Table 1 lists the updated MPRs of the first series of compounds as derived in 1991/1993, together with the new evaluations performed in the period 1999/2000.
The majority of the substances were just re-evaluated on the basis of new and additional information. For some substances or groups of substances, however, full new evaluations were carried out. These involved:

- The dioxins. These now include polychlorinated dibenzo-p-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs) and the co-planar polychlorinated biphenyls (the "dioxin-like" PCBs). The MPR is based on the recent WHO recommendation for this group of compounds.
- The polychlorinated biphenyls (PCBs), or better, the non-planar (non "dioxin-like") PCBs. Since there are a large number of congeners in this group, the MPR is based on the 7 indicator PCBs (IUPAC numbers # 28, 52, 101, 118, 138, 153, and 180) and also expressed in the (summed) amount of these indicator PCBs.
- The polycyclic aromatic hydrocarbons (PAHs). In the previous evaluation the MPR was based on the so-called "10 PAHs of VROM". In the present evaluation the number of PAHs has been extended from 10 to 17: the so-called "16 PAHs of US-EPA" plus naphthalene (which originally was not part of the 16 EPA-PAHs - currently it is), which in the past decade has become the internationally used standard. In addition, in the present evaluation the MPR is based on the carcinogenicity equivalence principle with the carcinogenicity of benzo(a)pyrene (BaP) as the standard, and expressing the carcinogenicity of other PAHs as fractions of BaP's carcinogenicity using "BaPEFs" (BaP equivalency factors; since BaP has the strongest carcinogenic potency of all PAHs, these factors are by definition between 0 and 1). Both new approaches are in full agreement with recent international developments regarding characterising and evaluating PAH mixtures.
- The group of total petroleum hydrocarbons (TPH; in Dutch *"minerale olie"*). The evaluation of these substances is now based on a tiered approach in which it is firstly investigated if the mixture can be evaluated on the basis of the "whole product" approach (namely, if the origin and source of the contamination is known to be one well known product, e.g., a particular jet fuel), and secondly if there are any carcinogenic substances present, which then must be evaluated as such. Finally, the components of the TPH mixture are evaluated for their (classical) toxicity by a fractional approach, distinguishing four fractions covering the aliphatic compounds, and three fractions covering the aromatic compounds. This new approach is in full agreement with recent international developments regarding characterising and evaluating TPH mixtures.

3.1. Odour thresholds

Some of the more volatile compounds have a rather strong and/or characteristic smell. Although the presence of such a compound can be detected by its smell, this gives no indication about its toxicity. Moreover, there are large individual differences in the capacity of humans to perceive certain odours. Finally, there is no uniform way in estimating odour thresholds, which results in quite large ranges as reported in the literature. Of course this does not imply that odour annoyance at contaminated sites is an aspect to be ignored in the decision process.

Table 2 lists odour thresholds for a selected number of compounds. For some of these also the range is presented, indicating the variability in sense of smell and methods of estimating odour thresholds.
In comparing the odour thresholds with the TCAs/CRs_{inhal} (table 1) it is evident that of the sixteen odour thresholds listed in table 2, only two (i.e., pyridine and styrene) have odour thresholds well below their TCAs, indeed demonstrating that the smell of a particular compound has no relation at all with its toxic and/or carcinogenic potential.

4. Re-evaluations

Table 1 presents the summarised results of the re-evaluations, the full re-evaluations are presented in the appendices of this report:

1 Metals
1.1 Arsenic
1.2 Barium
1.3 Cadmium
1.4 Chromium III
1.5 Chromium VI
1.6 Cobalt
1.7 Copper
1.8 Lead
1.9 Mercury
1.10 Molybdenum
1.11 Nickel
1.12 Zinc
2 Other inorganic compounds
2.1 Cyanides (free, complex, and thiocyanates)
3 Aromatic compounds
3.1 Benzene
3.2 Ethylbenzene
3.3 Toluene
3.4 Xylenes
3.5 Styrene
3.6 Phenol
3.7 Dihydroxybenzenes
3.8 Cresols
3.9 Phthalates
4 Polycyclic aromatic hydrocarbons
4.1 Polycyclic aromatic hydrocarbons (PAHs)
5 Chlorinated hydrocarbons
5.1 1,2-Dichloroethane
5.2 1,2-Dichloroethene (cis and trans isomers)
5.3 Trichloroethene
5.4 Tetrachloroethene
5.5 Dichloromethane
5.6 Trichloromethane (chloroform)
5.7 Tetrachloromethane (carbon tetrachloride)
5.8 Chlorobenzenes (mono-, di-, tri- and hexachlorobenzenes)
5.9 Chlorophenols (mono-, di-, tri-, tetra- and pentachlorophenols)
5.10 Chloronaphtalenes (monochloronaphtalenes)
5.11 Vinylchloride
5.12 Dioxins, furans and dioxin-like PCBs
5.13 Polychlorinated biphenyls (non-planar PCBs)
6 Pesticides
6.1 Aldrin, dieldrin and endrin
6.2 DDT and its metabolites DDD and DDE
6.3 α-, β-, γ- and δ-Hexachlorocyclohexane

TABLE 1 HUMAN-TOXICOLOGICAL MAXIMUM PERMISSIBLE RISK LEVELS - EVALUATIONS 1999/2000

(abbreviations and remarks: see notes at bottom of table)

Compound	MPR old (1991/1993)		MPR new (1999/2000)			
	type	value	type	value	remark	reliability
1. Metals						
Arsenic	TDI	2.1	TDI	1.0		high
			TCA	1.0		high
Barium, soluble	TDI	20	TDI	20	1	high
Barium, insoluble	TDI	-	TDI	-	1	high
			TCA	1.0		high
Cadmium	TDI	1.0	TDI	0.5	2	high
Chromium III	TDI	5.0	-	-		-
Chromium III, soluble	-	-	TDI	5.0		medium
Chromium III, insoluble & metallic	-	-	TDI	5000		medium
			TCA	60		medium
Chromium VI	pCR_{oral}	0.7×10^{-3}	pTDI	5.0	3, 4	low
	CR_{inhal}	2.5×10^{-3}	CR_{inhal}	2.5×10^{-3}	4	high
Cobalt	TDI	1.4	TDI	1.4		medium
			TCA	0.5		medium
Copper	TDI	140	TDI	140		medium
			TCA	1.0		medium
Lead	TDI	3.6	TDI	3.6	5	high
Mercury, metallic	-	-	TCA	0.2		high
Mercury, inorganic	TDI	0.6	TDI	2.0		high
Mercury, organic	TDI	0.6	TDI	0.1		high
Molybdenum	TDI	10	TDI	10		high
			TCA	12		high
Nickel	TDI	50	TDI	50		high
			TCA	0.05		high
Zinc	TDI	1000	TDI	500		high
2. Other inorganic compounds						
Cyanides, free	TDI	50	TDI	50		high
	pTCA	200	TCA	25		high
Cyanides, complex	TDI	13	TDI	800	6	high
Thiocyanates	TDI	11	TDI	11		high

Compound	MPR old (1991/1993)		MPR new (1999/2000)			
	type	value	type	value	remark	reliability
3. Aromatic compounds						
Benzene	pCR_{oral} 1991	170	pCR_{oral}	3.3	7	medium
	CR_{inhal} 1991	1200	CR_{inhal}	20		high
	TDI 1993	4.3				-
	pTCA 1993	30				-
Ethylbenzene	TDI	136	TDI	100		high
	TCA	77	TCA	770		high
Toluene	pTDI	430	TDI	223		high
	TCA	3000	TCA	400		high
Xylenes	pTDI	10	TDI	150		high
	TCA	54	TCA	870		high
Styrene	TDI	77	TDI	120		high
	TCA	800	TCA	900		high
Phenol	TDI	60	TDI	40		high
	pTCA	100	pTCA	20	26	low
Dihydroxybenzenes (total)	TDI	25	TDI	25	25	medium
- 1,2-dihydroxybenzene (catechol)	TDI	40	TDI	40	25	medium
- 1,3-dihydroxybenzene (resorcinol)	TDI	20	TDI	20	25	medium
- 1,4-dihydroxybenzene (hydroquinone)	TDI	25	TDI	25	25	medium
Cresols	TDI	50	TDI	50	25	medium
	TCA	170	TCA	170	25	medium
Phtalates (total)	TDI	25	TDI	4.0		medium
- bis(2-ethylhexyl)phthalate	-	-	TDI	4.0		high
- dibutyl phthalate	-	-	TDI	52		high
- diethyl phthalate	-	-	pTDI	200	27	low
- butylbenzyl phthalate	-	-	TDI	500		high
4. Polycyclic aromatic hydrocarbons (PAHs)						
PAHs, total	CR_{oral}	6.3	-	-		-
- acenaphtene	-	-	CR_{oral}	500		high
- acenaphtylene	-	-	CR_{oral}	50		high
- anthracene	TDI	50	TDI	40		high
- benz[a]anthracene	CR_{oral}	20	CR_{oral}	5.0		high
- benzo[b]fluoranthene	-	-	CR_{oral}	5.0		high
- benzo[j]fluoranthene	-	-	CR_{oral}	5.0		high
- benzo[k]fluoranthene	CR_{oral}	20	CR_{oral}	5.0		high
- benzo[g,h,i]perylene	CR_{oral}	20	TDI	30		high
- benzo[a]pyrene	CR_{oral}	2	CR_{oral}	0.5		high
- chrysene	CR_{oral}	2	CR_{oral}	50		high
- dibenz[a,h]anthracene	-	-	CR_{oral}	0.5		high
- fluoranthene	CR_{oral}	20	CR_{oral}	50		high
- fluorene	-	-	TDI	40		high
- indeno[1,2,3-c,d]pyrene	CR_{oral}	20	CR_{oral}	5.0		high
- naphtalene	TDI	50	TDI	40		high
- phenanthrene	CR_{oral}	20	TDI	40		high
- pyrene	CR_{oral}	20	CR_{oral}	500		high
5. Chlorinated hydrocarbons						
1,2-Dichloroethane	CR_{oral}	14	CR_{oral}	14		high
	pCR_{inhal}	48	pCR_{inhal}	48	18	low

Compound	MPR old (1991/1993)		MPR new (1999/2000)			
	type	value	type	value	remark	reliability
1,2-cis-Dichloroethene	TDI	6	TDI	6.0		medium
	pTCA	30	pTCA	30	8	low
1,2-trans-Dichloroethene	TDI	17	TDI	17		medium
	pTCA	80	pTCA	60	9	low
Trichloroethene	pTDI	540	pTDI	50	10	low
	TCA	1900	pTCA	200	10	low
Tetrachloroethene	TDI	16	TDI	16		high
	TCA	2500	TCA	250		medium
Dichloromethane	TDI	60	TDI	60		medium
	TCA	1700	TCA	3000		high
Trichloromethane (chloroform)	TDI	30	TDI	30		high
	TCA	100	TCA	100		high
Tetrachloromethane	TDI	4	TDI	4.0		high
	TCA	60	TCA	60		high
Monochlorobenzene	TDI	300	TDI	200		medium
			pTCA	500	11	medium
1,2-Dichlorobenzene	TDI	600	TDI	430		high
	TCA	600	pTCA	600		low
1,3-Dichlorobenzene	-	-	-	-	12	-
1,4-Dichlorobenzene	TDI	190	TDI	100		high
	TCA	1200	TCA	670		high
1,2,3-Trichlorobenzene	-	-	TDI	8.0		medium
			pTCA	50		low
1,2,4-Trichlorobenzene	-	-	TDI	8.0		medium
			pTCA	50		low
1,3,5-Trichlorobenzene	-	-	TDI	8.0		medium
			pTCA	50		low
Hexachlorobenzene	TDI	0.5	CR_{oral}	0.16		medium
			pCR_{inhal}	0.75	18	low
Monochlorophenols (total)	TDI	3	TDI	3.0	25	low
Dichlorophenols (total)	TDI	3	TDI	3.0	25	low
Trichlorophenols (total)	TDI	3	TDI	3.0	20	medium
Tetrachlorophenols (total)	TDI	3	TDI	3.0	20	medium
Pentachlorophenol	TDI	30	TDI	3.0		medium
Chloronaphtalenes	TDI	0.5	TDI	80	13	low
	TCA	600	pTCA	1.0	14	low
Vinylchloride	CR_{oral}	3.5	CR_{oral}	0.6		high
	CR_{inhal}	100	CR_{inhal}	3.6		high
Dioxins (PCDDs, PCDFs, planar PCBs)	TDI	10×10^{-6}	TDI	$1\text{-}4\times10^{-6}$	15	high
Polychlorinated biphenyls, non-planar	TDI	0.09	TDI	0.01	16	high
			TCA	0.5	16	medium
6. Pesticides						
Aldrin	TDI	0.1	TDI	0.1	17	high
			pTCA	0.35	8, 17	low
Dieldrin	TDI	0.1	TDI	0.1	17	high
			pTCA	0.35	8, 17	low
Endrin	TDI	0.2	TDI	0.2		high
			pTCA	0.7	8	low
DDT, DDD, DDE (total)	TDI	20	TDI	0.5	19	high

Compound	MPR old (1991/1993)		MPR new (1999/2000)			
	type	value	type	value	remark	reliability
α-Hexachlorocyclohexane	TDI	1	TDI	1.0		high
	TCA	0.25	TCA	0.25		high
β- Hexachlorocyclohexane	TDI	0.02	TDI	0.02		high
γ- Hexachlorocyclohexane	TDI	1	TDI	0.04		high
	TCA	0.25	pTCA	0.14	8	low
δ- Hexachlorocyclohexane	-	-	-	-	12	-
Carbamates: carbaryl	TDI	10	TDI	3.0		high
			TCA	10		high
Carbamates: carbofuran	TDI	10	TDI	2.0		high
Dithiocarbamates: maneb	TDI	50	TDI	50		high
			TCA	18		high
Triazines: atrazine	TDI	2	TDI	5.0		high
7. Other organic compounds						
Pyridine	TDI	1	TDI	1.0	25	medium
	TCA	120	TCA	120	25	low
Tetrahydrofuran	pTDI	10	pTDI	10	21, 25	low
	TCA	35	TCA	35	25	high
Tetrahydrothiophene	pTDI	180	pTDI	180	21, 25	low
	TCA	650	TCA	650	25	medium
Cyclohexanone	TDI	4600	TDI	4600	25	high
	TCA	136	TCA	136	25	high
Petrol/gasoline	TDI	3100	TDI	3100	25	high
	TCA	71	TCA	71	25	high
Total petroleum hydrocarbons	TDI	25×10^3	-	-	22	-
- aliphatic >EC5-EC8	-	-	TDI	2000	23, 24	medium
			TCA	18.4×10^3	23, 24	medium
- aliphatic >EC8-EC16	-	-	TDI	100	23	medium
			TCA	1000	23	medium
- aliphatic >EC16-EC35	-	-	TDI	2000	23	medium
- aliphatic >EC35	-	-	TDI	20.0×10^3	23	medium
- aromatic >EC5-EC9	-	-	TDI	200	23	medium
			TCA	400	23	medium
- aromatic >EC9-EC16	-	-	TDI	40	23	medium
			TCA	200	23	medium
- aromatic >EC16-EC35	-	-	TDI	30	23	medium

MPR: maximum permissible risk
TDI: tolerable daily intake (µg/kg bw/day)
TCA: tolerable concentration in air (µg/m^3)
CR_{oral}: 1:10^4 lifetime excess cancer risk oral (µg/kg bw/day)
CR_{inhal}: 1:10^4 lifetime excess cancer risk inhalation (µg/m^3)
p: provisional

Table 1 - Remarks

1. Only soluble barium-salts are orally biologically available and demonstrate toxic effects. Insoluble salts are orally not bioavailable and thus have no toxicological significance.
2. The TDI is based on a tolerable weekly intake of 3.5 µg/kg bw/week.
3. The TDI is provisional because the cancer risk following oral exposure cannot be estimated due to lack of data (thus this pTDI holds only for non-carcinogenic risks).

4. Chromium VI induces allergic contact dermatitis (ACD); the 10% threshold value (a level to which no more than 10% of the human subpopulation sensitised to chromium would respond, and that would protect at least 99.84% of the general population) amounts 0.001% Cr(VI) (equalling 10 mg/L) or 0.089 μg/cm^2.
5. The TDI is based on a tolerable weekly intake of 25 μg/kg bw/week.
6. The TDI (expressed as CN^-) holds for ferriferrocyanide (both solid and dissolved), and is derived from the TDI for free cyanide, based on the low bioavailibility of complex cyanides in general and ferriferrocyanide in particular.
7. The CR_{oral} is provisional because it was estimated by route-to-route extrapolation from the CR_{inhal}.
8. The TCA is provisional because it was estimated by route-to-route extrapolation from the TDI. The reliability is low due to indications for route-specific metabolism.
9. The TCA is provisional because it was derived from a limited semichronic study. The reliability is low due to indications for route-specific metabolism.
10. The TDI and TCA are provisional due to lack of reliable (semi)chronic studies.
11. The TCA is provisional because it was directly taken from WHO-IPCS without further evaluation.
12. Adequate toxicity studies are not available, and thus an MPR cannot be derived.
13. The TDI is derived for 1- and 2-chloronaphtalene. Literature indicates that higher chlorinated naphtalenes are more severily toxic, but adequate data are lacking. Hence the TDI is not to be used for others than the monochloronaphtalenes.
14. The TCA is derived for tri- and tetrachloronaphtalenes. Literature indicates that higher chlorinated naphtalenes are more severily toxic, but adequate data are lacking. Hence the TCA is not to be used for others than the mono-, di-, tri- and tetrachloronaphtalenes.
15. WHO emphasised that the limit value of 4 pg/kg bw/day should be considered a maximum tolerable daily intake on a provisional basis, and that the ultimate goal is to reduce human intake levels below 1 pg/kg bw/day.
16. The TDI and TCA are based on, and expressed as the amount of the 7 indicator PCBs (IUPAC numbers # 28, 52, 101, 118, 138, 153, and 180).
17. The MPRs also hold for the sum of aldrin and dieldrin.
18. The CR_{inhal} is provisional because it was estimated by route-to-route extrapolation from the CR_{oral}.
19. The TDI also holds for the sum of DDT, DDD and DDE.
20. For these compounds limited new information is available. Due to time constraints, however, this could not be evaluated in time to be included in the present report. Consequently, and for the time being, the limit values as derived in 1991 are maintained.
21. The TDI is provisional because it was estimated by route-to-route extrapolation from the TCA.
22. In Dutch: *"minerale olie"*.
23. These MPRs exclude carcinogenic risks, and are to be applied only after carcinogenic risks have been ruled out.
    EC: Equivalent carbon number index - the EC is based on equivalent retention times on a boiling point gaschromatographic column (non-polar capillary column), in order to normalise different hydrocarbons to n-alkanes.
24. These MPRs are only valid if the amount of n-hexane present in the mixture is < 10%. If 10% or more n-hexane is present, a more detailed estimation has to be made involving the TDI for n-hexane (which is 60 μg/kg bw/day).
25. These MPRs were not re-evaluated due to the lack of new significant information. Consequently the previous MPRs are maintained.
26. The TCA is provisional because of the limited database.

27. The TDI is provisional because of the limited database.

TABLE 2 ODOUR THRESHOLDS OF SELECTED COMPOUNDS

Compound	Odour threshold (mg/m^3)		Reference
	threshold value	range	
Cyanide (CN^-)	0.2	-	This report (appendices)
Dichloromethane	1000	500 - 2100	This report (appendices)
Trichloromethane (chloroform)	480	-	NorthEastern Univ., 2000
Tetrachloromethane	60	10 - 60	This report (appendices)
1,2-Dichloroethane	350	50 - 600	This report (appendices)
trans-1,2-Dichloroethene	68	-	Janssen et al., 1995
Trichloroethene	800	550 - 1100	This report (appendices)
Tetrachloroethene	7	-	This report (appendices)
Benzene	100	-	NorthEastern Univ., 2000
Toluene	0.75	-	NorthEastern Univ., 2000
Xylenes	4	-	This report (appendices)
Phenol	0.2	0.1 - 0.4	This report (appendices)
Vinylchloride	7800	-	This report (appendices)
Styrene	0.1	-	This report (appendices)
Monochlorobenzene	10	1 - 10	Vermeire et al., 1991
1,2-Dichlorobenzene	305	-	Vermeire et al., 1991
1,4-Dichlorobenzene	10	1 - 10	Vermeire et al., 1991
Pyridine	0.03		NorthEastern Univ., 2000
Tetrahydrofuran	100	60 - 150	Vermeire et al., 1991
Tetrahydrothiophene	3	-	Vermeire et al., 1991

Abbreviations

ADI	Acceptable Daily Intake
ATSDR	Agency for Toxic Substances and Disease Registry (USA)
bw	body weight
CR_{inhal}	Excess lifetime cancer risk, inhalation exposure
CR_{oral}	Excess lifetime cancer risk, oral exposure
CSR	Centre for Substances and Risk Assessment (RIVM)
DECOS	Dutch Expert Committee on Occupational Standards
FAO	Food and Agricultural Organisation (UN)
IARC	International Agency for Research on Cancer (WHO)
IPCS	International Programme of Chemical Safety (WHO)
IRIS	Integrated Risk Information System (US-EPA)
JECFA	Joint Expert Committee on Food Additives (FAO/WHO)
JMPR	Joint Expert Committee on Pesticide Residues (FAO/WHO)
LOAEL	Lowest Observed Adverse Effect Level
MPR	Maximum Permissible Risk (in Dutch: MTR)
MRL	Minimum Risk Level (ATSDR)
MTR	Maximum Toelaatbaar Risico
NOAEL	No Observed Adverse Effect Level
pTCA	Provisional Tolerable Concentration in Air
pTDI	Provisional Tolerable Daily Intake
RfC	Reference Concentration (US-EPA)
RfD	Reference Dose (US-EPA)
RIVM	Rijksinstituut voor Volkgezondheid en Milieu
TCA	Tolerable Concentration in Air
TDI	Tolerable Daily Intake
UF	Uncertainty Factor
US-EPA	Environmental Protection Agency (USA)
WHO	World Health Organisation

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References

1. Faustman EM & Omenn GS (1996):
   Risk assessment. In: Casarett & Doull's Toxicology - the Basic Science of Poisons, 5th ed, chapter 4. Klaassen CD, ed; McGraw-Hill, New York (NY), USA.
2. Janssen PJCM, Apeldoorn ME van, Koten-Vermeulen JEM van & Mennes WC (1995):
   Human-toxicological criteria for serious soil contamination - compounds evaluated in 1993 and 1994.
   RIVM report no. 715810009, August 1995; National Institute of Public Health and the Environment, Bilthoven, The Netherlands.
3. Janssen PJCM & Speijers GJA (1997):
   Guidance on the derivation of Maximum Permissible Risk levels for human intake of soil contaminants.
   National Institute of Public Health and the Environment, RIVM report no. 711701006, January 1997; Bilthoven, The Netherlands.
4. Northeastern University, Office of Health & Safety, Boston (MA), USA, at www.dac.neu.edu/oehs/tlv.htm (August 7, 2000)
5. Vermeire TG (1993):
   Voorstel voor de humaan-toxicologische onderbouwing van C-(toetsings)waarden - Addendum op RIVM rapport nr. 725201005
   National Institute of Public Health and the Environment, RIVM report no. 715801001, May 1993; Bilthoven, The Netherlands.
6. Vermeire TG, Apeldoorn ME van, Fouw JC de & Janssen PJCM (1991):
   Voorstel voor de humaan-toxicologische onderbouwing van C-toetsingswaarden.
   National Institute of Public Health and the Environment, RIVM-report no. 725201005, February 1991; Bilthoven, The Netherlands.
7. Vermeire T, Stevenson H, Pieters MN, Rennen M, Slob W & Hakkert BC (1999):
   Assessment factors for human health risk assessment - a discussion paper.
   Crit Rev Toxicol 29, 439-490.
8. Woodward KN (1996):
   Hazard identification, risk assessment, regulation and legislation. In: Toxicology - Principles and Applications, chapter 14. Niesink RJM, De Vries J & Hollinger MA, eds; CRC Press, Boca Raton (FL), USA.

APPENDICES

Appendix 1 Metals

1.1. ARSENIC

1.1.1. INTRODUCTION

Inorganic arsenic was evaluated within the scope of this project by Vermeire et al. (1991). They derived a TDI of 2.1 µg arsenic per kg body weight (bw) per day. The value was based on a provisional tolerable weekly intake (PTWI) of inorganic arsenic of 15 µg/kg bw for adults of 70 kg of body weight proposed by JECFA in 1989. The proposal of the JECFA was derived from a LOAEL of chronic intake of 100 µg arsenic/L in drinking water by humans, assuming a daily intake of drinking water of 1.5 L/day. It was concluded by the JECFA and Slooff et al. (1990) that marginal effects in humans at the dose level of 2.1 µg/kg bw/day can not be totally excluded.
There were suggestions that inorganic arsenic is a human carcinogen, but it was concluded that available studies demonstrate too few arguments to propose an exposure limit value by means of a non-threshold extrapolation. Carcinogenic effects can only be observed when also toxic effects are noticed.
Exposure of humans to inorganic arsenic through indoor or outdoor air was assumed to be negligible, thus a TCA was not proposed.
For the update additional literature was reviewed. This included a report of the Health Council of The Netherlands (1993), a draft report of ATSDR (1999), and a draft report of IPCS (1999). In addition the evaluation of the WHO drinking water quality guidelines was used (WHO 1996).
Inorganic arsenic of natural origin can be found in soils and rocks. At some places the background concentration can be substantial: levels up to 200 and 900 mg arsenic per kg are reported in rocks. In soils the concentrations can range from a few mg/kg to percent quantities. In The Netherlands “ijzeroer” soils are known to contain high concentrations of arsenic.
Arsenic compounds can be both of inorganic and organic nature. Various forms of valency states are known to exist. The positive trivalent and pentavalent state however predominates. In the soil the arsenic oxidation state and chemical species depends upon pH and redox potential.
Various human activities lead to emissions of inorganic arsenic into the environment. Smelters and chemical plants emit arsenic trioxide into the air. The electronic industry uses arsenic in GaAs. These activities may lead to soil contamination due to waste dumps. The use of pesticides and wood preservatives are another major source of inorganic arsenic in soil. In agriculture area organic arsenicals can be found from the application of sewage sludge that contain elevated levels of arsenic. A diffuse contamination of soils in urban areas is the result of the former use of arsenic in household pesticides. Arsenic is still used in normal household products today, such as in preserved wood and electronic devices, leading to arsenic in conventional waste dumps.
Due to the sources of emissions it can be expected that inorganic arsenic can be found in aerial dust. Other sources like dumps and direct applications of pesticides will cause soil and groundwater contamination both diffuse and hot spots (ATSDR 1999, IPCS 1999).

1.1.2. TOXICOLOGY

Toxicokinetics

Absorption
Both human studies and studies with experimental animals demonstrate that water-soluble inorganic arsenic compounds are well absorbed after oral intake, up to 95%. Gastrointestinal absorption of insoluble salts like arsenic triselenide and lead arsenate is much lower in the order of 25%. Studies of oral absorption of arsenic contaminated dust, soil, and bog ore showed a gastrointestinal absorption of 10% at the most. Absorption of inorganic arsenicals after inhalation from cigarette smoke, dust and fumes is estimated to be 75 to 90% in humans. Again, soluble forms are absorbed rapidly, whereas the rate of absorption of highly insoluble forms is lower. Studies of dermal absorption of inorganic arsenic in humans and rhesus monkeys are available for arsenic acid mixed with soil. From this it can be concluded that the percutaneous absorption of inorganic arsenic from soil is less than 1%.

Distribution
Studies in humans and experimental animals demonstrate that distribution does not depend on the route of exposure. Arsenic can therefore be found in all tissues of the body.
Metabolism and excretion
The metabolism of inorganic arsenic has been extensively studied in humans and animals. It was shown that the various inorganic forms of arsenic are converted by oxidation and reduction reactions to trivalent and pentavalent forms that are excreted urinary. Detoxification takes also place by a sequential methylation of trivalent arsenic in the liver, where it is transformed into monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA). In humans especially MMA is excreted via the urine to a great extent.
Excretion of arsenic by humans is predominantly via the urine, very little is excreted via the faeces; this holds for both inhalation and oral exposure. After an oral dose the whole body clearance has a half-life of 40 to 60 hours in humans.
Biomarkers
As accumulates in keratin-rich tissues, and thus hair and nails can be used as an indicator for chronic arsenic exposure. Studies have shown that the arsenic content of hair and nails correlates with increasing arsenic concentrations in drinking water and air. For the evaluation of a short-term exposure these markers are less well suited, since the concentrations in hair and nail rapidly return to background levels while they grow. Due to the rapid elimination of arsenic, blood levels are not suited as an indicator of chronic low level exposure to inorganic arsenic compounds. In many older studies total urinary arsenic was used as a biomarker of recent arsenic exposure. The results of this approach are debatable, as high concentrations of organic arsenicals in the urine are to be expected from the intake of foods, especially seafood. Here a specific analysis of the different metabolites in urine is a better marker as this might differ for different sources of arsenic exposure.

Toxicity

Essentiality
There are several studies in animals that suggest that low levels of arsenic in the diet are beneficial or essential. According to the ATSDR (1999) some researchers consider the weight of evidence inadequate, but in a review of the US-EPA (1988) it was concluded that essentiality is plausible. It was assumed that the daily requirement for humans is provided in a normal diet, and no cases of arsenic deficiency have ever been reported in humans.
Acute toxicity
Acute poisoning due to inorganic arsenic ingestion can lead to severe toxic effects (including death) within 30 to 60 minutes. Lowest levels reported are as little as 1 mg/kg for arsenic trioxide. Intake in combination with food may delay the effects. The most prominent effect is a gastrointestinal syndrome (vomiting, intestinal injury with bleeding and diarrhoea), followed by multi-organ failures (IPCS 1999).
Genotoxicity and carcinogenicity
From the available data it can be concluded that inorganic arsenicals are inactive or weak mutagens. They are able, however, to produce chromosomal effects in most *in vivo* and *in vitro* systems (Health Council of The Netherlands 1993). This conclusion holds for humans also (IPCS 1999).
The Health Council concluded that the trivalent inorganic arsenic compounds have clastogenic (chromosome damaging) properties. Furthermore it was stated that arsenic compounds damage DNA by a non-genotoxic mechanism. The existence of a toxic threshold is thus likely, and in the evaluation of the Health Council it was finally concluded that health based exposure limits should be derived from NOAELs.
The trivalent inorganic arsenic compounds demonstrate a carcinogenic potency in humans after inhalation exposure. Most prominent is an increased risk of lung cancer (Health Council of he Netherlands 1993, ATSDR 1999). IARC and EPA have therefore classified inorganic arsenic as a human carcinogen: group 1 and group A, respectively (IARC 1987, NTP 1994).
When exposed by the oral route, the main carcinogenic effect is an increased risk of skin cancer. Other epidemiological studies indicate also an increase of risk of internal tumours (liver, bladder, kidney, and lung). The LOAEC for lung cancer after human exposure to trivalent arsenic with a significant

SMR was reported to be 0.01 mg/m^3 (ATSDR 1999). Based on the skin cancer data, US-EPA has proposed a unit risk of 5×10^{-5} excess cancer risk for lifetime oral intake of drinking water with 1 µg arsenic/L. ATSDR (1999) criticised this proposal: it was stated that the slope factor might over-estimate cancer risks at low doses, since low doses may be detoxified by methylation. This would suggest a non-linear dose response curve.

Subchronic and chronic toxicity

In an overview of LOAELs and NOAELs from human studies after prolonged exposures it is shown that dermal and gastrointestinal effects can be noticed at the lowest oral doses of inorganic trivalent and pentavalent arsenic. Gastrointestinal, renal, and haematological effects have a NOAEL of 10 µg/kg bw/day. The LOAEL for the Blackfoot disease with damages to the vascular system is 14 µg/kg bw/day. In one study is a LOAEL reported for hyperpigmentation of 0.8 µg/kg bw/day in humans. In other studies of humans however the NOAEL for dermal effects such as hyperkeratosis and hyperpigmentation is 0.9 to 3 µg/kg bw/day.

In human inhalation studies respiratory effects were seen following exposure to trivalent inorganic arsenic; the NOAEC reported for chronic exposure is 1 mg/m^3. Inhalation studies of the pentavalent form of arsenic are not reported (ATSDR 1999).

Some studies with humans exposed to inorganic arsenic dust in the workplace have reported contact dermatitis, but the dermal contacts were not quantified. In mice exposed to 2.5 mg/kg bw/day a similar irritation was noted.

Mechanism of action

High dose toxicity appears to be the result of arsenic cytotoxicity, as arsenic reacts with sulphyldryl groups in proteins and inactivates many enzymes. In these cases the methylation capacity is not adequate to prevent cytotoxic levels reaching tissues, and many organs are thus vulnerable targets for arsenic toxicity.

The mechanism of the carcinogenic action of inorganic arsenic is not well understood. It has been suggested that arsenic might interfere with DNA repair processes, perhaps by inhibiting DNA ligase. In addition it was suggested that hypermethylation might take place in the promotor suppressor gene p53, resulting in an aberrant gene expression and malignant transformation (ATSDR 1999).

1.1.3. EVALUATION

There is general consensus that the carcinogenic action of inorganic arsenic is based on a non-genotoxic type of mechanism. Consequently, a health based exposure limit should be derived from a NOAEL.

Since the proposal of the WHO of a PTWI of 15 µg/kg bw/week, that was translated by Vermeire et al. (1991) into 2.1 µg/kg bw/day, a series of national and international bodies have assessed inorganic arsenic. The Health Council of The Netherlands (1993) has criticised the proposal of the WHO. It stated that the value of 2.1 µg/kg bw/day can be considered as a NOEL but it is advised to use an additional uncertainty factor using data from epidemiological studies. The Health Council suggested an additional uncertainty factor of 2 to compensate for the observation errors that are inevitable in epidemiological studies. Mild hyperpigmentation was reported in one study at a dose level of 0.8 µg/kg bw/day, but in other studies a dose level of 0.9 to 3 µg/kg bw/day was the NOAEL for dermal effects like hyperkeratosis or hyperpigmentation. It is proposed to follow the recommendations of the Health Council to derive an oral TDI of inorganic arsenic to 1 µg/kg bw/day. On the basis of the human data discrimination between trivalent and pentavalent arsenic can not be made, and it is proposed to use this TDI for both forms of arsenic compounds.

The most critical effect after chronic inhalation exposure of humans is lung cancer. The LOAEC for trivalent arsenic for this effect is 10 µg/m^3. For the variation in susceptibility of humans an extrapolation factor of 10 is used to derive a TCA for chronic inhalation exposure of 1 µg/m^3. It is proposed to use this TCA for both trivalent and pentavalent forms of arsenic.

1.1.4. EVALUATIONS BY OTHER ORGANISATIONS

According to IARC (1987) inorganic arsenic compounds are classified in group 1 as carcinogenic to humans, on the basis of sufficient evidence for carcinogenicity in humans and limited evidence for carcinogenicity in animals.
The US-EPA lists an oral RfD for arsenic of 0.3 μg/kg bw/day. The value was based on a NOAEL of 0.8 μg/kg bw/day with an uncertainty factor of 3 for intra-human variation. The NOAEL was derived from epidemiological data of humans exposed to inorganic arsenic in drinking water (IRIS, revised 1993). No RfC for chronic inhalation exposure was reported. The US-EPA presented an estimate of carcinogenic risk from oral exposures with a slope factor of 1.5 $[mg/kg.day]^{-1}$ and a drinking water unit risk of 0.00005 $[\mu g/L]^{-1}$. The inhalation unit risk for cancer is 0.0043 $[\mu g/m^3]^{-1}$ (IRIS, revised 1998).
The ATDSR presented a MRL of 0.3 μg/kg bw/day for chronic oral intake. The value was based on a NOAEL of 0.8 μg/kg bw/day, that was derived from a dose-response curve of skin lesions in two studies of high exposure of arsenic in well water in Taiwan and a control group. An uncertainty factor of 3 was used for human variability (ATDSR 1999).
The WHO Drinking Water Quality Guideline is 10 μg/L. This value is based on a provisional maximum tolerable weekly intake (PMTWI) of inorganic arsenic of 15 μg/kg bw/week presented by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 1988. The estimated excess lifetime of skin cancer risk associated with the exposure reported is 6×10^{-4} (WHO 1996).
Hassauer et al. (1993) advised the UBA, Germany, an oral "Orientierungswert" of 0.7 μg/kg bw/day for long term exposure of arsenic compounds, based on dermal effects in humans. This was based on a LOAEL of 0.7 μg/kg bw/day with no additional uncertainty factor applied, and 100% absorption. The associated excess lifetime cancer risk was reported to be 0.7×10^{-3} to 1.4×10^{-3}. In their proposal an inhalation "Orientierungswert" of 0.1 $\mu g/m^3$ was included for neurotoxic and dermal effects in humans with an associated cancer risk of 10^{-3} - 10^{-4}. The value is based on a LOAEC of 50 $\mu g/m^3$ with an uncertainty factor of 100, and 30% absorption.

1.1.5. BACKGROUND EXPOSURE

Vermeire et al. (1991) concluded that the daily intake of total arsenic from food en drinking water in The Netherlands is 50 μg/day at most, similar to 0.7 μg/kg bw/day. Currently more recent data on a dietary intake from food in various countries is available. These are based on both market basket and total diet studies, and duplicate diet studies. Such studies are well suited for an evaluation of the human dietary intake. For the UK, USA, Canada, and Australia the intake of total arsenic is in the order of 50 to 75 μg/day for adults. In Japan the dietary intake reported is substantially higher with 180 μg/day. This can be understood from differences in consumption habits; fish is a major contributor of intake of total arsenic (IPCS 1999). Exposure through inhalation is estimated to be about 1 μg/day up to 6 μg/day from cigarette smoking. This is insignificant compared to the dietary intake.
The consumption pattern of The Netherlands with respect to the consumption of fish is more similar to the UK, USA, Canada, and Australia than to Japan. Consequently, the dietary intake of total arsenic is in the order of 50 to 75 μg/day rather than 180 μg/day. It is concluded that the background exposure to total arsenic in The Netherlands can be estimated 1 μg/kg bw/day, mainly from foods. According to data in IPCS (1999) about 25% of the total exposure can be expected to be inorganic arsenic, so the intake of inorganic arsenic compounds in The Netherlands is estimated 0.3 μg/kg bw/day.

1.1.6. CONCLUSION

Compound	TDI	TCA	Background exposure
Arsenic (inorganic)	1.0	1.0	0.3

TDI: tolerable daily intake (oral exposure); μg/kg bw/day
TCA: tolerable concentration in air (inhalation exposure); $\mu g/m^3$
Background exposure; μg/kg bw/day

Available data indicate that the gastrointestinal absorption of inorganic arsenic from soil is 10% at most.

1.1.7. REFERENCES

ATSDR (1999):
Toxicological Profile for Arsenic (update); draft for public comment.
Agency for Toxic Substances and Disease Registry, US Public Health Service.

Hassauer M, Kalberlah F, Oltmans J & Schneider K (1993):
Basisdate Toxikologie für umweltrelevante Stoffe zur gefahrenbeurteilung bei Altlasten.
Umweltbundesamt, Berichte 4/93, Erich Schmidt Verlag, Berlin, Germany.

Health Council of The Netherlands (1993):
Arseen, toetsing van een basisdocument.
Report no. 1993/02, Den Haag, The Netherlands.

IPCS (1999):
Arsenic and arsenic compounds, unedited draft, april 1999.
Environmental Health Criteria 99/14, World Health Organization, Geneva, Switzerland.

Slooff, W, Haring, B., Hesse, J., Janus, J., and Thomas, R. (1990)
Basisdocument arseen
Bilthoven, RIVM, 758701.002

Vermeire TG, Apeldoorn ME van, Fouw JC de & Janssen PJCM (1991):
Voorstel voor de humaan-toxicologische onderbouwing van C-toetsingswaarden.
National Institute of Public Health and the Environment, RIVM-report no. 725201005, February 1991; Bilthoven, The Netherlands.

US-EPA (1988)
Special report on ingested inorganic arsenic: skin cancer, nutritional essentiality
Washington DC US-EPA, Risk assessment forum EPA/625/3-87/013

WHO (1996):
Guidelines for drinking-water quality, 2nd ed. Volume 2, Health criteria and other supporting information.
World Health Organization, Geneva, Switzerland.

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1.2. BARIUM

1.2.1. INTRODUCTION

Barium was previously evaluated within the scope of this project (Vermeire et al. 1991). At low doses of barium chloride in drinking water, long-term effects were noticed on blood pressure in experimental animals. The cardiovascular system was described to be the most sensitive system. An oral TDI was derived on the basis of a NOEL in a study with human volunteers. They were exposed to barium in drinking water with 0.2 mg/kg bw/day as the lowest dose. Although no clear no effect level was found in this study, a TDI of 20 µg/kg bw/day was derived using an uncertainty factor of 10. A TCA was not presented. In the evaluation an additional remark was made about differences between soluble and insoluble barium salts. The insoluble salts were reported to be not biologically available, and considered to be not toxic.
Since the 1991 evaluation several reviews have been published. The ATSDR published a toxicological profile for barium and compounds in 1992. The NTP presented a report of its toxicology and carcinogenesis studies of barium chloride in rats and mice in 1994. In 1997 the UK Health and Safety Executive prepared a risk assessment document on barium sulphate.
The soluble barium chloride is used in pigments, ceramics and glass, and paper products. Besides it is used in various industrial activities such as tanning and magnesium production (NTP 1994). These activities might lead to diffuse top-soil contaminated sites. Contamination of ground water is usually the result of naturally occurring barium (US-EPA Office of Drinking Water Health Advisories 1989).
The insoluble barium sulphate ("barite") is used in large quantities as weighing agent in oil well drilling mud. These drilling activities might lead to very local contamination of deep soil with very high concentrations (Health and Safety Executive 1997). Groundwater will then be contaminated if the concentrations of barium sulphate are very high.

1.2.2. TOXICOLOGY

Toxicokinetics

Absorption
Reports on absorption of barium after oral exposure are not conclusive. The absorption of barium in the form of a soluble salt depends on the presence of foods, and other parameters such as the age of the animal. Tracer studies indicate that gastrointestinal absorption decrease with age from 85% for young animals down to 7% for adult animals (IPCS 1990). For adult humans the absorption of barium is less than 5% (ATSDR 1992).
By inhalation the absorption of barium in soluble salts is reported to be about 65% in the nasal region (ATSDR 1992). It was concluded that the absorption is high for soluble aerosols > 5 µm diameter (IPCS 1990). Insoluble particles are also inhaled, but at least 50% is removed from the lungs by the ciliated epithelium, and swallowed afterwards.
Distribution
Barium distributes in experimental animals and humans predominantly to the skeleton and teeth, both after oral exposure and inhalation (ATSDR 1992, IPCS 1990). Levels in human bones appear to be constant for adults of 33 to 74 years of age, suggesting a steady state condition (US-EPA Office of Drinking water Health Advisories 1989).
Metabolism and excretion
The metabolism of barium is not well characterised, but it might resemble the metabolism of calcium and strontium (IPCS 1990).
Disappearance of barium from the bones in rats was found to be similar for well-soluble and poorly soluble compounds. Its half-life was 460 days. The excretion of barium by humans is predominantly via the faeces, and a minor quantity via the urine (IPCS 1990). An elimination half-life of barium for humans, however, has not been reported.
The term "baritosis" is used to describe the lungs of humans exposed to finely ground barite, which consists of a high percentage of barium sulphate. Lung X-ray and microscopy studies of humans that were exposed to dust for many years with insoluble barium sulphate showed that barium sulphate may

remain in the lungs for long periods of time, after cessation of exposure (Health and Safety Executive 1997).

Toxicity

Essentiality
There is no indication that barium can be considered an essential element for humans (WHO, 1996).
Acute toxicity
In cases of acute human poisoning with barium, haematological effects and renal insufficiency are reported. Dose levels in these cases are not known (ATSDR 1992).
Genotoxicity and carcinogenicity
The carcinogenic potential of barium was investigated by NTP (1994). It was concluded from a 2-years drinking water study that there is no evidence of carcinogenic activity of barium chloride, neither in F344/N rats nor in B6C3F mice of both sexes.
Concerning the genotoxic properties of barium, ATSDR (1992) concluded that the data available are insufficient to support a conclusive statement regarding the genotoxicity.
Subchronic and chronic toxicity
After semichronic and chronic oral exposure the most prominent effects of barium in experimental animals are found in the cardiovascular system. Most common is hypertension and abnormalities of heart rhythm. At low doses increased blood pressure in rats is presented. In these studies the animals were exposed to soluble barium salts in drinking water. For insoluble barium sulphate there are no oral studies with animals available. (IPCS 1990; ATSDR 1992).
NOAELs for toxic effects in various organ systems following chronic oral exposure of experimental animals to soluble barium salts are presented by ATSDR (1992). According to this evaluation, the NOAEL for respiratory, hepatic and renal effects is in the order of magnitude of 1 mg/kg bw/day. For cardiovascular effects in experimental animals the NOAEL is 0.054 mg/kg bw/day, based on hypertension. In the evaluation of the WHO (1996) however, it was stated that the NOAEL in this study is 0.051mg/kg bw/day. The differences can be understood as the animals were exposed to barium chloride in drinking water, and both reviews used different assumptions regarding the intake of water and the animal's body weight.
The US-EPA has presented data of a 10 week study with healthy men exposed to barium in drinking water. No cardiovascular effects were found at dose levels of 5 and 10 mg barium/L (US-EPA Office of Drinking water Health Advisories 1989). This finding is consistent with the results of an epidemiological study of people exposed to elevated barium levels in drinking water in the USA. Here it was concluded that levels of 2 to 10 mg barium per L drinking water (7.3 mg/L on average) do not elevate blood pressure levels in adult males or females (IPCS 1990; WHO 1996).
Insoluble barium sulphate is used as an X-ray contrast medium in humans. Single oral doses in the order of 6 g/kg body weight can cause incidental gastrointestinal tract blockage problems (Health and Safety Executive 1997). Cardiovascular effects are also reported after inhalation. In a study in which male rats were exposed to insoluble barium carbonate dust (4 months, 6 days/week, 4 hours/day), the NOAEC was 1.15 mg barium carbonate/m^3 (IPCS 1990). This equals a concentration of 0.16 mg/m^3 if extrapolated to continuous exposure. Rats exposed to 40 mg barium sulphate/m^3 for 8 weeks (5 days/week, 5 hours/day) demonstrated minor effects on lung epithelium (Health and Safety Executive 1997).
Toxic mechanism of action
Special studies on the mechanism of action of barium toxicity showed that barium blocks potassium efflux from cells. This will lead to a prolonged depolarisation of the nerve impulses. As a consequence releases of neurotransmitters are affected. This might cause hypertension by direct interaction with smooth muscle (IPCS 1990).

1.2.3. EVALUATION

The available data demonstrate that barium is not a genotoxic compound. Consequently a TDI can be derived on the basis of a NOAEL and uncertainty factors.

In 1991 Vermeire et al. derived a TDI of 20 µg barium/kg bw/day, based on the evaluation of human data of cardiovascular effects. When these data are compared with the results of the studies that are published ever since, it can be concluded that there is little new information. The information since the previous evaluation does not lead to a change of opinion about the toxicity of barium compounds. It is therefore proposed to maintain the TDI of 20 µg/kg bw/day for soluble barium salts.
The present evaluation supports the remarks by Vermeire et al (1991) about insoluble barium compounds such as barium sulphate. There it was stated that these compounds are not toxic. Consequently there is no need for a TDI of insoluble barium compounds.
There are no data on toxicity after inhalation of soluble barium compounds in experimental animals or humans. Kinetic studies however show that the absorption after inhalation of soluble and insoluble barium salts is not very different. For continuous inhalation of insoluble compounds a NOAEC of 0.16 mg/m^3 barium carbonate in rats was found. This equals to a NOAEC of 0.11 mg barium/m^3. Using an extrapolation factor of 100 for intra- and interspecies extrapolation a TCA of 1 µg of barium/m^3 for humans can be derived.

1.2.4. EVALUATIONS BY OTHER ORGANISATIONS

US-EPA presented a Lifetime Health Advisory for drinking water of 5 mg/L, whereas the National Academy of Sciences proposed a Suggested No Adverse Response Level (SNARL) for chronic exposure of 4.7 mg/L (US-EPA Office of Drinking water Health Advisories 1989).
There is no suggestion for a Minimal Risk Level (MRL) by the ATSDR (1992), neither for inhalation nor for oral exposure of humans. In their report it was concluded that a chronic MRL for barium should be based on blood pressure effects, but that the resulting MRL is lower than the estimated total daily intake.
The US-EPA proposed a RfD for barium and compounds of 70 µg/kg bw/day (IRIS 1999). This value was derived of a NOAEL for humans of 7.3 mg/L in drinking water. This NOAEL was the average concentration of barium in drinking water in an epidemiological study with 1175 adults in the US. This concentration equals to a daily intake of 0.21 mg/kg bw/day. The RfD was derived using an uncertainty factor of 3. A RfC was not recommended, due to lack of appropriate data.
The WHO (1996) proposed a TDI of 51 µg of barium/kg bw/day, on the basis of a NOAEL of 0.51 mg/kg bw/day in a chronic study of rats and an uncertainty factor of 10 for intraspecies variation. For interspecies variation it was said that epidemiological data indicate that humans are not more sensitive to barium than rats. Based on this TDI a drinking water quality guideline of 0.3 mg/L was suggested.

1.2.5. BACKGROUND EXPOSURE

According to ATSDR (1992) the human background exposure of the general population is 650 to 1880 mg of barium/person/day in the US. This equals 10 up to 26 mg/kg bw/day. The major source is food. These estimates were based on data of 1966 and 1969. In IPCS (1990) however, the numbers of that same study were 650 to 1880 µg/person/day. The latter data are in agreement with data from the UK. Here the estimate was 650 to 1330 µg/person/day (IPCS, 1990), which equals 9.3-19 µg/kg bw/day. According to Vermeire et al (1991) the daily intake in The Netherlands amounts to 9 µg barium/kg bw/day. This figure was derived from the UK estimate, for biological available (soluble) barium only. It is proposed to maintain this estimate.

1.2.6. CONCLUSION

Compound	TDI	TCA	Background exposure
Barium (soluble salts only)	20	1.0	9
Barium (insoluble salts)	*	1.0	-

TDI: tolerable daily intake (oral exposure); µg/kg bw/day
TCA: tolerable concentration in air (inhalation exposure); µg/m^3
Background exposure; µg/kg bw/day
* not toxic

The TDI of 20 µg/kg bw/day of Vermeire et al. (1991) is maintained, this TDI is to be used for oral intake of soluble barium salts only. For oral intake of insoluble barium salts a TDI is not derived: these compounds can be assumed to be not toxic. For inhalation of dusts of both soluble and insoluble barium salts a TCA of 1 µg/m^3 is derived.

1.2.7. REFERENCES

ATSDR (1992):
Toxicological profile for barium and compounds.
Agency for Toxic Substances and Disease Registry, US Public Health Service TP-91/03.

Health and Safety Executive (1997):
Barium sulphate.
Risk assessment document EH72/9, HSE Books, Sudbury, UK.

IPCS (1990):
Environmental Health Criteria 107 - Barium.
World Health Organization, Geneva, Switzerland.

IRIS (1999)
CD-ROM database Silverplatter, London, UK.

NTP (1994)
Toxicology and carcinogenesis studies of barium chloride dihydrate in F344/N rats and B6C3F1 mice (drinking water studies).
US Dept. Health Human Services, NIH Publication No. 94-3163.

US-EPA Office of drinking water health advisories (1989):
Barium.
Rev Environm Contam Toxicol 107, 13-23.

Vermeire TG, Apeldoorn ME van, Fouw JC de & Janssen PJCM (1991):
Voorstel voor de humaan-toxicologische onderbouwing van C-toetsingswaarden.
National Institute of Public Health and the Environment, RIVM-report no. 725201005, February 1991; Bilthoven, The Netherlands.

WHO (1996):
Guidelines for drinking-water quality, 2nd ed. Volume 2, Health criteria and other supporting information.
World Health Organization, Geneva, Switzerland.

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1.3. CADMIUM

1.3.1. INTRODUCTION

Cadmium (Cd; CAS no. 7440-43-9, molecular weight 112.41) is a silvery-white soft metal, one of the so-called "heavy metals". The generally bivalent cadmium compounds include soluble salts (e.g., $CdCl_2$ and $CdSO_4$) as well as virtually insoluble salts (e.g., CdS and $CdCO_3$). It is a widely but sparsely distributed element found in the earth's crust at concentrations ranging from 0.1 to 1 ppm, primarily in association with zinc ores (ATSDR 1997).
The oral human-toxicological MPR (maximum permissible risk) for Cd was derived in 1991, and set at 1 µg per kg bw (body weight) per day (Vermeire et al. 1991), based upon kidney toxicity as being the most sensitive effect after oral exposure. This MPR-value was also established by WHO-JECFA (1989).
The average daily intake of Cd in The Netherlands was estimated at 20 µg/day for non-smokers (equal to 0.28 µg/kg bw/day); the intake for smokers (10 cigarettes/day) was estimated to be 22 µg/day.
There were no indications for Cd being carcinogenic, mutagenic and/or genotoxic.
Relevant route of exposure in cases of soil contamination: oral exposure (see paragraph 1.3.2).

1.3.2. TOXICOLOGY

Virtually all toxicology data of Cd are derived from studies with inorganic Cd compounds; data on metallic Cd are not available.

Toxicokinetics

After oral ingestion by human volunteers (as radiolabelled Cd in the food or in drinking water), about 25% of the dose was retained after 3-5 days, but retention decreased to 4.6-6% after 2 to 3 weeks. Apparently part of the dose is trapped in the intestinal mucosa without crossing into the blood or lymph. Body iron influences Cd absorption: subjects with low iron had an average absorption of 8.9% while those with adequate iron stores absorbed on the average 2.3%. The presence of divalent and trivalent cations (e.g., Ca, Cr, Mg, Zn) tends to decrease Cd uptake. Thus, the absorption following oral exposure to Cd is likely to depend on physiological status (age, body stores of Fe, Ca and Zn, pregnancy history, etc.) and also on the presence and levels of ions and other dietary components ingested together with the Cd compound. In general, however, most ingested Cd (> 90%) passes through the gastrointestinal tract without being absorbed. In animals, Cd absorption following oral exposure is somewhat lower than in humans (ATSDR 1997, Järup et al. 1998).
Cd metal and salts have very low volatility and exist in air primarily as fine suspended particulate matter. Upon inhalation some fraction is deposited in the airways or the lungs (approximately some 50%, depending on particle size), the rest is exhaled (ATSDR 1997, Järup et al. 1998).
Regarding dermal absorption, Wester et al. (1992) demonstrated that Cd is hardly absorbed by skin.
With regard to soil contamination the inhalatory and dermal routes of exposure can thus considered to be negligible.
Following absorption by any route of exposure, Cd distributes widely throughout the body, with the major portion ending up in the liver and kidney, and lower levels spreading throughout the rest of the body (ATSDR 1997). Cd readily binds to anionic groups (especially -SH groups) of endogenous compounds, particularly metallothionein (MT), a low-molecular protein capable of binding up to seven Cd ions per molecule. MT is inducible in most tissues by Cd, Zn and other metal ions (ATSDR 1997).
Initially, Cd in liver increases rapidly following absorption, and is redistributed slowly to the kidneys, so that the higher the intensity of exposure, the higher the liver-to-kidney ratio (WHO-JECFA 1989).
In humans, average Cd concentrations in liver and kidney are near zero at birth, and rise roughly linearly with age to peak values of around 40-50 mg/kg (w/w) in the kidney between ages 50 and 60 (after which kidney levels plateau or decline), and 1-2 mg/kg (w/w) in the liver by age 20-25 (and increase only slightly thereafter) (ATSDR 1997). After "normal" exposure to average background levels, about 50% of the body burden is found in the kidneys, about 15% in the liver, and about 20% in the muscles (WHO-JECFA 1989). The placenta is only a partial barrier to foetal exposure (ATSDR 1997).

Absorbed Cd is excreted very slowly, with urinary and faecal excretion being approximately equal. Due to its high accumulation, only a small part of the absorbed Cd is excreted in the urine: normally less than 2 μg Cd per day. Cd can be excreted in human milk at levels from 5 to 10% of the levels in blood (ATSDR 1997). Total daily Cd excretion of the average adult has been calculated to be about 0.007% of the body burden (Ros and Slooff 1988). Half-lives for human kidney and liver have been estimated at 6-38 years and 4-19 years, respectively (ATSDR 1997).
Cd does not metabolically convert via oxidation, reduction or alkylation.
A physiologically based pharmacokinetic model for the human metabolism of Cd was developed by Kjellström, Nordberg and Nordberg (Kjellström and Nordberg 1985, Nordberg et al. 1985, both reviewed in ATSDR 1997).

Toxicity

Acute toxicity
The LD_{50} after the injection of soluble Cd compounds is in the range of 2.5-25 mg/kg bw. For most Cd compounds the LD_{50} after oral administration is about 10-20 times higher than after parenteral administration, and the soluble compounds have lower LD_{50} values than the insoluble ones (IPCS, 1992).
Chronic and subchronic toxicity
Nephrotoxicity
Cd-induced renal toxicity is the most sensitive toxic effect of Cd: long-term exposure to Cd results in an irreversible tubular nephropathy which may develop into renal insufficiency. Cd ions absorbed by the gastrointestinal and respiratory tracts are stored in the liver in the form of a complex with MT, which is transported by the systemic blood flow to the kidneys. Cd-MT is efficiently filtered through the glomerular membrane, taken up by renal tubular cells, and rapidly degraded by lysosomes. It is now generally accepted that part of the Cd thus liberated escapes renewed binding to MT and reaches other subcellular targets. As a result, the reabsorption of low molecular-weight proteins (e.g., β2-microglobulin, retinol-binding protein, N-acetylglucosaminidase) is irreversibly impaired, indicating tubular damage, and manifesting itself as proteinuria. Tubular proteinuria is a relatively specific effect of Cd on the kidneys. At higher levels or longer durations of exposure, increased excretion of high molecular weight proteins occurs, indicating either glomerular damage or severe tubular damage. Numerous studies in experimental animals (e.g., rats, mice, pigs, monkeys) have confirmed the renal damage following long-term oral exposure to Cd compounds (IPCS 1992, CEPA 1994, ATSDR 1997, Järup et al. 1998).
Nogawa et al. (1989) investigated the dose-response relation in humans for renal effects of long-term Cd exposure, using the average Cd concentration in locally produced rice as the measure for intake and urinary β2-microglobulinuria as the index of renal damage. Subjects were 1850 Cd-exposed inhabitants of a polluted area and 294 nonexposed controls. The authors arrived at a NOAEL of 2.1 μg/kg bw/day for Cd-induced β2-microglobulinuria.
On the basis of human occupational studies Lauwerys et al. (1979, cited in IPCS 1992) suggested a biological threshold of 10 μg Cd per g urinary creatinine [2]) as a biomarker indicative for Cd-induced nephropathy in males occupationally exposed to Cd.
However, more recent studies indicated that this limit may not be adequate. Reviewing all available studies, Järup et al (1998) concluded that 50 mg Cd per kg (w/w) in the kidney cortex (corresponding to a urinary Cd excretion of ca. 2.5 μg/g creatinine) is the lowest value at which renal effects can be detected in approximately 4% of the general population (the PPC-4: population critical concentration for 4% of the general population); the population critical level of 10% (PPC-10) would be at a kidney cortex level of around 125 mg/kg, at which level the urinary Cd-excretion is approximately 6.5 μg Cd per g creatinine. Individuals with low body stores of iron and smokers, however, are at higher risks. Based on detailed analyses of the human datasets these authors concluded that the critical Cd-level of 50 mg per kg in the kidney cortex would be reached after some 45 years of daily intake of 50 μg Cd per day. Finally, they concluded that the lifetime daily intake should be lowered to less than 30 μg per day (for the adult individual) in order to maintain the risk level intended earlier by WHO (WHO-JECFA 1989; cf. paragraph 1.3.4).

[2]) 1 μg Cd = 8.9 nmol Cd; 1 μg Cd per g creatinine ≈ 1 nmol Cd per mmol creatinine.

ATSDR (1997), however, concluded to some controversy regarding the critical concentration of urinary Cd and followed Roels et al. (1993) who identified three groups of thresholds of Cd in urine for the development of incipient nephropathy. The first one of these is around 2 µg Cd/g creatinine and is mainly associated with biochemical alterations, such as increased urinary 6-keto-prostaglandin F_{1x} and urinary sialic acid. The second one is around 4 µg Cd/g creatinine, in excess of which the glomerular barrier function is progressively compromised and cytotoxic effects appear in the proximal tubule; this threshold is associated with increased excretion of high molecular weight proteins (possibly due to disruption of the glomerular membrane polyanionic charge) such as tubular brush border antigens and N-acetylglucosaminidase. The third threshold is around 10 µg Cd/g creatinine, corresponding to the onset of proximal tubular dysfunction with increased urinary excretion of low molecular weight proteins and other indicators of renal dysfunction.

Osteotoxicity

Apart from renal damage, Cd is also able to induce bone damage. The Itai-Itai syndrome, first reported from Japan in the mid-fifties, is the best known example of this effect. Its main characteristics are osteomalacia and osteoporosis, with a tendency to fractures. A clear dose-effect relation, however, could not be demonstrated. Whether the mechanism of this bone demineralisation is secondary to nephrotoxic damage or results from a direct effect on bone tissue, however, is at present unknown. Vitamin D is of vital importance for bone physiology, and it has been suggested that normal vitamin D_3 metabolism in the renal tubular cells is impaired due to Cd-induced damage of renal tubular cells, which subsequently would lead to bone toxicity. However, there is also evidence that persons without previous renal lesions may develop adverse bone effects due to Cd exposure, probably through a more direct disruption of vitamin D metabolism (IPCS 1992, Järup et al. 1998).

Cardiovascular toxicity

Data from animal experiments indicated that chronic oral administration of Cd at low doses (approximately 0.1-0.7 mg/kg bw/day) caused a rise of arterial blood pressure and thus may play a role in the causation of cardiovascular diseases (IPCS 1992, ATSDR 1997, Järup et al. 1998). The mechanism of the hypertensive effect, however, has not been clarified, and the associations of these findings in humans have been weak and inconclusive. The overview of population based Belgian studies on environmental exposure to Cd refuted the hypothesis that Cd exposure would lead to an increased blood pressure or to a higher prevalence of hypertension and other cardiovascular diseases (Staessen et al. 1996, cited in Järup et al. 1998). Also a Swedish study of occupationally exposed workers failed to show a relation between Cd exposure and ischemic heart disease (Järup et al. 1998). On the other hand, a recent study in Japan showed an increased relative risk for cardiovascular mortality in Cd-exposed persons (Nishijo et al. 1995, cited in Järup et al. 1998).

Reproductive and developmental toxicity

It is common knowledge that babies of smoking mothers are smaller than those of non-smokers, but epidemiological studies failed to show a positive correlation between mothers exposed to environmental Cd levels causing considerably enhanced Cd concentrations in their placenta (similar to the levels seen in smokers), and decreased birthweight. Only few studies on humans have been published, and current evidence is insufficient to prove that impairment of the male and female reproductive system (as seen in some animal experiments) following exposure to low levels of Cd should be considered as a critical effect (ATSDR 1997, Järup et al. 1998).

Genotoxicity

In the 1991 derivation of a human oral MPR it was concluded that there were no indications for Cd being mutagenic and/or genotoxic (Vermeire et al. 1991). Since that time a number of reviews regarding the genotoxicity of Cd have been published.

In general, Cd compounds fail to induce point mutations in bacterial systems. In studies using cultured animal cells, however, damage to genetic material has been observed: DNA strand breaks, mutations, chromosomal damage and cell transformation have been reported. Also a number of studies using human lymphocyte cultures exposed to Cd compounds showed chromosome damage, but others did not. IARC (1993) concluded that ionic Cd causes genotoxic effects in a variety of eukaryotic cells, including human cells, albeit that positive results were often weak and/or seen at high concentrations that also caused cytotoxicity (IPCS 1992, IARC 1993, CEPA 1994, CE 1995, WHO 1996, ATSDR 1997). Several mechanisms are conceivable: (1) direct damage by interacting with the chromatin, generating strand breaks, crosslinks or structural alterations in DNA, (2) indirect damage by depleting antioxidant

levels, thus increasing intracellular hydrogen peroxide, and (3) by interacting at metal-binding sites of proteins involved in DNA transcription, replication or repair; the evidence thus far suggests that Cd is not directly genotoxic (Misra et al. 1998).

Carcinogenicity

In the 1991 derivation of a human oral MPR it was concluded that there were no indications for Cd being carcinogenic after oral exposure (Vermeire et al. 1991). However, the potential carcinogenicity of Cd is still a matter of debate.
The relationship between occupational exposure to Cd and increased risk of cancer (specifically lung and prostate cancer) has been explored in a number of epidemiological studies. The positive results have all come from exposures via the inhalation route, but in most studies the presence of confounding factors such as concomitant exposure to arsenic and nickel could not be ruled out, while almost all studies lacked data on smoking habits of the cohorts. In experimental animals Cd compounds have been shown to be carcinogenic via the inhalatory route of exposure in studies with rats and in some studies with mice. Studies with hamsters and some studies with mice were either negative or inconclusive. Local sarcomas were seen in several studies with rats following single or multiple subcutaneous or intramuscular injections of $CdCl_2$, CdS, $CdSO_4$, and CdO (IARC 1993, CEPA 1994, ATSDR 1997, Järup et al. 1998).
There are no human studies that associate an increase in cancer with occupational or environmental exposures via the oral route. The indication for carcinogenicity of Cd via oral exposure is limited to one animal study, out of ten oral studies with rats and mice, which showed increased tumour incidence: $CdCl_2$ (3.5 mg/kg bw/day) given to Wistar rats in the diet during 77 weeks was associated with large lymphocyte leukaemia and proliferative lesions of the prostate (IARC 1993, CEPA 1994, ATSDR 1997, Järup et al. 1998). Overall, the available data do not indicate that Cd is carcinogenic via the oral route.
When combined with known carcinogens, Cd enhanced, suppressed or had no effect on tumour incidence, depending on a complex set of circumstances including the dose, route and time sequence of administration, and site of tumour. Administration of excess Zn by inhalation, parenteral and oral routes has been shown to reduce the carcinogenic potential of Cd after inhalatory or systemic exposure.

1.3.3. EVALUATION

Carcinogenicity
On the basis of the studies outlined in paragraph 1.3.2 it can be concluded that humans exposed to Cd via inhalation are apparently at higher risk of lung cancer, but the available data do not allow an unambiguous discrimination between a true (direct) carcinogenic effect of Cd and an effect from other carcinogens or environmental and/or life-style factors. Probably an indirect mechanism (with a threshold) is responsible for the carcinogenicity of Cd after inhalatory exposure. Thus, Cd should be considered as 'probably carcinogenic to humans by the inhalatory route'.
In our opinion the evidence for carcinogenic properties by the oral route is insufficient. This is in line with the conclusion of the Health Council of The Netherlands, who stated that it is not possible to classify Cd as a carcinogenic compound (Gezondheidsraad 1995). Consequently, the (potential) increase of cancer following Cd exposure in cases of soil contamination is irrelevant.

Toxicity
A range of non-neoplastic effects has been observed in humans and experimental animals exposed to Cd compounds. The critical effect of long-term exposure is renal tubular dysfunction, characterised initially by an increased excretion of low molecular weight proteins in the urine. This effect is irreversible; chronic renal failure is the final and severe endpoint. As outlined in paragraph 1.3.2 and in agreement with the earlier evaluation (Vermeire et al. 1991), Cd levels in the renal cortex and the urine should be kept below 50 mg/kg (w/w) and 2.5 µg/g creatinine, respectively, to prevent renal tubular damage that can proceed to clinical disease and perhaps contribute to early death. Recent human datasets (including the study of Nogawa et al. 1989) indicate that the lowest level of Cd in the kidney

cortex at which adverse renal effects can be detected in approximately 4% of the general population (PPC-4) is around 50 mg/kg (corresponding to a urinary Cd level of 2.5 µg/g creatinine), a level which is likely to be reached after 40-50 years of intake of 50 µg Cd per day (approximately 1 µg/kg bw/day).
So, considering that an exposure period of 40-50 years (compared to an average lifetime of 60-70 years) to 1 µg/kg bw/day already results in adverse effect(s) in 4 % of the population, the TDI should be set at a level below the TDI of 1 µg/kg bw/day established earlier (WHO-JECFA, 1989, 1993; Vermeire et al. 1991), as also suggested by ATSDR (1997) and Järup et al. (1998). Application of a UF of 2 on this population based adverse effect level results in a tolerable daily intake of 0.5 µg/kg bw/day (approximately 30 µg per adult human per day). In view of the accumulating properties of Cd due to its long biological half-life, the tolerable daily intake is preferably to be referred to as a TWI (tolerable weekly intake) of 3.5 µg/kg bw/week.

1.3.4. EVALUATIONS BY OTHER ORGANISATIONS

Although the potential carcinogenicity of Cd is not relevant in case of soil contamination, the evaluations of Cd's carcinogenicity by international organisations is summarised hereafter, mainly in view of the ongoing discussion regarding this issue.
In 1987, IARC classified Cd as *'probably carcinogenic to humans'* (group 2A), based upon sufficient evidence for the carcinogenicity of specified Cd compounds in experimental animals and limited evidence for carcinogenicity in humans exposed to Cd (IARC 1987). IPCS (1992) joined the conclusion of IARC of 1987 in considering Cd as a probable human carcinogen (IARC group 2A).
In its evaluation of 1993, however, IARC classified Cd and Cd compounds as *human carcinogens* (group I) (IARC 1993), although it was noted that there were serious constraints influencing the evaluation (i.e., limited number of persons studied, scarcity of historical Cd exposure data, difficulties in accounting for confounding factors like smoking and associated exposures), which is why this classification has been heavily criticised by, e.g., ATSDR (1997) and Järup et al. (1998).
Mainly on the basis of results from inhalation studies in animals and supporting data on genotoxicity, CEPA (1994) classified inorganic Cd compounds in Group II: *'probably carcinogenic for humans'*.
US-EPA has classified Cd as a *probable human carcinogen by inhalation* (Group B1), based on limited evidence of an increase of lung cancer in humans and sufficient evidence of lung cancer in rats. Applying the two-stage extrapolation method, US-EPA concluded to an inhalation unit cancer risk of 1.8×10^{-3} per µg/m^3, and thus a 10^{-4} lifetime excess cancer risk at 60 ng/m^3. US-EPA did not conclude with respect to the carcinogenic potential of Cd by the oral route due to lack of positive studies of orally ingested Cd suitable for quantitation (IRIS 1999, last revision dated June 1992).
ATSDR (1997) concluded that neither the human, nor the animal studies provide sufficient evidence to determine whether or not Cd is a carcinogen by the oral route. Regarding the inhalation route of exposure, ATSDR (1997) concluded to strong evidence that Cd inhalation can cause lung cancer, but only in rats, and pointed to the differences in morphology of the rat respiratory tract compared to that of humans.
Järup et al. (1998), reviewing the available information, concluded that the evidence for Cd as a human carcinogen is rather weak, particularly after oral exposure. They considered a classification of Cd as *'probably carcinogenic to humans'* (IARC group 2A) more appropriate.
According to Directive 67/548/EEG of the European Union and the various adaptations since, CdO, $CdCl_2$, CdF_2, and $CdSO_4$ are labelled as "*carcinogenic, category 2*" which implies that these substances '*should be considered as if they are carcinogenic to man'*. Similarly, CdS is labelled as *"carcinogenic, category 3"*, which implies that this substance *'causes concern for man owing to possible carcinogenic effects'*.
Tolerable daily intakes of Cd as estimated by various organisations arrived all at values between 0.2 and 1 µg/kg bw/day.
In 1994, US-EPA established an oral RfD (reference dose) of 1 µg/kg bw/day in food and 0.5 µg/kg bw/day in drinking water, based upon toxicokinetic calculations of chronic human studies with proteinuria as the critical effect, applying an UF of 10 for intrahuman variability (IRIS 1999, last revision dated February 1994). US-EPA stated high confidence in these RfDs since they reflect data from many studies in both humans and animals.

WHO-JECFA (1989) recommended a PTWI (provisional tolerable weekly intake) of 7 µg/kg bw (for adults) in order to prevent kidney Cd levels from exceeding 50 mg/kg in renal cortex after continuous exposure for 50 years. WHO-JECFA stated that excursions above this figure may be tolerated if not sustained for a long time, and that the estimate took into account the higher Cd intake of infants and children. In 1993, WHO-JECFA maintained its earlier PTWI, and repeated its concern that there is only a relatively small safety margin between exposure in the normal diet and exposure that produces deleterious effects (WHO-JECFA 1993). For arithmetric purposes this PTWI can be interpreted as a TDI of 1 µg/kg bw/day.
ATSDR (1997) arrived at a MRL (minimum risk level) for chronic exposure by the oral route of 0.2 µg/kg bw/day, based upon the human study of Nogawa et al. (1989) who concluded to a NOAEL of 2.1 µg/kg bw/day for renal damage as the critical effect. For the MRL estimation ATSDR applied a UF of 10 to correct for human variability.
The Health Council of The Netherlands (Gezondheidsraad 1995) advised a Health-Based Occupational Exposure Limit for a 8 h working day of 5 µg Cd (dusts and fumes) per m^3, on the basis of a NOAEL of 10 µg/m^3 in animal experiments showing alveolar proteinosis, interstitial fibriosis and bronchiolar hyperplasia, applying a UF of 2 for species differences.

1.3.5. BACKGROUND EXPOSURE

The major route of exposure to Cd for the non-smoking general population is via the food. In (non-smoking) exposed workers, however, lung absorption following inhalation of workplace air is the major route.
According to IPCS (1992), the average intake of an adult from air in non-contaminated areas is 0.15 µg/day (resulting in an uptake -actually absorbed amount of Cd - of 0.04 µg/day), in contaminated areas the intake from air amounts up to 7.5 µg/day (resulting in an uptake of 2 µg/day). Smoking 20 cigarettes daily adds 2-4 µg to the inhalatory intake (an uptake of 1-2 µg/day). Daily intake from water and food is 12-25 µg (resulting in an uptake of 0.6-1.3 µg/day). Thus, the average intake of non-smokers would be 0.17-0.46 µg/kg bw/day (non-contaminated vs. contaminated areas).
Järup et al. (1998) estimated the average dietary intake for the Swedish population at 15 µg/day, equalling 0.22 µg/kg bw/day.
Regarding the Dutch situation, Vermeire et al. (1991), citing the Integrated Criteria Document on Cadmium (Ros and Slooff 1988), estimated an average daily uptake of 0.28 µg/kg bw/day, and almost twice this exposure (0.53 µg/kg bw/day) for smokers. In 1993, TNO calculated the daily dietary intake through food and beverages in The Netherlands (period 1988-1989) to be 15.7 ± 5.3 (equalling 0.22 µg/kg bw/day) and 11.6 ± 3.9 µg (equalling 0.17 µg/kg bw/day) for male and female adults, respectively (note: these intakes exclude intake through smoking and occupational exposure) (Brussaard et al. 1993).

1.3.6. CONCLUSION

Compound	TDI	TCA	Background exposure
Cadmium	0.5	-	0.22 & 0.17 *)

TDI: tolerable daily intake (oral exposure); µg/kg bw/day
TCA: tolerable concentration in air (inhalation exposure); µg/m^3
Background exposure; µg/kg bw/day
*) males and females, respectively; excluding smoking

Oral TWI: 3.5 µg/kg bw/week. For arithmetric purposes the TWI can be converted to a tolerable daily intake (TDI) of 0.5 µg/kg bw/day.
The relevant route of exposure in cases of soil contamination is oral. Neither Cd itself nor its compounds are volatile, so inhalatory exposure from contaminated soil will be negligible. Likewise, significant uptake from dermal exposure is negligible.

1.3.7. REFERENCES

ATSDR (1997):
Toxicological profile for cadmium, draft for public comment (update).
US Dept. of Health & Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta (GA), USA.

Brussaard JH, Schneijder P, Aken AMMAM van, Dokkum W van & Vos RH de (1993):
Dietary intake of food contaminants in The Netherlands - Input from TNO Total Diet Study 1988-1989, Part 1: Cadmium, lead, organochlorine compounds, nitrate and malathion.
TNO Nutrition and Food Research, TNO report no. V93567, December 1993; Zeist, The Netherlands.

CE (1995):
Cadmium in food - health protection of the consumer.
Council of Europe, Committee of experts on health control of foodstuffs.
Council of Europe Publishing, Strasbourg, France.

CEPA (1994):
Cadmium and its compounds.
Canadian Environmental Protection Act, Priority Substances List Assessment Report, Cat. no. En-40/215/40E of the Ministry of Supply & Services Canada.
Bureau of Chemical Hazards, Health Canada, Environmental Health Centre, Tunney's Pasture, Ottawa, Ontario, Canada.

Gezondheidsraad (1995):
Cadmium and inorganic cadmium compounds - health based recommended occupational exposure limit.
Dutch Expert Committee on Occupational Standards, Health Council of The Netherlands, report no. 1995/04WGD, October 1995; Den Haag, The Netherlands.

IARC (1987):
Monographs on the evaluation of carcinogenic risks to humans.
- Supplement 6: Genetic and related effects - an updating of selected IARC monographs from volumes 1 to 42 - cadmium and cadmium compounds; pp 132-135.
- Supplement 7: Overall evaluations of carcinogenicity - an updating of IARC monographs volumes 1 to 42 - cadmium and cadmium compounds; pp 139-142.

International Agency for Research on Cancer, World Health Organization, Lyon, France.

IARC (1993):
Monographs on the evaluation of carcinogenic risks to humans. Vol. 58: Beryllium, cadmium, mercury, and exposures in the glass manufacturing industry; pp 119-237.
International Agency for Research on Cancer, World Health Organization, Lyon, France.

IPCS (1992):
Environmental Health Criteria 134: Cadmium.
International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland.

IRIS (1999):
Integrated Risk Information System: Cadmium (update May 1999, last revision inhalatory carcinogenicity June 1992, last revision oral toxicity February 1994).
US Environmental Protection Agency, Washington DC, USA.

Järup L, Berglund M, Elinder CH, Nordberg G & Vahter M (1998):
Health effects of cadmium exposure - a review of the literature and a risk estimate.
Scand J Work Environm Health 24 suppl 1: 1-52.

Kjellström T & Nordberg GF (1985):
Kinetic model of cadmium metabolism. In: Friberg L, Elinder CG, Kjellström T, Nordberg GF (eds): Cadmium and health, a toxicological and epidemiological appraisal, Vol I: Exposure, dose and metabolism, effects and response; pp 179-197.
CRC Press, Boca Raton (FL), USA *(cited in ATSDR 1997, and Järup et al. 1998).*

Lauwerys R, Roels H, Regniers M, Buchet JP, Bernard A & Goret A (1979):
Significance of cadmium concentration in blood and urine in workers exposed to cadmium.
Environm Res 20: 375-391 *(cited in IPCS 1992).*

Misra RR, Smith GT & Waalkes MP (1998):
Evaluation of the direct genotoxic potential of cadmium in four different rodent cell lines.
Toxicol 126: 103-114.

Nishijo M, Nakagawa H, Morikawa Y, Tabata M, Senma M & Miura K (1995):
Mortality of inhabitants in an area polluted by cadmium - 15 year follow up.
Occup Environm Med 52: 181-184 *(cited in Järup et al. 1998).*

Nogawa K, Honda R, Kido T, Tsuritani I, Yamada Y, Ishizaki M & Yamaya H (1989):
A dose-response analysis of cadmium in the general environment with special reference to total cadmium intake limit.
Environm Res 48: 7-16.

Nordberg GF, Kjellström T & Nordberg M (1985):
Kinetics and metabolism. In: Friberg L, Elinder CG, Kjellström T, Nordberg GF (eds): Cadmium and health, a toxicological and epidemiological appraisal, Vol I: Exposure, dose and metabolism, effects and response; pp 103-178.
CRC Press, Boca Raton (FL), USA *(cited in ATSDR 1997, and Järup et al. 1998).*

Roels H, Bernard AM, Cárdenas A, Buchet JP, Lauwerys RR, Hotter G, Ramis I, Mutti A, Franchini I, Bunschuh I, Stolte H, DeBroe ME, Nuyts GD, Taylor SA & Price RG (1993):
Markers of early renal changes induced by industrial pollutants. III: Application to workers exposed to cadmium.
Brit J Ind Med 50: 37-48.

Ros JPM & Slooff W (1988):
Integrated criteria document cadmium.
National Institute of Public Health and the Environment, RIVM report no. 758476004, May 1988; Bilthoven, The Netherlands.

Staessen JA, Buchet JP, Ginucchio G, Lauwerys RR, Lijnen P & Roels H (1996):
Public health implications of environmental exposure to cadmium and lead - an overview of epidemiological studies in Belgium.
J Cardiovasc Risk 3: 26-41 *(cited in Järup et al 1998).*

Vermeire TG, Apeldoorn ME van, Fouw JC de & Janssen PJCM (1991):
Voorstel voor de humaan-toxicologische onderbouwing van C-(toetsings)waarden.
National Institute of Public Health and the Environment, RIVM report no. 725201005, February 1991; Bilthoven, The Netherlands.

Wester RC, Maibach HI, Sedik L, Melendres J, DiZio S & Wade M (1992):
In vitro percutaneous absorption of cadmium from water and soil into human skin.
Fund Appl Toxicol 19: 1-5.

WHO (1996):
Guidelines for drinking-water quality, 2nd. ed., vol. 2: Health criteria and other supporting information.
World Health Organization, Geneva, Switzerland.

WHO-JECFA (1989):
Toxicological evaluation of certain food additives and contaminants; the 33rd Meeting of the Joint FAO/WHO Expert Committee on Food Additives.
WHO Food Additives Series 24, pp 163-219.
International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland.

WHO-JECFA (1993):
Evaluation of certain food additives and contaminants; the 41st Meeting of the Joint FAO/WHO Expert Committee on Food Additives.
WHO Technical Report Series 837, pp 28-30.
International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland.

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1.4. CHROMIUM III

1.4.1. INTRODUCTION

Chromium was evaluated within the scope of this project by Vermeire et al in 1991, who proposed a TDI of 5 µg/kg bw/day for oral intake. A TCA was not suggested. In the report it was stated that the proposal applies to chromium (III), as the most stable form of chromium in soil. Chromium (VI) was excluded due to its carcinogenic action; a provisional TDI of 5 µg/kg bw/day and a TCA with 10^{-4} lifetime tumour risk of 2.5 ng/m^3 was derived for hexavalent chromium by the RIVM in 1999 (RIVM 1999, rep. id. 7317A00). For chromium (III) it was reported that is it not genotoxic and carcinogenic. The TDI was derived on the basis of a NOAEL of 2.5 mg/kg bw/day for rats. An uncertainty factor of 100 was selected for intra- and interspecies extrapolation, and an additional factor of 5 for limitations in the study. For this update additional and more recent literature was consulted. This included reviews of the IPCS (1988), IARC (1990), WHO (1996), and ATSDR (1998).
Chromium is ubiquitous in nature; it can be detected in air, water and soil. It can exist in oxidation states of 2+ to 6+. Naturally occurring chromium in soils is almost always trivalent chromium; it is assumed that hexavalent chromium found in the environment is almost totally derived from human activities. Background natural occurrence of chromium in soil is in the order of 125 mg/kg on average, but concentrations as high as a few grams per kg of soil are known to exist.
Chromium is used in various processes and materials. Its principal use is in metallurgical processes making steels and alloys, and plating. Besides chromium compounds are used in pigments and leather tanning, in various fungicides, and wood preservatives.
Major sources of soil contamination with chromium will be waste disposal, both industrial and household waste. In some industries also wastewater disposal can lead to sediment contamination. Due to the various sources both local and diffuse contamination is to be expected.

1.4.2. TOXICOLOGY

Toxicokinetics

Absorption
Studies with humans following oral exposure of chromium III compounds indicate that it is poorly absorbed in the gastrointestinal tract. . The absorption rate is dependent on the dietary intake. For human adults a mean absorption of 2.8% is reported (ATSDR 1998). According to the IPCS (1988) the absorption of many trivalent chromium compounds is so low that they are used as faecal markers in man and animals.
Human data on absorption after inhalation exposure is very limited. No estimates are reported. In animal studies the absorption after inhalation of chromium (III) was reported to be 5 to 30%.
Distribution
Chromium can be found in most organs such as heart, kidneys, and liver. Highest concentrations in humans, however, are found in the lungs and lymph nodes after inhalation exposure.
Metabolism and excretion
Biologically active chromium (III) is suggested to exist in a chromium-glutathione-like complex. Unabsorbed chromium is excreted with the faeces. Absorbed chromium, however, will be excreted via the urine.
Biomarkers
In studies of humans exposed to chromium no correlation could be found between the concentration of trivalent chromium in blood and the rate of exposure. That same observation is reported for urine, showing a poor association with trivalent chromium. Consequently, the chromium detected in urine of humans can not be used as a biomarker for chromium (III) exposure.
By analysis of chromium in hair, differences can be noticed that appears to reflect the nutritional chromium status. Changes of concentrations in hair can be demonstrated during pregnancy and in diabetes, which is in agreement with expected changes in the normal chromium balance (IPCS 1988).

Toxicity

Essentiality
Chromium can be considered an essential nutrient for humans. Chromium(III) is essential for the normal metabolism of glucose, protein, and fat metabolism. The daily requirement for adults is estimated 0.5 to 2 μg of absorbed chromium(III), equivalent to a dietary intake of 0.03 to 0.13 μg/kg bw/day (WHO 1996).
Acute toxicity
A small number of accidental deaths is reported after acute oral ingestion and after dermal application of chromium. Most of them referred to (acute) exposure to chromium VI compounds. Prominent effects are a gastrointestinal ulceration, and severe liver and kidney damage after oral intake. Renal failure is noticed after dermal exposure.
Genotoxicity and carcinogenicity
The IPCS (1988) reviewed the mutagenicity studies of chromium compounds, and concluded that only hexavalent chromium shows mutagenic activities. This conclusion was supported by the Health Council of The Netherlands (1998). Data on the genotoxicity of metallic chromium is lacking (IARC 1990).
The carcinogenic potency of chromium (III) compounds and metallic chromium was reviewed by IARC (1990) in human studies of very different populations. Both positive and negative results were noted, and the review concluded that there is inadequate evidence in humans for the carcinogenicity of chromium III compounds and metallic chromium.
Subchronic and chronic toxicity
Results of chronic studies with laboratory animals of chronic exposure are very diverse. In ATSDR (1998) a NOAEL is presented for rats of 2040 mg/kg bw/day after exposure to trivalent Cr_2O_3 whereas a NOAEL of 3.6 mg/kg bw/day was presented after exposure to trivalent $CrCl_3$, and of 0.46 for trivalent $Cr(CH_3COO)_3$. These compounds differ in their water solubility: chromium(III)oxide is insoluble in water, whereas chromium(III)chloride is slightly soluble, and chromium(III)acetate is well soluble. Apparently the oral toxicity of trivalent chromium compounds is related to their water solubility.
There is considerable data of chronic exposure of humans from inhalation of chromium. Most studies refer however to chromium VI compounds. In the review of the ATSDR (1998) NOAELs are presented for other chromium compounds in occupationally exposed persons. For metallic chromium a NOAEL of 0.6 mg/m^3 is presented, and of 1.99 mg/m^3 for trivalent Cr_2O_3 and $Cr_2(SO_4)_3$. Data of toxic effects after inhalation of water-soluble trivalent chromium compounds are not reported. Consequently, in contrast to the oral intake of chromium compounds, for inhalation it can not be assessed whether insoluble trivalent chromium compounds demonstrate a different rate of toxicity than the soluble compounds.
There is little data of chronic dermal exposure to trivalent chromium by humans. Metallic chromium is known to produce contact dermatitis in sensitised humans. Many people that are occupationally exposed to chromium develop allergic reactions. In experimental animals both tri- and hexavalent chromium yield the same dermal reactions, hexavalent chromium however, being far more potent.
Mechanism of action
Because of the various oxidation states of chromium, interactions with different enzyme systems and DNA can occur. As a consequence it can affect biological systems in different ways. Chromium(VI) can be expected to be the most reactive form; reports about interactions of biomolecules with chromium(III) are scarce.
ATSDR (1998) concluded that chromium toxicity is very complex and involves many mechanisms. It can generate free radicals which can form adducts with DNA. Besides it was concluded that hexavalent chromium is more toxic in vivo than trivalent chromium due to a better absorption and uptake by the cells. Hexavalent chromium is reduced after entering the cells, and experiments in vitro show that the reduced forms of chromium play a central role in interactions with DNA.

1.4.3. EVALUATION

The data indicate that chromium(III) is not a genotoxic compound, whereas chromium(VI) is. There is no proof of any carcinogenic action of chromium(III) in humans. Consequently a TDI for trivalent chromium compounds can be derived on the basis of a NOAEL, applying uncertainty factors.
The toxicity of chromium (III) compounds appears to depend on its solubility in water. On the basis of a chronic NOAEL of 0.46 mg/kg bw/day in rats and an extrapolation factor of 100 for inter- and intraspecies extrapolation, the TDI for soluble compounds will be 4.6 µg/kg bw/day. Vermeire et al (1991) derived a TDI of 5 µg/kg bw/day on the basis of a NOAEL of 2.5 mg/kg bw/day in another study with rats with another chromium (III) compound. The TDI was derived using an extrapolation factor of 100 and an additional factor of 5 for extrapolation factor for the time of exposure. As the results of both proposals are comparable it is suggested to maintain the TDI of 5 µg/kg bw/day for water soluble chromium (III) compounds.
According to the chronic NOAELs the toxicity of insoluble chromium (III) compounds is approximately 1000 times less, and hence a TDI of 5 mg/kg bw/day can be derived for insoluble chromium (III) compounds. This will include metallic chromium.
For human inhalation exposure to metallic chromium a NOAEC of 0.6 mg/m^3 was reported; studies with insoluble chromium (III) compounds resulted in NOAECs of about 2 mg/ m^3. It is proposed to set a TCA of 60 µg/m^3 for metallic and insoluble chromium (III) compounds, using an extrapolation factor of 10 for intraspecies extrapolation. A TCA for soluble chromium (III) compounds can not be estimated due to lack of appropriate data.

1.4.4. EVALUATIONS BY OTHER ORGANISATIONS

The US-EPA proposed a RfD of 1.5 mg/kg bw/d. for insoluble chromium (III) salts, based on a NOAEL of 5% in the diet (adjusted to 1500 mg chromium/kg bw/day) in a chronic rat feeding study with chromium (III) oxide (IRIS, revised 1998). The dose level of 5% was the highest dose tested.
The ATDSR did not present a MRL for trivalent chromium (ATDSR 1998).
The WHO did not propose a Drinking Water Quality Guideline for chromium. It was stated that different guideline values are needed for tri- and hexavalent chromium, but that analytical methods favour a guideline for total chromium (WHO 1996).

1.4.5. BACKGROUND EXPOSURE

For trivalent chromium compounds Vermeire et al (1991) presented a maximal background exposure of 2.9 µg/kg bw/day. Data in IPCS (1988) and ATSDR (1998) indicate a range for dietary intake of 50 up to 200 µg/person/day, with an average daily intake in the order of 60 µg/person. The exposure of the general population to chromium from other sources such as water and air is negligible. So the background exposure in The Netherlands can be estimated to be 1 µg/kg bw/day.

1.4.6. CONCLUSION

Compound	TDI	TCA	Background exposure
Chromium III (soluble compounds)	5	-	1
Chromium III (metallic and insoluble compounds)	5000	60	

TDI: tolerable daily intake (oral exposure); µg/kg bw/day
TCA: tolerable concentration in air (inhalation exposure); µg/m^3
Background exposure; µg/kg bw/day

The oral TDI of 5 µg/kg bw/day as derived for soluble chromium (III) compounds is similar to the previous proposal of Vermeire et al. (1991). For insoluble chromium (III) compounds and metallic chromium a TDI of 5 mg/kg bw/day is derived.
A TCA of 60 µg/m^3 is derived for insoluble chromium (III) compounds and metallic chromium. For soluble chromium (III) compounds a TCA was not derived.

1.4.7. REFERENCES

ATSDR (1998):
Draft toxicological profile for chromium (update).
Agency for Toxic Substances and Disease Registry, US Public Health Service, USA.

Health Council of The Netherlands (1998):
Chromium and its organic compounds (revised version),.
Report no. 1998/01, Gezondheidsraad WGD, Den Haag, The Netherlands.

IPCS (1988):
Environmental Health Criteria 61 - Chromium.
World Health Organization, Geneva, Switzerland.

IARC (1990):
Chromium, nickel and welding.
IARC Monographs on the evaluation of carcinogenic risks to humans, Volume 49, Lyon, France

Vermeire TG, Apeldoorn ME van, Fouw JC de & Janssen PJCM (1991):
Voorstel voor de humaan-toxicologische onderbouwing van C-toetsingswaarden.
National Institute of Public Health and the Environment, RIVM-report no. 725201005, February 1991; Bilthoven, The Netherlands.

WHO (1996):
Guidelines for drinking-water quality, 2nd ed. Volume 2, Health criteria and other supporting information.
World Health Organization, Geneva, Switzerland.

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1.5. CHROMIUM VI

1.5.1. INTRODUCTION

Hexavalent chromium (Cr(VI)) is thermodynamically instable (CCME 1997); it is generally produced by industrial processes and released to the environment by human activities. Cr(VI) compounds are primarily used in production of ferrochromium alloys and chromium metal, production and welding of stainless steels, manufacture of chromium chemicals, production and use of chromium containing catalysts, production and use of cement, use of chromium refractories, chrome plating, paints (dyes and pigments), and production and use of wood preservatives (Cross et al. 1997).
Cr (VI) compounds include soluble (solubility in water >100 g/L) Cr(VI) compounds (e.g. ammonium dichromate, chromium trioxide, potassium dichromate, sodium dichromate, sodium chromate), slightly soluble (solubility in water 1-10 g/L) Cr(VI) compounds (e.g. calcium chromate, strontium chromate, zinc chromate, basic zinc chromate) and poorly soluble (solubility in water <1 g/L) Cr(VI) compounds (e.g. barium chromate, basic lead chromate, lead chromate, molybdenum orange) (Cross et al. 1997, DECOS 1998).
Cr(VI) can be reduced by various reducing agents to Cr(III) (e.g. S^{2-}, Fe(II), fulvic acid, low molecular weight organic compounds, proteins). The effectiveness of these reducing agents varies with pH, redox conditions, and total concentrations of chromium (CEPA 1994).
A small percentage of total chromium in soil exists as soluble Cr(VI). The sorption of chromium to soil depends primarily on the clay content of the soil, and, to a lesser extent, on Fe_2O_3 and the organic content of soil. Organic matter in soil is expected to convert Cr(VI) to insoluble Cr_2O_3. Chromium in soil may be transported to the atmosphere as aerosol. Soluble and unadsorbed Cr(VI) in soil may leach into groundwater. Leachability of Cr(VI) in the soil increases as the pH of the soil increases. On the other hand, lower pH present in acid rain may facilitate leaching of acid-soluble Cr(VI) compounds in soil. Chromium has a low mobility for translocation from roots to aboveground parts of plants (ATSDR 1998).
A MPR for chromium (III and VI) was established in 1991 (Vermeire et al. 1991), who concluded that Cr (VI) was a genotoxic carcinogen for animals and men, and consequently a threshold method for derivation of a limit value was not considered appropriate. For the inhalation route an extra cancer risk of 1 per 10^4 lifetime exposed persons was calculated to occur at 2.5 ng Cr(VI)/m^3 (derived from human data).
For the oral route no adequate chronic studies were available for a non-threshold extrapolation to an oral limit value. Therefore Vermeire et al. (1991) applied route to route extrapolation, despite the fact that the inhalation limit was based on the induction of lung tumors. For the oral route an extra cancer risk of 1 per 10^4 lifetime exposed persons was calculated to occur at 0.7 ng/kg bw/day.
Exposure routes considered relevant in the present context: inhalation, oral and dermal.

1.5.2. TOXICITY

Toxicokinetics

Toxicokinetics of chromium in animals and humans are basically similar.
Absorption of inhaled chromium is believed to be up to 30% for Cr (VI) compounds; some Cr (VI) is reduced to Cr (III) by the epithelial lining of the lung. The absorption of Cr (VI) compounds is also dependent on the solubility of the compound. Absorbed chromium is widely distributed throughout the body, including to the fetus, via the bloodstream. After crossing cellular membranes, Cr (VI) may be reduced to trivalent forms. Absorbed chromium is eliminated from the body largely in the urine, while most of the unabsorbed chromium is excreted in the feces (CEPA 1994).
After oral exposure up to 10% of ingested Cr (VI) is absorbed from the gastrointestinal tract; organic complexes are even more readily absorbed. Much of the ingested Cr (VI) is reduced to Cr (III) before absorption, limiting the bioavailability of Cr(VI) after ingestion (CEPA 1994). Only intakes that exceed the reducing capacity of the stomach, will result in significant absorption of Cr(VI) across the gastrointestinal mucosa (Felter and Dourson 1997). In a recent study 5 human volunteers received an oral bolus dose of Cr (VI) (2.5 or 5 mg as a 10 mg/L solution in water within 2 minutes ~ 0.03 and

0.05 mg/kg bw). Bioavailability of Cr (VI), as assessed by urinary excretion for 4 days after dosing, averaged 5.7% (range 1.1-14.5%) of the administered dose. Three of the same human volunteers received 3 doses of 5 mg (~0.05 mg/kg bw) or 10 mg Cr (VI) (~0.1 mg/kg bw) with a 6 h time interval between doses. Bioavailability averaged 1.7% and 3.5% of the administered dose, respectively. (Kerger et al. 1997 as cited in ATSDR 1998). One human volunteer received 5 times each day for 17 days 0.8 mg Cr (VI) in drinking water. Biovailability was 2% of the administered dose and plasma elimination half-time was 36 hours (Paustenbach et al. 1996 as cited in ATSDR 1998).
Dermal absorption percentages up to 4% are reported from studies in guinea-pigs with soluble Cr (VI) compounds in aqueous solution. Dermal absorption rates in humans vary from 0.03 ng/cm^2/h to 10 µg/cm^2/h dependent on solvent, exposure condition and the concentration of Cr (VI) (Corbett et al. 1997 as cited in Van Raay et al. 1998, Cross et al. 1997). The USEPA recommends the use of a dermal absorption estimate of 1 µg/cm^2/h for risk assessment purposes (USEPA 1992 as cited in Van Raay et al. 1998).
Remark:
Diabetic patients may absorb up to 4 times more chromium from the gastrointestinal tract compared to healthy individuals (IPCS 1988).

Acute toxicity

Acute inhalation LC_{50} values in rats range from 29-82 mg Cr(VI)/m^3 for sodium chromate, sodium-, potassium- and ammonium dichromate and from 87-137 mg Cr(VI)/m^3 for chromium trioxide. Oral LD_{50} values in rats range from 13-28 mg Cr(VI)/kg bw for sodium chromate, sodium-, potassium- and ammonium-dichromate, from 108-249 mg Cr(VI)/kg bw for calcium chromate and from 25-29 mg Cr(VI)/kg bw for chromium trioxide. Lethal oral doses in man varying from 4.1-29 mg Cr(VI)/kg bw are reported (ATSDR 1998). Dermal LD_{50} values in rabbits range from 336-763 mg Cr(VI)/kg bw for sodium chromate, sodium-, potassium- and ammonium dichromate. For chromium trioxide a dermal LD_{50} value in rabbits of 30 mg Cr(VI)/kg bw (24 h exposure) is reported (ATSDR 1998).
In general, females appeared to be more susceptible for acute toxic effects of chromium than males (ATSDR 1998).

Skin irritation

Dermal application of soluble Cr(VI) compounds (42-55 mg/kg bw) to the intact skin of rabbits induced skin inflammation, edema and necrosis. Skin corrosion and eschar formation occurred at lethal doses. Application of 0.35 or 1.9 mg Cr(VI)/kg (as a 0.34 M solution of $K_2Cr_2O_7$) to the abraded skin of guinea-pigs resulted in skin ulcers and skin corrosion, respectively, whereas after application to the unabraded skin no ulcers were observed (ATSDR 1998, Cross et al. 1997).
In occupationally exposed workers exposure to (soluble) Cr(VI) compounds causes skin irritation, skin ulcers and severe burns. Irritation or ulceration of the skin may be facilitated at skin sites with abrasions, scratches or other types of skin damage. Local exposure to Cr(VI) at high concentrations may induce so-called ‘chrome-holes’. The prevalence of skin irritation and skin ulcers in workers in the chromate producing industry may be as high as 50% (ATSDR 1998, Cross et al. 1997).

Eye and respiratory tract irritation

Severe eye irritation, necrosis of the conjunctivae, and ulceration of the cornea in rabbits was reported after instillation of potassium dichromate either as powder or in solution (7 mg Cr(VI) daily for 7 days) (Cross et al. 1997).
In humans direct contact of soluble Cr(VI) compounds with the eyes may cause irritant and corrosive effects. Effects reported are erosion and ulceration, corneal vesication and congestion of the conjunctivae (in about 40% of accidentally exposed eyes of workers in the chromate producing industry). These effects are mostly reported without quantitative exposure data (ATSDR 1998, Cross et al. 1997).
See under short-term/long-term toxicity - exposure by inhalation for irritation to the respiratory tract.

Skin sensitization

Animal studies clearly show that soluble Cr(VI) compounds are skin sensitizers, inducing a type IV cell mediated immune response. Skin sensitization was observed in guinea-pig maximization tests and ear swelling tests. There is evidence for cross-reactivity to both Cr(VI) and Cr(III) compounds, although Cr(VI) compounds have the greater sensitizing potential. Current understanding of the mechanism involved is that Cr(III) is the ultimate hapten. The available evidence suggests that Cr(VI) once diffused through the skin, is reduced to Cr(III) which then forms protein-conjugates which serve as the full antigen (Cross et al. 1997).
Chromium induces allergic contact dermatitis (ACD) in man. Especially soluble Cr(VI)-compounds are known to be extremely potent skin sensitizers (Cross et al. 1997). The prevalence of chromium sensitivity in the general population has been conservatively estimated at 0.7% (ATSDR 1998). Some authors concluded that elicitation of ACD was dependent on Cr(VI) concentration in the test-patch and a 10% threshold value (level at which 10% of Cr(VI) sensitive individuals showed a sensitization reaction) of 0.001% Cr(VI) (10 mg/L) was derived for potassium chromate (Stern et al. 1993 as cited in ATSDR 1998). In other studies threshold values for the induction of ACD were expressed as amount of Cr(VI) per skin surface area. In a patch testing study, the concentration of potassium dichromate producing an allergic skin response in 10% of a group of Cr(VI) sensitized volunteers was calculated to be 0.089 $\mu g/cm^2$ (Nethercott et al. 1994 as cited in Cross et al. 1997). Paustenbach et al. (1992) evaluated eight published patch tests studies with K_2CrO_4 in order to establish a threshold dose of Cr(VI) to which no more than 10% of the subpopulation sensitized to chromium would respond, and that would protect at least 99.84% of the general population. A weighted mean 10% threshold of approximately 150 ppm K_2CrO_4 or 54 ppm Cr(VI) was identified from the eight studies.

Short-term and long-term toxicity

Inhalation exposure
In various short-term and long-term inhalation studies in animals, besides a reduced body weight gain and increased weight of lungs and other organs, primarily irritant and corrosive effects in the respiratory tract and effects on respiratory defense sytems were observed (a.o. macrophage function) (ATSDR 1998, CEPA 1993, Cross et al. 1997, Slooff et al. 1990). However, many of the studies were limited by small group sizes, inadequate histopathological examination, and/or single exposure levels. In rats effects on the respiratory system including accumulation of eosinophilic substances inside the alveolar lumen, focal thickened septa, interstitial fibrosis and focal bronchiolo-alveolar hyperplasia, granulomata, giant cells and abscesses were reported. Effects on the respiratory system in mice included perforated nasal septum, loss of cilia, proliferation of globet cells or basal cells, squamous metaplasia or hyperplasia of the trachea, larynx, bronchus or lungs, emphysema, necrosis and alveolar bronchiolization and proteinosis. In addition respiratory effects were observed in rabbits (perforated nasal septum) and guinea-pigs (alveolar and interstitial inflammation and alveolar hyperplasia) (CEPA 1993). LOAEL's of 100 $\mu g/m^3$ (interstitial fibrosis of lungs at exposure to a 3:2 mixture of Cr(VI) and Cr(III)) (CEPA 1993), 50 $\mu g/m^3$ (increased lung and spleen weight, stimulated humoral immune system) (Cross et al. 1997), and 25 $\mu g/m^3$ (increased percentage of lymphocytes in bronchoalveolar lavage fluid) (Glaser et al. 1985 as cited in ATSDR 1998) are reported in rats. A NOAEL could not be determined (Cross et al. 1997).
Data on repeated inhalation exposure in humans is mainly derived from occupationally exposed workers and case-reports. The most predominant effects in humans reported for long-term exposure to Cr(VI)-compounds are irritative effects to the skin and mucous membranes, and allergic responses. Workers exposed to Cr(VI) compounds for intermediate- and chronic-durations were found to exhibit epistaxis, chronic rhinorrhea, nasal itching and soreness, nasal mucosa atrophy, perforations and ulcerations of the nasal septum, bronchitis, pneumonoconiosis, decreased pulmonary function and pneumonia (ATSDR 1998). Effects on the mucous membranes of the upper respiratory tract are frequently observed after exposure to Cr(VI). Cr(VI) compounds are found to induce immediate ulceration and perforation of the nasal septum. The nasal septum appears to be particularly sensitive to the effects of Cr(VI) given the very low vascularization of its cartilagenous structure and the causticity of Cr(VI) compounds. Exposure for $\leq$1 year to atmospheric levels of CrO_3 of approximately 90-100 μg

(Cr(VI)/m^3 was sufficient to induce lesions (nasal ulceration and perforation, epitaxis rhinorrhea). Exposure for at least one year to concentrations from 10 µg (Cr(VI)/m^3 onwards, resulted in high incidences of nasal septum perforation, septal atrophy and ulcerations, sinusitis, pharyngitis and bronchitis among 65 workers in dichromate and chromium trioxide production (ATSDR 1998, DECOS 1998). For long-term inhalation exposure to Cr(VI)-compounds a NOAEL of 1 µg/m^3 has been identified in humans working with chromium trioxide mist for periods of 0.2 to 23.6 years (average 2.5 years) based on nasal irritation, mucosal atrophy and ulceration, and slight, transient decreases in spirometric parameters at next higher measured concentration of 2 µg/m^3 (Lindberg and Hedenstierna 1983 as cited in ATSDR 1998).

Oral exposure

Oral exposure to Cr(VI) of animals results mainly in effects on gastrointestinal tract, liver, kidneys and probably the haematopoietic system. In most of the oral studies with Cr(VI) compounds the numbers of animals per group were too small, only one dose-level was used and/or an incomplete set of parameters was examined (IPCS 1988). Studies with lowest adverse effect levels and highest no adverse effect levels are summarized hereafter.

In a multigeneration study in mice given $K_2Cr_2O_7$ in the diet, dose-related decreases in mean corpuscular volume values at all dose-levels were seen (lowest dose-level 7.8 mg Cr(VI)/kg bw). No effects on body weight and no hepatic, renal or gastrointestinal effects were seen in this study at dose-levels up to and including 36.7 mg Cr(VI)/kg bw (ATSDR, 1998). In mice and rats given potassium dichromate in their diet for 9 weeks a NOAEL of 7.35- 12 mg/Cr(VI) per kg bw for mice and 2.1-2.45 mg Cr(VI)/kg bw for rats could be established based on reduced mean corpuscular volume and mean corpuscular haemoglobin values at the next higher dose-level (ATSDR 1998). In rats (8/sex/dose), receiving in their drinking water up to 25 mg Cr(VI)/L (as (K_2CrO_4) (equivalent to 2.4 mg Cr(VI)/kg bw) for up to 1 year, only an approximate 20% reduction in water consumption and increased Cr tissue levels were observed. There were no changes in blood or pathological changes in tissues (liver, kidneys, spleen, femur) (MacKenzie et al. 1958 as cited in Dourson 1994). In female dogs (2/group) receiving up to 11.2 mg Cr(VI)/L in drinking water (as K_2CrO_4) (equivalent to 0.30 mg Cr(VI)/kg bw) for 4 years, no effects were seen (Dourson 1994). Effects on liver and kidneys (lipid accumulation and changed enzyme activities) in rats were seen at oral doses ≥ 13.5 mg/kg bw/day for 20 days (ATSDR 1998). USEPA used the 1 year drinking water study in rats as principal study to establish an oral reference dose (NOAEL 2.4 mg/kg bw; uncertainty factor 500; RfD oral 5 µg/kg bw) (MacKenzie et al. 1958 as cited in IRIS 1996). However, data on enzyme activities, morphology of gonads (see under reproduction) and effects on the immune system have not been addressed in this drinking water study (Cross et al. 1997).

Only some case-reports are available with respect to repeated oral exposure of humans. In occupationally exposed workers who were suspected of ingesting chromium dust, an increased incidence of gastric ulcers and hyperthrophic gastritis were reported (ATSDR 1998). A report on 155 villagers in China who ingested contaminated well water for 4 years (estimated dose 0.57 mg Cr(VI)/kg bw/day) described increased incidences of oral ulcers, diarrhea, abdominal pain, indigestion and vomiting, and an increase in leukocytosis and immature neutrophils (ATSDR 1998). No adverse health effects (by physical examination) were detected in four persons who drank for 3 years from a private well containing ~ 1 mg Cr(VI)/L (equivalent to 0.03 mg/kg bw for a 70 kg human) (Dourson 1994). Exacerbation of chromium dermatitis was observed in chromium-sensitive individuals given once orally 0.036-0.04 mg Cr(VI)/kg bw as $K_2Cr_2O_7$ (ATSDR 1998).

Dermal exposure

Daily skin painting of mice with 0.5% aqueous solution of $K_2Cr_2O_7$ (~0.175% Cr(VI)) for 20 days resulted in a local inflammatory reaction, an increase in both skin and liver serotonin levels, an increase of serum acetylcholine in blood, decreased activities of acetylcholinesterase and cholinesterase in plasma and erythrocytes and increased glycoprotein hexose in serum. These changes were seen already early in the study and indicated changes in carbohydrate metabolism (ATSDR 1998; IPCS, 1988).

Immunotoxicity

In rats exposed by inhalation to sodium dichromate at concentrations of 0.025 - 0.2 mg Cr(VI)/m^3, various changes within the immune system were induced both after 20 and 90 days of exposure. Effects included: increased spleen weight, increased SRBC-response, increased serum Ig levels, increased mitogen response of lymphocytes from the spleen and the bronchoalveolar fluid, and changes in the phagocytic activity of pulmonary macrophages. A NOAEL could not be established since effects were also noted at the lowest dose level (ATSDR 1998).
Splenocytes prepared from rats given in their drinking water for 3 weeks 16 mg Cr(VI)/kg bw (as K_2CrO_4) showed an elevated proliferative response of T- and B-lymphocytes to mitogens indicating chromium-induced sensitization (ATSDR 1998).
For immunotoxic effects following dermal exposure see the preceeding paragraph on skin sensitization.

Carcinogenicity

IARC (1990) placed Cr(VI) in group I: carcinogenic to humans.
Animal studies with exposure by inhalation showed that some Cr(VI) compounds induced lung tumours (sodium dichromate in rats, calcium chromate in rats, chromium trioxide in mice) whereas other Cr(VI) compounds failed to demonstrate a carcinogenic effect. Almost all inhalation studies in animals showed deficiencies (ATSDR 1993, Cross et al. 1997, IARC 1990, IPCS 1988). Based on these animal data DECOS (1998) concluded that there is evidence to suggest a potency difference between Cr(VI) compounds, probably related to solubility and bioavailability.
Clear evidence for carcinogenicity of slightly soluble and poorly soluble Cr(VI) compounds in humans after exposure by inhalation was shown in epidemiological studies. Circumstantial evidence was observed for the carcinogenicity of soluble Cr(VI) compounds in epidemiological studies (DECOS 1998). DECOS (1998) considered all Cr(VI) compounds as genotoxic carcinogens at exposure by inhalation.
The available data on the occurrence of cancer after oral exposure to Cr(VI) are very limited. Some studies in workers indicated an increased incidence of cancer also in the stomach and urinary tract as well as increased incidences of cancer in other tissues (bone cancer, leukemia a.o.) (Costa 1997).
One limited chronic study in mice exposed orally to Cr(VI) is available. The animals received 9 mg Cr(VI)/kg bw/day (as potassium chromate) via the drinking water for three generations (880 days). Except for a non-significantly increased incidence of forestomach tumors (2/66 f carcinoma, no carcinoma in controls; 1/35 m and 10/66 f papillomas, in controls 3/47 m and 2/79 f) no indications for carcinogenesis were found (ATSDR 1998).
Carcinogenicity studies involving dermal exposure are not available.

Mutagenicity

Cr(VI) compounds were positive in several genotoxicity assays in non-mammalian systems and in *in vitro* and *in vivo* mammalian systems, detecting gene-mutations, chromosomal aberrations, DNA damage, sister chromatic exchanges, aneuploidy, cell transformations and dominant lethal mutations. (CEPA 1993, Cross et al. 1997). Also DECOS (1998) concluded that Cr(VI) compounds are genotoxic.

Reproduction and fertility

Little information is available on the reproductive or developmental toxicity of Cr(VI) compounds in experimental animals exposed by inhalation or by the oral route. Toxicokinetic studies in animals have shown chromium to cross the placenta into embryonic tissues in pregnant females, and in males to be distributed to the testis.
A 3-generation drinking study with mice (the only dose tested ± 9 mg Cr(VI)/kg bw/day) showed a slight effect on growth and survival but no data on other parameters were reported. In rats exposed by inhalation to 0.2 mg Cr(VI)/m^3 (as $Na_2Cr_2O_7$) lifetime for three generations (130 days per generation)

no effects on reproduction parameters were observed. However, comparisons between successive generations disclosed an increase of the immunosuppression, hyperplasia of especially the lungs and changes in haematological variables (ATSDR 1998, DECOS 1997). In various inhalation studies in rats (0.1-0.2 mg Cr(VI)/m^3; 28 days - 18 months) no changes in weights or histopathological lesions of reproductive organs were seen (ATSDR 1998, CEPA 1993). A NOAEL could not be established.
Cr(VI) compounds administered orally, are reproductive toxicants in mice and rats. Male mice given 15.2 mg Cr(VI)/kg bw as $K_2Cr_2O_7$ in their diet for 7 weeks, showed reduced sperm counts and degeneration of the outer layer of seminiferous tubules; at 28 mg/kg bw morphologically altered sperm was observed. Female mice given ≥46 mg Cr(VI)/kg bw (as $K_2Cr_2O_7$) via the drinking water showed increased preimplantation and post implantation loss, and decreased litter size. Also pregestational treatment of female mice with $K_2Cr_2O_7$ via drinking water (52 mg Cr(VI)/kg bw) resulted in preimplantation loss: increased resorptions were observed at doses ≥78 mg/kg bw In male rats at doses ≥20 mg Cr(VI)/kg bw as $Na_2Cr_2O_7$ given by gavage for 90 days, reduction in testicular weight, decrease in testicular testosterone, Leydig cells and decreases in pachytene spermatocytes and stage-7 spermatids were observed (ATSDR 1998). In contrast to the effects reported above, no changes in reproductive parameters were observed in a multigeneration-continuous breeding study in mice exposed to Cr(VI) doses ranging from 6.8-36.7 mg/kg bw. Also in mice given 1.05-48 mg Cr(VI)/kg bw, and rats given 0.35-9.8 mg/kg bw in their feed as $K_2Cr_2O_7$ for 9 weeks, no adverse effects on the reproductive system of males and females were observed (ATSDR 1998). A NOAEL could not be established.
Among pregnant woman inhalatory exposed to Cr(VI) compounds, limited Russian studies reported an increased incidence of complications during pregnancy and childbirth. However, since the reliability of these studies could not be verified, no conclusions can be drawn. In a study among 2520 women whose spouses worked in the chromium stainless steel welding industry, rate of spontaneous abortions was not different from non-exposed populations (ATSDR 1998). A cross-sectional study on welders demonstrated that workers with urinary Cr concentrations between 0.08 and 2.18 µg per g creatinine did not show changes in quality of semen or sexual hormones, follicle stimulating hormone and luteinizing hormone, although after adjustments of confounding factors a slight decrease of testosterone levels in serum was found (DECOS 1997).
Regarding reproductive toxic affects following dermal exposure, no data in animals or humans are available.

Developmental toxicity

In rats exposed lifetime for three generations to 0.2 mg Cr(VI)/m^3 (as $Na_2Cr_2O_7$) (130 days per generation) no developmental or embryotoxic effects were observed. However, severe developmental effects in the absence of maternal toxicity were observed in mice at maternal oral doses ≥57 mg Cr(VI)/kg bw as $K_2Cr_2O_7$, including decreased crown-rump length, decreased fetal weight, increased resorptions, increased post-implantation loss, and increased incidence of gross abnormalities (ATSDR 1998). In mice exposed via their drinking water to 52 mg Cr(VI)/kg bw (as $K_2Cr_2O_7$) pregestationally or during organogenesis increases in resorptions, post-implantation loss, reduction in ossification and decreased fetal weights were seen (ATSDR 1998). A NOAEL could not be established. Regarding humans, no data are available.

1.5.3. EVALUATION

It has been proposed by some investigators (De Flora et al. 1997, Jones 1990) that there may be a threshold for the carcinogenicity of hexavalent chromium, based on the hypothesis that the administered dose must exceed the extracellular capacity to reduce Cr (VI) to Cr(III). After oral administration Cr(VI) would be reduced to Cr(III) in gastrointestinal tract, blood and liver and after inhalation a reducing effect would be operative in epithelial lining fluid, pulmonary macrophages and parenchyma cells resulting in a decreased bioavailability of Cr(VI). It is indicated that a greater reducing capacity is present in the digestive tract than in the respiratory tract (De Flora et al. 1997). However, quantitative data on the reducing capacity via the different exposure routes and on the reducing capacity in the different tissues are lacking. In addition there is general agreement that Cr(VI) compounds possess

genotoxic properties. Therefore the application of a threshold concept for genotoxicity/carcinogenicity of Cr(VI) compounds does not seem justified for any exposure route.
For the inhalation route the non-threshold concept was applied using the results of epidemiological studies. An extra cancer case of 1 per 10^6 lifetime exposed persons at exposure to 0.025 ng Cr(VI)/m^3 was calculated based on the lifetime risk of 4 x 10^{-2} at exposure to 1 µg/m^3 derived from studies in workers (Slooff et al. 1990, WHO 1994). This means that lifetime exposure by inhalation to 2.5 ng Cr(VI)/m^3 will result in 1 extra cancer case per 10^4 persons.
In Vermeire et al. (1991) an extra cancer case per 10^4 persons lifetime exposed via the oral route to Cr(VI) was calculated by means of route to route extrapolation from the inhalatory value. Given the differences in kinetics, the differences in reducing capacity of Cr(VI) to Cr(III) between the oral (and also the dermal) and the inhalation route and because the fact that the inhalatory value was based on lung tumour incidences, it is now considered not appropriate to apply route to route extrapolation.
Appropriate long-term oral or dermal studies in animals as well as epidemiological studies in man are lacking. So there are no data available to which the non-threshold concept for derivation of an extra cancer risk of 1 per 10^4 lifetime exposed persons via the oral or the dermal route can be applied.
In view of the absence of appropriate chronic data and given the indication for a greater reducing capacity of Cr (VI) to Cr (III) after oral exposure than after inhalatory exposure, for the time being a provisional oral limit value (TDI) is derived based on non-carcinogenic effects, using the threshold concept. All available long-term oral studies in animals as well as man showed deficiencies, but as yet the one-year drinking water study in rats by MacKenzie et al. (1958 as cited in IRIS 1996) seemed the most appropriate study to derive a provisional TDI (also following EPA, see IRIS 1996). The NOAEL in this study was 2.4 mg/kg bw. Using an uncertainty factor of 500 (10 for interindividual and 10 for interspecies variability, additional factor 5 to compensate for the less-than-lifetime exposure) a provisional TDI of 5 µg/kg bw is calculated. This follows the USEPA approach who also arrived at a RfD of 5 µg/kg bw/day based on these data (IRIS 1996); they expressed the level of confidence in this RfD as *'low'* [3]).
Also for the dermal exposure route appropriate chronic studies are lacking. Concerning the non-carcinogenic effects after dermal exposure, the induction of allergic contact dermatis (ACD) is the most sensitive effect. Some authors concluded that elicitation of ACD was dependent on Cr(VI) concentration in the test-patch and a 10% threshold value (level at which 10% of Cr(VI) sensitive individuals showed a sensitization reaction) of 0.001% Cr(VI) (10 mg/L) was derived for potassium chromate.
In other studies threshold values for the induction of ACD were expressed as amount of Cr(VI) per skin surface area. In a patch testing study, the concentration of potassium dichromate producing an allergic skin response in 10% of a group of Cr(VI) sensitized volunteers was calculated to be 0.089 µg Cr(VI)/cm^2. One investigator evaluated eight published patch tests studies with K_2CrO_4 in order to establish a threshold dose of Cr(VI) to which no more than 10% of the subpopulation sensitized to chromium would respond, and that would protect at least 99.84% of the general population. A weighted mean 10% threshold of approximately 150 ppm K_2CrO_4, equivalent to 54 ppm Cr(VI), was identified from the eight studies.

1.5.4. EVALUATIONS BY OTHER ORGANISATIONS

Allergic contact dermatitis

For allergic reactions after skin contact, a 10% threshold value (i.e., the level at which 10% of sensitive individuals show a sensitisation response) of 10 mg Cr(VI)/L (in solution) is proposed. Another investigator preferred to use the amount of applied substance per unit of skin area and proposed a value of 0.089 µg Cr(VI)/cm^2 (ATSDR 1998). Based on eight published studies Paustenbach et al., (1992) derived a mean 10% threshold value of 54 ppm Cr(VI).

[3]) USEPA uses a classification of three confidence levels: *low*, *medium*, and *high*.

Toxicity following inhalatory exposure

ATSDR (1998) derived an MRL of 0.0005 mg/m^3 for intermediate exposures to particulate Cr(VI) compounds from a minimal LOAEL of 0.025 mg Cr/m^3 in rats after conversion to a human equivalent dose and applying an uncertainty factor of 90. The minimal LOAEL of 0.025 mg Cr/m^3 was based on lower respiratory effects (increased number of bronchoalveolar lavage macrophages in telophase) in rats exposed to particulate aerosols of $Na_2Cr_2O_7$ for 22 hrs/day for 28 or 90 days.
An MRL of 0.0001 mg Cr(VI)/m^3 was derived for both intermediate (15-364 days) and chronic exposures (≥ 365 days) as chromic acid (chromium trioxide mist) and other dissolved hexavalent chromium aerosols and mists based on a NOAEL of 0.001 mg Cr(VI)/m^3 for upper respiratory effects in humans occupationally exposed to Cr(VI) applying un uncertainty factor of 10 (ATSDR 1998).

Toxicity following oral exposure

USEPA (IRIS 1996) used a 1-year drinking study in rats (dated 1958) to calculate an oral reference dose (RfD). The NOAEL in this study was 2.4 mg Cr(VI)/kg/day. Using an uncertainty factor of 500 (10 for interindividual and 10 for interspecies variability; additional factor 5 to compensate for the less-than-lifetime exposure) a RfD of 5 µg Cr(VI)/kg/day was calculated. Level of confidence in RfD was low.

Cancer risk

Based on various epidemiological studies on occupationally exposed workers, inhalatory life time unit risks (UR) (i.e the risk for lung cancer at a life-long exposure to 1 µg/m^3) were calculated. The WHO (1987) reported several URs based on different epidemiological studies. From a study on two cohorts of chromium production workers, URs of 1.5×10^{-2} and 7.2×10^{-3} were calculated. A study on ferrochrome workers in Norway revealed an UR of 4.3×10^{-2} whereas a high UR of 1.3×10^{-1} was obtained from a study on a small working population in Norway (WHO 1987). The EPA (IRIS 1996) determined a UR of 1.2×10^{-2}. A life-time risk of 1×10^{-6} for lung cancer was associated with a life-time exposition to 0.025 ng Cr(VI)/m^3 as proposed in the RIVM criteria-document for chromium which was based on a mean UR of 4×10^{-2} as calculated by the WHO (1987). The type of risk assessment performed by the RIVM and the obtained value was supported by the Health Council of the Netherlands (1991). In a recent update, the WHO (1994) maintained their mean UR value of 4×10^{-2} as proposed in 1987.

Occupational standard in The Netherlands

In 1998 the Dutch Expert Committee on Occupational Standards (DECOS 1998) evaluated chromium and its inorganic compounds. All Cr(VI)-compounds were considered to be mutagenic and carcinogenic. DECOS calculated an additional cancer mortality risk of 4×10^{-3} after 40 years of occupational exposure to 2 µg Cr(VI)/m^3 as inhalable dust and an additional cancer mortality risk of 4×10^{-5} after 40 years of occupational exposure to 0.02 µg Cr(VI)/m^3 as inhalable dust.

Soil quality criteria

CCME (1997) classified Cr(VI) compounds as "carcinogenic to humans" based on documented carcinogenicity in human populations exposed by inhalation in occupational environments and furthermore the Government of Canada could not identify any experimental animal study of chronic duration considered adequate as a basis to assess carcinogenicity or to determine a N(L)OAEL for non-neoplastic endpoints after administrating via ingestion or inhalation. CCME concludes that there is no basis for the derivation of soil quality guidelines for Cr(VI) with respect to human health.
Felter and Dourson (1997) reported that a soil concentration of 400 mg Cr(VI)/kg for children and 3500 mg/kg for adults was supposed to protect against adverse effects after oral exposure (non-cancer effects) and that soil concentrations ranging from 130 -270 mg/kg were supposed to protect against cancer (risk one in a million) after exposure by inhalation (using extensive calculation methods). Soil

concentrations of 15, 350-500 mg/kg, 450 mg/kg and 10000-54000 mg/kg were supposed to protect against allergic contact dermatitis (ACD) from dermal exposure. The wide variation is due primarily to assumptions of bioavailability (i.e., the degree to which Cr (VI) is extracted from soil and from which it may be solubilized on human skin) and the appropriate measure of exposure in patch-test studies (concentrations in mg/L or mg/cm^2 skin). Clearly this range was indicative of a significant degree of uncertainty in the risk assessment for ACD (Felter and Dourson 1997).

1.5.5. BACKGROUND EXPOSURE

According to Slooff et al. (1990) total chromiun in the outdoor air in the Netherlands ranges from 2 - 5 ng/m^3. The concentration of Cr(VI) in outdoor air was estimated to be 0.01-30% of total chromium (~2×10^{-4} - 1.5 ng/m^3).

1.5.6. CONCLUSION

Compound	TDI	TCA	CR_{oral}	CR_{inhal}	Background exposure
Chromium VI	5 *)	-	-	2.5×10^{-3}	5.7×10^{-6} - 0.43×10^{-3}

TDI: tolerable daily intake (oral exposure); µg/kg bw/day
TCA: tolerable concentration in air (inhalation exposure); µg/m^3
CR_{oral}: $1:10^{-4}$ excess lifetime cancer risk, oral exposure; µg/kg bw/day
CR_{inhal}: $1:10^{-4}$ excess lifetime cancer risk, inhalation exposure; µg/m^3
Background exposure; µg/kg bw/day
*) Provisional MPR, non-carcinogenic effects

Oral excess 10^{-4} lifetime tumour risk: cannot be established
Dermal excess 10^{-4} lifetime cancer risk: cannot be established
Skin notation: Cr(VI) induces allergic contact dermatitis (ACD)
10% threshold value for ACD [4]): 0.001% Cr(VI) (10 mg/L) or 0.089 µg/cm^2

Additional data:
Absorption:
- oral: 1.1-14.5% (average 5.7% after a single dose; average ranged from 1.7-3.5% after repeated doses) in humans
- inhalation: up to 30% in humans
- dermal: up to 4% in guinea-pigs
in humans 0.03 ng/cm^2/h to 10 µg/cm^2/h dependent on solvent, exposure condition and the concentration of Cr (VI). USEPA recommends the use of a dermal absorption estimate of 1 µg/cm^2/h for risk assessment purposes.

1.5.7. REFERENCES

ATSDR (Agency for Toxic Substances and Disease Registry) (1998):
Toxicological Profile for Chromium (Update).
Draft for Public Comment; U.S. Department of Health & Human Services.

CCME (Canadian Council of Ministers of the Environment) (1997):
Recommended Canadian Soil Quality Guidelines; dated March 1997.

CEPA (Canadian Environmental Protectian Act) (1994):
Priority Substances List Assessment Report: Chromium and its Compounds.
Government of Canada.

[4]) A level to which no more than 10% of the subpopulation sensitized to chromium would respond, and that would protect at least 99.84% of the general population.

Costa M (1997):
Toxicity and Carcinogencity of Cr(VI) in Animal Models and Humans.
Crit. Rev. Toxicol. 27: 431-442.

Cross HH et al. (1997):
Criteria document for hexavalent chromium.
Commissioned by International Chromium Development Association (ICDA), April 1997.

DECOS (Dutch Expert Committee on Occupational Standards) (1998):
Chromium and its inorganic compounds. Health-based recommended occupational exposure limit (revised version).
Report of DECOS, Health Council of the Netherlands, DECOS report nr. 1998/01(R)WGD, Rijswijk, September 24, 1998.

DeFlora S et al. (1997):
Estimates of the chromium (VI) reducing capacity in human body compartments as a mechanism for attenuating its potential toxicity and carcinogencity.
Carcinogenesis 18: 531-537.

Dourson ML (1994):
The chromium reference dose. In: Risk Assessment of essential elements (eds. W Mertz, CO Abernathy, SS Olin), ILSI Press, Washington, USA; pp 207-212.

SP Felter, ML Dourson (1997):
Hexavalent Chromium-Contaminated Soils: Options for Risk Assessment and Risk Management.
Regulat. Toxicol. Pharmacol. 25: 43-59.

Health Council of The Netherlands (1991):
Chromium: assessment of an integrated criteria document.
Publication no. 1993/03; The Hague, The Netherlands.

IARC (International Agency for Research on Cancer) (1990):
Chromium, Nickel, and Welding.
IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 49; IARC, Lyon, France.

IPCS (International Programme on Chemical Safety) (1998):
Chromium.
Environmental Health Criteria 61, IPCS/WHO, Geneva, Switzerland.

IRIS (Integrated Risk Information System) (1996):
Chromium (VI).
Update code: 9612.

Jones RE (1990)
Hexavalent chrome: threshold concept for carcinogenicity.
Biomed. Environm. Sci. 3: 20-34.

Paustenbach DJ et al. (1992):
Review of the allergic contact dermatiitis hazard posed by chromium-contaminated soil: identifying a "safe" concentration.
J. Toxicol. Environm. Health 37: 177-207.

Van Raay MTM et al. (1998): Advisory report:
Toxicological evaluation of CCA-products and their components chromium trioxide, copper oxide, and arsenic pentoxide.
RIVM-CSR advisory report no. 05318A01, April 8, 1998.

Slooff W (1990):
Integrated criteria document chromium.
RIVM-report no. 710401002; including appendix to the report: JA Janus, EI Krajnc (1990): Integrated criteria document chromium: effects.

Vermeire TG, Apeldoorn ME van, Fouw JC de & Janssen PJCM (1991):
Voorstel voor de humaan-toxicologische onderbouwing van C-toetsingswaarden.
National Institute of Public Health and the Environment, RIVM-report no. 725201005, February 1991; Bilthoven, The Netherlands.

WHO (World Health Organization) (1987):
Air quality guidelines for Europe
WHO Regional Publications, European Series, no. 23.
WHO Regional Office for Europe; Copenhagen, Denmark.

WHO (World Health Organization) (1994):
Updating and revision of the air quality guidelines for Europe.
Report of the WHO Working Group on Inorganic Air Pollutants, publication nr. EUR/ICP/EHAZ 94 05/MT04.
WHO Regional Office for Europe; Copenhagen, Denmark.

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1.6. COBALT

1.6.1. INTRODUCTION

Cobalt was evaluated within the scope of this project by Vermeire et al. in 1991. In this report a TDI was presented of 1.4 µg/kg bw/day; a TCA was not given. The TDI was based on a migration limit of 100 µg cobalt per day for humans from packaging materials. Furthermore it was stated that this TDI is not in conflict with a TDI based on a LOAEL of 1 mg/kg bw/day in a subacute study with rats, and an uncertainty factor of 1000.
For the update of this TDI additional literature (published since 1991) was reviewed. These included evaluations of IARC (1991), ATSDR (1992), and a study of the NTP (1998).
Cobalt is a metal and occurs in nature usually in minerals associated with other metals, such as copper, nickel, manganese, and arsenic. It background value in soil is in the order of 1 to 40 mg/kg, with an average of 25 mg/kg (IARC, 1991; ATSDR, 1992). Many complex cobalt salts with di- or trivalent forms of Co, and numerous metal alloys with cobalt are known. Its major commercial use is in alloys, less relevant uses are in paint and in enamel, and as a catalyst in the chemical industry. Besides, cobalt is used in feed and nutritional additives (such as vitamin B12).
Disposal of mining, industrial and household waste, and sewage sludge can be expected to be the major sources of soil contamination with cobalt (IARC 1991, ATSDR 1992). Only minor concentrations are to be expected in ambient air and surface waters.
It is known that plants demonstrate uptake of metals from soil. Uptake of cobalt is species dependent, and it is high in most leafy vegetables (IARC 1991). According to the ATSDR (1992) the transfer coefficients of cobalt from soil to plants are 0.01 to 0.3, but the transfer increases substantially in acidic soils (pH<5). Thus, vegetables grown on an acid soil may become serious sources of human exposure to cobalt.

1.6.2. TOXICOLOGY

Toxicokinetics

Absorption
According to ATSDR (1992), gastrointestinal absorption of cobalt in humans varies considerably (from 18 to 97%). Absorption appears to depend on iron concentrations; in experimental animals it appeared also to depend on dose and nutritional status.
Data of humans who inhaled cobalt oxide showed retention in the lungs in the order of 50% of the initial dose after 180 days. Small differences could be noticed for particle sizes.
Data on dermal absorption of cobalt compounds are not available. However, since sensitive humans demonstrate allergic reactions after dermal application, dermal absorption appears to occur.
Distribution
Cobalt is found in most body tissues. Increased levels were found in the lungs of copper smelters and metal workers, due to inhalation exposure. After oral intake by experimental animals cobalt was primarily retained in the liver and kidneys (ATSDR 1992).
Metabolism
Cobalt is a component of vitamin B12, and will be retained within the body for many years (NTP 1998).
Excretion
In humans cobalt is eliminated via faecal and urinary excretion. The percentage of both routes varies considerably, and depends on exposure route, dose and type of cobalt, and nutritional status (ATSDR 1992).
Biomarkers
Blood levels of cobalt from occupational exposure of humans demonstrate a positive correlation with cobalt in air and cobalt in urine. According to a study of Stokinger and Wagner in 1958 (cited in ATSDR, 1992), indications of cobalt exposure may also be found in serum protein levels (i.e., alpha globulin and associated serum neuraminic acid). Finally, IgE and IgA serum antibodies may be monitored in relation to sensitisation by cobalt.

Toxicity

Essentiality
Cobalt is an essential nutrient for humans. Cobalt can be found in vitamin B12. According to Elinder and Friberg (cited in Vermeire et al. 1991) is the requirement for humans 0.012 to 0.02 µg of cobalt per day. Doses up to 1 mg/kg bw of cobalt have previously been used as a treatment for anaemia in pregnant women, because it causes red blood cells to be produced (ATSDR 1992).
Acute toxicity
Poisoning of humans with cobalt is known from oral intake of cobalt in beer in the 1960s. The exposed developed a cardiomyopathy; 18% of the patients died within a few days. It should be noted, however, that the cardiac effect might be enhanced by a simultaneous exposure of cobalt with alcohol.
In experimental animals cobalt compounds were shown not to be very toxic after oral intake. Reported LOAELs for acute oral exposure are between 90 and 320 mg of cobalt/kg bw/day.
Genotoxicity and carcinogenicity
Based on the available literature it can be concluded that most bacterial mutagenicity *in vitro* tests for cobalt and its compounds are negative. Some positive results were reported for mammalian cell DNA damage studies. It was concluded in NTP (1998) that the mutagenic response is weak and can only seen at high concentrations and after a long exposure period.
In a two-year inhalation study with rats and mice exposed to cobalt sulphate heptahydrate, tumours were observed in lungs and nose with a LOAEL of 1 mg/m^3. The NOAEL in this study was 0.3 mg/m^3 cobalt sulphate heptahydrate at an exposure of 6 hours per day, 5 days per week NTP (1998). For continuous inhalation this is equivalent to 0.01 mg cobalt per m^3.
Subchronic and chronic toxicity
Chronic oral studies of cobalt or cobalt compounds are not available, neither for humans, nor for experimental animals. For subchronic exposure of humans (up to 8 months) the lowest LOAEL reported was 0.04 mg/kg bw/day for cardiomyopathy and systemic effects in other organ systems. In this study the significance of combined exposure to cobalt and alcohol can however not be excluded (ATSDR 1992).
A few inhalation studies of occupational exposure of humans are summarised by ATSDR (1992); LOAECs for cobalt dust of 0.05 mg/m^3 for interstitial lung disease and of 0.007 mg/m^3 for asthma were reported. The latter value was also the LOAEC for sensitisation. For laboratory animals there are only semichronic studies reported. In these studies respiratory effects were observed in rat and mice by 0.11 mg/m^3.
It has been demonstrated that about 5% of the human population show allergic reactions to cobalt in a human patch test. Most often there is a simultaneous allergy to cobalt and nickel. This might be significant in persistent hand eczema. The process starts through skin contact with the metal in a soluble state. A study with humans resulted in positive result of the patch test for 2.3 mg cobalt per L petrolatum or distilled water after pre-treatment of the skin with surfactants. None of the volunteers reacted to 0.23 mg/L cobalt in petrolatum or distilled water. Sensitisation was also found in guinea pigs with 2.3 mg cobalt/L (ECETOC 1992).
Mechanism of action
Exposure to cobalt results in a wide spectrum of toxic effects in mammals. Cobalt can replace and mimic Mg^{2+} and Ca^{2+}, and may influence many biochemical reactions. For example, it may block calcium channels, it alters the activity of enzymes, binds to sulfhydryl groups, and might stop the oxidative metabolism (NTP 1998).

1.6.3. EVALUATION

Based on the weight of evidence it is concluded that cobalt is not a genotoxic agent. Consequently the TDI can be derived from a NOAEL.
In the previous evaluation of Vermeire et al. (1991) a TDI of 1.4 µg/kg bw/day was derived based on a migration limit for packaging materials. The lowest LOAEL for humans reported is 0.04 mg/kg bw/day, for cardiomyopathy after intermediate oral exposure. This effect was noticed in a small population of humans, for with the adverse effects due to intake of alcohol can not be excluded. So it

can be expected that the lowest effect level will be higher for the general population, and an uncertainty factor for intra-human variation of 3 is to be used. An additional factor of 10 is needed for extrapolation to a NOAEL. Consequently the TDI of 1.4 µg/kg bw/day can be maintained.
For inhalation of cobalt a LOAEC for asthma and sensitisation in humans of 7 µg/m^3 cobalt is reported. For such effects however it is not possible to derive a NOAEL from the available data. The LOAEL for interstitial lung disease in humans was 0.05 mg/m^3. From this value a TCA of 0.5 µg/m^3 of cobalt can be derived using an uncertainty factor of 10 for the extrapolation from a LOAEL and a factor of 10 for intrahuman variability.

1.6.4. EVALUATIONS BY OTHER ORGANISATIONS

Cobalt has not been evaluated by US-EPA (IRIS 1999).
ATSDR presented an intermediate inhalation MRL of 0.03 µg/m^3 based on a LOAEL of 0.11 mg/m^3 in rats with an uncertainty factor of 1000 (which includes adjustment for continuous exposure). A chronic inhalation MRL was not derived because it was concluded that the lowest effect is sensitisation and ATSDR does not derive an MRL on effects such as sensitisation. Oral and dermal MRLs were not derived due to lack of appropriate data (ATSDR 1992).
WHO did not include a Drinking Water Quality Guideline for cobalt (WHO 1996).
In the classification of IARC (1991) cobalt and cobalt compounds are classified as *possibly carcinogenic to humans* (group 2B).

1.6.5. BACKGROUND EXPOSURE

The major source of background exposure of the general population is food. Most cobalt is ingested in an inorganic form from consumption of vegetables. The estimated total daily intake from food varies substantially between countries. According to Vermeire et al. (1991) the intake in The Netherlands is estimated to be 0.7 µg/kg bw/day. Estimates from Europe and the US and Canada range from 2 to 100 µg/day. The differences might be caused by large variations in concentrations of cobalt in drinking water (IARC 1991). Concentrations of cobalt in drinking water in The Netherlands can be expected to be very low. Estimates for countries with comparable dietary habits as The Netherlands and low concentrations in drinking water indicate a cobalt intake in the order of magnitude of 20 µg/day. The background exposure would then be 0.3 µg/kg bw/day.

1.6.6. CONCLUSION

Compound	TDI	TCA	Background exposure
Cobalt	1.4	0.5	0.3

TDI: tolerable daily intake (oral exposure); µg/kg bw/day
TCA: tolerable concentration in air (inhalation exposure); µg/m^3
Background exposure; µg/kg bw/day

1.6.7. REFERENCES

ATSDR (1992):
Toxicological profile for cobalt.
ATSDR report no. TP-91/10, Agency for Toxic Substances and Disease Registry, US Public Health Service, Atlanta (Georgia), USA.

ECETOC (1992):
Nickel, cobalt and chromium in consumer products: allergic contact dermatitis.
ECETOC technical report no. 45.
European Chemical Industry Ecology and Toxicology Centre, Brussels, Belgium.

IARC (1991):
Monographs on the evaluation of carcinogenic risks to humans. Volume 52: chlorinated drinking water; chlorinating by-products; some other halogenated compounds; cobalt and cobalt compounds.
IARC, Lyon, France

IRIS (1999):
US-EPA database.
CD-ROM, Silverplatter, London, UK.

NTP (1998):
Toxicology and carcinogenesis studies of cobalt sulphate heptahydrate in F344/N rats and B6C3F1 mice (inhalation studies).
US Dept. of Health & Human Services, NIH Publication no. 98-3961.

Vermeire TG, Apeldoorn ME van, Fouw JC de & Janssen PJCM (1991):
Voorstel voor de humaan-toxicologische onderbouwing van C-toetsingswaarden.
National Institute of Public Health and the Environment, RIVM-report no. 725201005, February 1991; Bilthoven, The Netherlands.

WHO (1996):
Guidelines for drinking-water quality, 2nd ed. Volume 2, Health criteria and other supporting information.
WHO, Geneva, Switzerland.

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1.7. COPPER

1.7.1. INTRODUCTION

Copper was evaluated within the scope of this project by Vermeire et al. in 1991, who derived a TDI of 140 µg/kg bw/day. It was noted that a NOAEL of 8 mg/kg bw/day in experimental animals and an extrapolation factor of 100 to be used would result in a TDI of 80 µg/kg bw/day. This value is only slightly higher than the daily demand according to Vermeire et al. (1991) of 20 to 50 µg/kg bw/day of copper, being an essential element. It was therefore concluded that the TDI should be equal to the maximal daily intake of the population of 140 µg/kg bw/day.
For the update literature published since 1991 was reviewed. Relevant documents consulted are the reports of the ATSDR (1990) and of the WHO (IPCS 1998, WHO 1996, WHO 1998).
Copper occurs naturally in many minerals, and can be found as metal. Its natural abundance in the earth′s crust is 50 to 60 mg/kg on average. Background levels in soils and sediments can be as high as 5000 mg/kg (IPCS 1998).
Copper and copper alloys are mainly used in electrical systems. Their use in buildings and constructions are second in importance. Copper sulphate and other copper salts are used in agriculture as fungicides and algaecides, and as feed additives (ATSDR 1990, WHO 1996). Soil contamination will therefore occur from disposal of industrial and household waste, sludge of wastewater, and from direct use of pesticides on soils.

1.7.2. TOXICOLOGY

Toxicokinetics

Absorption
Copper is well absorbed after oral intake. Being an essential element, however, the rate of intestinal absorption of copper in humans depends on numerous physiological and dietary factors. Data of reported absorption following oral intake range from 15 to 97 %.
Pulmonary absorption of copper through inhalation of dust, fumes, and smoke does occur, but the rate and extend of the absorption in humans is not known.
Copper can pass dermal barriers when applied in a vehicle like salicylic acid or phenylbutazone, but the rate and extend of dermal absorption in humans is also not known (ATSDR 1990, IPCS 1998).
Distribution
The liver is the major organ for copper distribution in humans. Most copper is stored complexed with metallothionein. Via the blood copper is transported to various tissues, especially muscle and brain. This transport system is well regulated as copper is an essential element.
Metabolism
Metabolism of copper consists mainly of its transfer to and from organic ligands, especially binding proteins.
Excretion
Bile is the major pathway for excretion of copper. In healthy humans about 70% copper is excreted with the faeces (ATSDR 1990).
Genetic disorders are known to be associated with defective copper transport and accumulation. These disorders are characterised by a decreased biliary copper excretion (IPCS 1998).
Biomarkers
Blood and serum levels relate to recent copper exposure; increased levels were reported after exposure to copper dust and oral ingestion of copper. Also increased hair copper levels have been reported.
Specific effects are known for humans with copper deficiency: poor growth, anaemia and effects on the central nervous system. These effects are very different from the effects observed in cases of copper poisoning.

Toxicity

Essentiality
Copper is an essential element. According to the WHO (1996) a daily copper intake of 1 to 5 mg is needed for adults. This is equal to a daily requirement of 20 to 80 µg/kg bw/day.
Acute toxicity
Acute poisoning resulting in deaths has been reported for cases of suicide with copper sulphate. Estimations of doses in these cases were 6 to 637 mg of copper per kg body weight. In the exposed humans gastrointestinal, hepatic, and renal effects have been observed (ATSDR 1990, WHO 1996).
Genotoxicity and carcinogenicity
There are very few studies on the genotoxicity of copper or copper compounds. Most studies in *in vitro* test-systems did not demonstrate mutagenic activity. In mice *in vivo* a dose related increase of chromosome aberrations was reported, but in other test systems no evidence of genotoxic activity was found (IPCS 1998).
No studies regarding carcinogenic effects in humans after oral, dermal, or inhalation exposure to copper were reported. In a study in rats and mice exposed to copper in the diet cancer was not observed (ATSDR 1990). From a review of epidemiological studies, IPCS (1998) concluded that copper does not seems to play a role in the development of cancer in humans.
Subchronic and chronic toxicity
There are no data regarding the oral toxicity of copper or copper compounds in humans. For experimental animals the database is limited, and most of the studies relate to semichronic exposure. A LOAEL of 4.2 mg Cu/ per kg bw per day was reported for decreased body weight of mice after chronic oral exposure to copper gluconate (ATSDR 1990).
There is very little data on the inhalation of copper. Adverse effects were observed in humans exposed to levels of 111 mg/m^3 for a few years. In rabbits a NOAEC of respiratory and immunological effects of 0.6 mg copper chloride per m^3 was reported for an intermediate exposure period (6 weeks, 5 days per week, 6 hours per day).
There are very limited data on dermal exposure to copper. In some human individuals, however, allergic contact dermatitis has been reported following a patch test with copper.
Mechanism of action
The requirement for copper in organs or systems is effectively regulated by homeostatic control mechanisms. Toxicity is likely to occur only when the homeostatic control is overwhelmed or when repair mechanisms are impaired.
Toxicity can occur by structural impairment of metal binding sites, or binding of copper to macromolecules and enzymes. In addition, cellular injury can occur due to production of radicals when copper reacts with peroxide.
Metallothionein is the main binding site for copper. Toxic effects occur if metallothionein appears to become saturated with copper (IPCS 1998). Thus toxic effects can be expected to demonstrate threshold levels.

1.7.3. EVALUATION

There is no convincing evidence for genotoxic properties of copper. The proposed mechanism of toxic action suggests a threshold for toxic effects. Consequently a TDI can be derived from NOAELs.
Deficiency of copper leads to effects that are equally critical for human health as the toxic effects. According to IPCS (1998) risk of deficiency exists for healthy infants receiving less than 100 µg Cu per kg bw per day. However, the LOAEL of 4.2 mg/kg bw/day for chronic oral exposure in mice will result in a tolerable intake of 4 µg/kg bw/day if an uncertainty factor of 1000 is applied with 10 for LOAEL to NOAEL, 10 for the extrapolation of experimental animals to humans, and 10 for human intravariability. Such a TDI is beyond the limit-value for deficiency and can thus not be applied. In the case of copper the conventional extrapolation factors are obviously not appropriate.
It is therefore recommended to maintain the proposal of Vermeire et al. (1991), i.e. a TDI of 140 µg/kg bw/day, which is above the minimum requirements of copper of 20 to 80 µg/kg bw/day. In relation to the LOAEL of 4.2 mg/kg bw/day in experimental animals it leaves a margin of safety of 30.

For a TCA it is proposed to apply the NOAEC of 0.6 mg/m^3 from the subacute study with rabbits, with an extrapolation factor of 100 for intra- en interspecies extrapolation, and a correction factor of 6 (5/7×6/24) for continuous exposure. This results in a TCA of 1 µg/m^3.

1.7.4. EVALUATIONS BY OTHER ORGANISATIONS

The IARC classified copper in group 3 (*not classifiable as to its carcinogenicity in humans*) in 1987.
The US-EPA did not propose a RfD or RfC for copper (IRIS 1999).
The ATSDR did not present a MRL for copper (ATSDR 1990).
The WHO Drinking Water Quality Guideline is 2 mg/L. This value is a provisional proposal that was based on a NOAEL of 5 mg/kg bw/day in dogs with an uncertainty factor of 10, leading to a TDI of 0.5 mg/kg bw/day. In the evaluation process this particular uncertainty factor was selected with regard to the essentiality of copper (WHO 1996, 1998).

1.7.5. BACKGROUND EXPOSURE

The major source of copper exposure for the general population is food. Dietary intakes were presented for different countries in Europe and the USA, based on market basket studies, total diet studies, or duplicate diets. In these studies the intake is 1 to 2 mg/day (1.5 mg/day for The Netherlands). The intake can be higher due to the consumption of drinking water from copper pipings, with concentrations of 40 to 690 µg/L (IPCS 1998). This can lead to an additional intake up to 1 mg/day.
Assuming a daily intake of 2 mg/day, the average background exposure to copper in The Netherlands is 30 µg/kg bw/day.

1.7.6. CONCLUSION

Compound	TDI	TCA	Background exposure
Copper	140	1	30

TDI: tolerable daily intake (oral exposure); µg/kg bw/day
TCA: tolerable concentration in air (inhalation exposure); µg/m^3
Background exposure; µg/kg bw/day

1.7.7. REFERENCES

ATSDR (1990):
Toxicological profile for copper.
ATSDR report no. TP 90-08, Agency for Toxic Substances and Disease Registry, US Public Health Service, Atlanta (Georgia), USA.

IPCS (1998):
Environmental Health Criteria 200 - Copper.
World Health Organization, Geneva, Switzerland.

IRIS (1999):
US-EPA database .
CD-ROM, Silverplatter, London, UK.

Vermeire TG, Apeldoorn ME van, Fouw JC de & Janssen PJCM (1991):
Voorstel voor de humaan-toxicologische onderbouwing van C-toetsingswaarden.
National Institute of Public Health and the Environment, RIVM-report no. 725201005, February 1991; Bilthoven, The Netherlands.

WHO (1996):
Guidelines for drinking-water quality, 2nd ed. Volume 2, Health criteria and other supporting information.
World Health Organization, Geneva, Switzerland.

WHO (1998):
Guidelines for drinking-water quality, 2nd ed., Addendum to Volume 1- Recommendations.
World Health Organization, Geneva, Switzerland.

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1.8. LEAD

1.8.1. INTRODUCTION

Lead is a silvery-grey heavy metal. The generally bivalent lead compounds include well-soluble salts (e.g., lead acetate) as well as practically insoluble ones (e.g., lead oxides). Organic lead compounds include the gasoline additives tetramethyllead and tetraethyllead.
The human-toxicological MPR (maximum permissible risk) for lead was derived in 1991 (Vermeire et al. 1991), and set at 3.6 μg Pb per kg bw per day. This figure is directly derived from the FAO/WHO recommendation of an intake of 25 μg/kg bw Pb per week at most (PTWI: provisional tolerable weekly intake) (FAO/WHO 1987); it is based on children being the most sensitive to lead. In 1991 the background exposure to Pb was estimated to be 1.2 μg/kg bw/day (32-34 μg/day via food and water, 2 μg/day via air for adults and 0.8 μg/day via air for children) (Vermeire et al. 1991).
Relevant route to be considered in cases of soil contamination: oral.

1.8.2. TOXICOLOGY

In recent years the toxicology and epidemiology of lead have been extensively and critically reviewed and evaluated by the FAO/WHO (FAO/WHO 1993), the IPCS (1995), and the Health Council of The Netherlands (Gezondheidsraad 1997). In addition the draft evaluation of lead of the RIVM was consulted (Janus et al. 1997), together with earlier evaluations by the FAO/WHO (FAO/WHO 1972, 1987), the WHO (WHO 1980, 1987), and the IARC (IARC 1987).
Lead (Pb) is absorbed in humans and animals following ingestion or inhalation. Percutaneous absorption is minimal in humans. Up to 50 % of the inhaled Pb compound may be absorbed, while (in adult humans) approximately 10 % of the dietary Pb is absorbed. In infants and young children, however, as much as 50 % of dietary Pb is absorbed.
Blood lead (PbB) levels are used as measure of body burden and absorbed (internal) doses of Pb. The relationship between PbB and the Pb concentration in exposure sources is curvilinear, i.e., at low exposure the absorption is relatively high, while at high exposure the absorption is relatively low. The half-life for Pb in blood and soft tissues is about 28-36 days, but is much longer (approx. 30 years) in the bone compartments. Pb is readily transferred to the foetus during gestation.
An increase of the daily intake of Pb with 1 μg/day results in an increase of PbB concentration of 1.6 and 0.5 μg/L in children and adults, respectively. In children of 4 years old generally the excretion of Pb exceeds its intake if the intake is less than 5 μg/kg bw/day; at an intake of 5 μg/kg bw/day the retention of Pb in the body is about 0.43 μg/kg bw/day, leading to an increase of the child's PbB level with 10-20 μg/L in about 6 months. On the basis of these studies the US-EPA derived a (linear) slope factor of 1.6 μg Pb/L blood per μg Pb intake per day, for a child of 10 kg bw with a median PbB level of 100 μg/L.
In humans, Pb can result in a wide range of biological effects depending upon the level and duration of exposure. Effects at the subcellular level as well as effects on the overall functioning of the organism have been noted, and range from inhibition of enzymes to the production of marked morphological changes and death. Such changes occur over a broad range of doses, the developing human generally being more sensitive than the adult.
At elevated PbB levels the haem synthesis is affected. Increased levels of erythrocyte protoporphyrin and increased urinary excretion of coproporphyrin and δ-aminolaevulinic acid are observed; inhibition of δ-aminolaevulinic acid dehydratase and dihydrobiopterin reductase are already observed at lower levels. These changes results in decreased haemoglobin synthesis, and anaemia has been observed in children at PbB concentrations of 400 μg/L and in adults at concentrations above 800 μg/L.
Pb has shown to be associated with impaired neurobehavioural functioning in children, which has also been found in (adult) workers after long-term Pb exposure. Cross-sectional and prospective studies of populations with PbB levels generally below 250 μg/L indicate decrements in intelligence quotients (IQ). A deficit of on the average 1-3 points (on a scale at which 100 represents the IQ of the average human individual) is seen for an increment of the PbB level of 100 μg/L as assessed at 4 years of age and above; at levels above 250 μg/L the relationship between PbB and IQ may differ. Epidemiological studies do not provide definitive evidence of a threshold.

Animal studies suggest a causal relationship between Pb and nervous system effects, reporting deficits in cognitive functions at PbB levels as low as 110-150 μg/L, which can persist well beyond the termination of Pb exposure. This is in agreement with observations in humans (children and adults) indication that Pb-caused neurological and cognitive damage is often irreversible.
A decrease in human peripheral nerve conduction velocity may occur at PbB levels as low as 300 μg/L. In addition, sensory motor functions may be impaired at PbB levels of about 400 μg/L, and autonomous nervous system functions may be affected at an average PbB level of approximately 350 μg/L.
The effect of Pb on the heart is indirect and occurs via the autonomous nervous system; Pb has no direct effect on the myocardium.
Pb is known to cause proximal renal tubular damage, characterised by generalised aminoaciduria, hypophosphataemia with relative hyperphosphaturia and glycosuria accompanied by nuclear inclusion bodies, mitochondrial changes and cytomegaly of the proximal tubular epithelial cells. Tubular effects are noted after relative short-term exposures and are generally reversible, whereas sclerotic changes and interstitial fibrosis, resulting in decreased kidney function and possible renal failure, require chronic exposure to high Pb levels. Increased risk from nephropathy was noted in workers with a PbB level of over 600 μg/L, but renal effects have recently been seen among the general population when more sensitive indicators of function were measured.
The reproductive effects of Pb in the male are limited to sperm morphology and count. In the female, some adverse pregnancy outcomes have been attributed to Pb. According to WHO recommendations (WHO 1980), PbB levels of women within the reproductive age should not exceed 300 μg/L (WHO biological exposure limit). However, see below for a more recent opinion on the exposure of women in the reproductive age.
Pb does not appear to have deleterious effects on skin, muscle or the immune system.
Both in children and adults levels of exposure sufficient to induce PbB concentrations of 1000 μg/L or higher may result in serious consequences such as brain damage. At this level also one of the classic symptoms of Pb poisoning, i.e., lead colic, can occur.
After careful reviewing and evaluating the vast amount of toxicological and epidemiological literature on Pb, the FAO/WHO JECFA (FAO/WHO 1993) and the IPCS (IPCS 1995) concluded that up to PbB levels of 50 g/L no health damage will occur. In order to protect particularly children against exceeding this level, the FAO/WHO JECFA re-evaluated in 1986 its earlier provisionally tolerable weekly intake (PTWI) of 50 μg/kg bw for adults (which was established in 1972 (FAO/WHO 1972), based on a net absorption of 10 % for Pb from food and drinking water), and established a PTWI of 25 μg/kg bw for children (FAO/WHO 1987). This PTWI refers to Pb intake from all sources and was set to protect particularly infants and children as being the most sensitive to Pb. The aim was to avoid PbB levels in children to increase above 50 μg/L (and thus to prevent a net accumulation of Pb in the body), and was based on a net absorption of dietary Pb of 40 % and a net Pb retention of 30 %. In 1993 the FAO/WHO JECFA re-evaluated these PTWIs and decided to withdraw its 1972 PTWI of 50 μg/kg bw for adults, and to declare the PTWI of 25 μg/kg bw for children valid for all humans, i.e., children and adults (published by the IPCS (IPCS 1995)). This decision was based on the consideration that, although adults are less sensitive to the adverse effects of Pb, the protection of foetuses - which are at least as sensitive as infants to the effects of Pb on the mental development - requires a PTWI for adults (in particular women of child-bearing age) as low as that for children.

1.8.3. EVALUATION

The PTWI of 25 μg/kg as derived by the FAO/WHO JECFA in 1995 (IPCS 1995), which is still valid, has been adopted by the RIVM (Janus et al. 1997). It was also adopted by the Health Council of The Netherlands (Gezondheidsraad 1997).

1.8.4. EVALUATIONS BY OTHER ORGANISATIONS

The IARC concluded to inadequate evidence for the carcinogenicity of Pb and inorganic Pb compounds in humans, but sufficient evidence for carcinogenic potential of specific inorganic Pb com-

pounds in experimental animals (rats). Pb was classified as a group 2B compound (possibly carcinogenic to humans) (IARC 1987).
Regarding occupational health, the WHO (WHO 1980) recommends that PbB levels of workers should not exceed 400 µg/L (WHO biological exposure limit).
Drinking water guidelines recommend 10 µg/L (WHO 1993, European Union 1998).
The WHO recommends in its air quality guideline (WHO 1987) 0.5-1 µg/m^3 as a long-term average (such as annual mean).

1.8.5. BACKGROUND EXPOSURE

The Health Council of The Netherlands estimated in 1997 the background exposure of Pb resulting from intake of food, water and air for children aged 1-4 years to be 2.0 µg/kg bw/day (including the intake of soil and dust particles). For children aged 5 years and older and adults the intake from background exposure was estimated to be 0.64 µg/kg bw/day. These estimations are based on drinking water containing 10 µg Pb per L (Gezondheidsraad 1997).

1.8.6. CONCLUSION

Compound	TDI *)	Background exposure	
		adults	children
Lead and lead compounds (as lead)	3.6	0.6	2.0

TDI: tolerable daily intake (oral exposure); µg/kg bw/day
Background exposure; µg/kg bw/day
*) see remark

Remark:
There are no health-based arguments to change the current PTWI for Pb, i.e., the current FAO/WHO PTWI of 25 µg/kg bw/week for adults and children (IPCS 1995) at which intake a net accumulation of Pb in human organisms is considered highly unlikely. However, for practical reasons, i.e., calculations of the so-called *severe risk concentrations* with the CSOIL model (van den Berg 1995), a tolerable intake per day is needed. For this application the PTWI is divided by 7, resulting in a figure of 3.6 µg/kg bw representing the tolerable intake per day. Hence the human MPR for Pb is maintained at the level of 3.6 µg/kg bw/day.

1.8.7. REFERENCES

Berg R vd (1995):
Blootstelling van de mens aan bodemverontreiniging. Een kwalitatieve en kwantitatieve analyse leidend tot voorstellen voor humaan-toxicologische C-toetsingswaarden (beperkt herziene versie).
RIVM report nr. 725201006, March 1995; Bilthoven.

European Union (1998):
Council Directive 98/83 regarding the quality of water for human consumption.
Council of the European Union, October 1998; Brussels.

Gezondheidsraad (1997):
Lood in drinkwater / Lead in drinking water.
Health Council of The Netherlands, Committee on lead in drinking water, Report no. 1997/07; The Hague.

FAO/WHO (1972):
Evaluation of mercury, lead, cadmium and the food additives amaranth, diethylpyrocarbonate and octyl gallate.
16th Meeting of the Joint FAO/WHO Expert Committee on Food Additives.
World Health Organisation Food Additives Series no. 4; Geneva.

FAO/WHO (1987)
Evaluation of certain food additives and contaminants.
30st Meeting of the Joint FAO/WHO Expert Committee on Food Additives.
World Health Organisation Food Additives Series no. 21; Geneva.

FAO/WHO (1993):
Evaluation of certain food additives and contaminants.
41st Meeting of the Joint FAO/WHO Expert Committee on Food Additives.
World Health Organisation Technical Report Series no. 837; Geneva.

IARC (1987):
Lead and lead compounds.
In: Overall evaluations of carcinogenicity - an updating of IARC monographs volumes 1 - 42.
IARC monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Supplement 7; Lyon.

IPCS (1995):
Inorganic lead.
International Programme on Chemical Safety, Environmental Health Criteria 165.
World Health Organisation; Geneva.

Janus JA, Annema JA, Aben JMM & Slooff W (1997):
Evaluatiedocument lood.
RIVM draft report nr. 601014003; Bilthoven.

Vermeire TG, Apeldoorn ME van, Fouw JC de & Janssen PJCM (1991):
Voorstel voor de humaan-toxicologische onderbouwing van C-(toetsings)waarden.
RIVM report nr. 725201005, February 1991; Bilthoven.

WHO (1980):
Recommended health-based limits in occupational exposure to heavy metals.
World Health Organisation Technical Report Series no. 647; Geneva.

WHO (1987):
Air quality guidelines for Europe.
World Health Organisation European Series, No. 23; Copenhagen.

WHO (1993):
Guidelines for drinking-water quality, 2nd ed., volume 1: Recommendations.
World Health Organisation; Geneva.

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1.9. MERCURY

1.9.1. INTRODUCTION

Mercury was evaluated within the scope of this project by Vermeire et al. in 1991. They derived a TDI of 0.61 µg/kg bw/day. This value was based on a provisional tolerable weekly intake (PTWI) of 300 µg/week of the WHO/JECFA of 1989. The proposal applied for both inorganic mercury and methyl-mercury, but the permissible intake of methylmercury was said to be less than 200 µg/week. The value was derived from epidemiological studies of humans exposed through consumption of fish with high methylmercury concentrations.
For the update additional literature was reviewed published since 1990. This included evaluations of IPCS (1991), IARC (1993), ATSDR (1999), and the WHO/JECFA (final draft 1999).
Mercury is a naturally occurring element most often found as mercuric-sulphide in soils and rocks. It is mined and refined to its metallic form. Chemically it can be present in the form of inorganic salts, but also as organic mercury compounds.
The average concentration of inorganic mercury of natural occurrence in soil is in the order of 0.5 mg/kg (ATSDR 1999). According to IPCS (1991) some mercury originally generated by human activities may have been deposited from the atmosphere. Thus it is difficult to assess the contributions of naturally occurring mercury versus anthropogenic mercury.
Uses of mercury are various. Relevant users are the electrical and chloroalkali industry, but it is also used in paints, pesticides, medicines (i.e. dental amalgams), chemicals and reagents, and instrumentation like switches and thermometers (IARC 1993).
Disposal of industrial and household waste will be the major source of soil contamination. It can spread by volatilisation but also within short distances in water-soluble forms. Inorganic mercury can change in the organic methyl mercury that accumulates in the food chain. Consequently methyl mercury will be found on a global scale.

1.9.2. TOXICOLOGY

Toxicokinetics

Absorption
Metallic mercury vapour is well absorbed in humans, approximately 70 to 80%. Absorption of metallic mercury after oral intake is negligible. Absorption of inorganic salts ranges from 2 to 38%. Organic mercury is nearly completely absorbed. Dermal absorption of inorganic mercury is estimated to be in the order of 3%. Some organic mercury compounds such as dialkyl-mercurials are very well absorbed; absorption was demonstrated from diapers treated with phenyl-mercury (a fungicide).
Distribution
Mercury (both the metal, inorganic, and organic forms) accumulates in the kidneys. It can also be found in the brain; especially methyl-mercury can pass the blood-brain and placental barriers.
Metabolism
Metallic mercury is oxidised to Hg^{2+} in red blood cells and lungs. Oxidation occurs in the hydrogen peroxidase-catalase pathway. The ions in turn can be reduced and exhaled as metallic mercury vapour. The oxidation may also occur in the brain and the liver.
Methyl-mercury can be converted into the inorganic form, and thus enter the oxidation pathway.
Excretion
Mercury is eliminated via urine, faeces, and exhaled air, predominantly in the inorganic form. Inorganic and organic mercury are also excreted in breast milk. Elimination half-lives was reported to range from 2 days for blood and lungs to 60 days for the whole body and the kidneys.
Biomarkers
Blood and urine mercury concentrations are commonly used as biomarkers for exposure. For methyl-mercury most often hair has been used. Regarding effects, biomarkers for neurological and renal dysfunction can be considered. These effects are correlated with blood and urine levels. Well known are urinary proteins and elevation of serum creatinine as a marker for renal function. For neurological

functions studies have reported associations with tremors, insomnia, abnormal EEGs and alike (ATSDR 1999).

Toxicity

Essentiality
Mercury is not considered to be an essential element.
Acute toxicity
Death of humans was reported following inhalation of metallic mercury vapours after heating. In all cases death was attributed to respiratory failure. Experimental animals died from pulmonary oedema at concentrations of 27 mg/m^3 of mercury vapours in air.
Oral intake of inorganic mercury by humans leads to gastrointestinal lesions, cardiovascular collapse, and serious renal effects. According to the ATSDR (1999) the latter can lead to death.
Genotoxicity and carcinogenicity
Mercury is known to affect the mitotic spindle, which may lead to an abnormal distribution of chromosomes. *In vitro* it does, however, not induce chromosomal aberrations in human and mammalian cells (IPCS 1991). In an overview by IARC (1993) it was noted that methyl-mercury is negative in bacterial mutation tests, but there are chromosomal aberrations in some *in vivo* test systems. According to ATSDR (1999) human data on occupational exposure of inorganic mercury vapours are inconclusive with regard to structural and numerical chromosome aberrations. A positive correlation was found in people who consumed methyl-mercury contaminated fish. This correlation, however, is disputable as confounding factors could not be excluded.
Studies of cancer in humans were reported for various groups of potentially exposed persons such as dentists, industrial workers, and mercury miners. In a few studies a small excess of cancer risk was reported after exposure to inorganic mercury, but in most studies no carcinogenic effects could be found. In studies of humans exposed to methyl-mercury only weak (non significant) correlations were found.
Subchronic and chronic toxicity
Inorganic mercury
There is no information on chronic oral exposure to inorganic mercury by humans. In studies with experimental animals the reports describe renal and endocrine effects. From data of the NTP (1993) on chronic exposure to rats and mice it can be noted that renal toxicity is prominent, with a LOAEL of 1.9 mg/kg bw/day for microscopic changes in the kidneys. Besides a NOAEL for kidney weight of 0.23 mg/kg bw/day was reported.
A LOAEC of 0.026 mg/m^3 was reported for chronic inhalation of metallic mercury vapours in humans. The effects concerned were an increased frequency of mild tremors and cognitive skills that were associated with increased creatinine and mercury blood levels (ATSDR 1999).
There are some case studies of humans exposed to inorganic mercury by dermal exposure in which allergic reactions were reported. Also mild neurological effects after topical application of cream with a mercury salt have been reported (IPCS 1991, ATSDR 1999).
Organic mercury
For organic mercury the information from studies with experimental animals indicate neurotoxicity and teratogenicity. A study was done on developing children exposed *in utero* by mothers who were exposed to methyl-mercury in fish. From this study a NOAEL of 1.3 µg/kg bw/day for developmental effects was calculated using concentrations of total mercury in hair and blood as a marker for exposure of the mothers versus the development of the children for a period of 66 months (ATSDR 1999).
Data on inhalation of organic mercury in humans or experimental animals are not available.
Mechanism of action
A major mechanism for the biological activity of mercury is believed to be a high affinity binding of the mercuric ion to thiol- or sulphyldryl groups of proteins. This can promote oxidative stress, lipid peroxidation, mitochondrial dysfunction, and changes in the heme metabolism. Its leads to various effects such as porphyrins in urine and neuronal degeneration, which is in agreement with the known effects, i.e., renal toxicity and neurotoxicity of mercury in humans and experimental animals (ATSDR 1999).

1.9.3. EVALUATION

The available data do not allow a clear conclusion on the genotoxic potency of organic and inorganic mercury. Mercury exposure can lead to chromosome aberrations, but it is negative in bacterial mutagenicity tests. As mercury binds to proteins the clastogenic effect can be understood, but genotoxicity is not likely as there are no indications that mercury binds to DNA. The toxic mechanism demonstrates various effects that can be caused by interaction of mercury with cellular structures and functions. Assuming that the repair mechanisms can protect the cells up to a certain level of exposure a threshold mechanism of action is to be expected, and a TDI can be proposed on the basis of a NOAEL and extrapolation factors.

Inorganic mercury

In experimental animals renal toxicity is prominent after chronic oral exposure to inorganic mercury. Such effects were also reported after acute exposure of humans. For the proposal of an oral TDI, the NTP study provides a NOAEL for renal effects of 0.23 mg/kg bw/day. Using an extrapolation factor of 100 (for inter- and intraspecies extrapolation) an oral TDI of inorganic mercury of 2 μg/kg bw/day can be derived.

Organic mercury

For organic mercury a TDI can be derived on the basis of the NOAEL of 1.3 μg/kg bw/day for developmental effects in humans. Using an extrapolation factor of 10 for intraspecies variation an oral TDI of 0.1 μg/kg bw/day for organic mercury can be derived.

Mercury vapours

For metallic mercury vapours a TCA can be proposed. The data provides a LOAEC of 0.026 mg/m^3 for mild tremors. This is equal to a LOAEC for continuous inhalation of 0.006 mg/m^3 mercury in humans. The reported effects can be considered less serious effects and therefore an extrapolation factor of 3 is proposed for the conversion of the LOAEC to a NOAEC. A factor of 10 is to be used for intraspecies variation. Thus for metallic mercury vapour a TCA of 0.2 μg/m^3 is derived.

1.9.4. EVALUATIONS BY OTHER ORGANISATIONS

Inorganic mercury

IARC (1993) classified the carcinogenicity of inorganic mercury in group 3: *not classifiable for humans*.

US-EPA did not propose a RfD for inorganic mercury (IRIS, revision 1995).

For oral exposure to inorganic mercury ATSDR (1999) derived an intermediate MRL of 2 μg/kg bw/day. This value is based on a NOAEL of 0.23 mg Hg/kg bw/day in a NTP toxicology and carcinogenicity oral gavage study with rats with an extrapolation factor of 10 for animal to humans and 10 for human variability.

The WHO Drinking Water Quality Guideline is 1 μg/L for total mercury. This value is based on a PTWI of 5 μg per kg bw per week of the JECFA from 1989. According to WHO (1996) almost all mercury in drinking water is inorganic.

Hassauer et al. (1993) advised the Umwelt Bundes Amt (Germany) to an oral ”Orientierungswert” of 0.08 μg/kg bw/day for long term exposure to inorganic mercury. This value is based on a LOAEL for immunotoxic effects of 16 μg/kg bw/day in rats with an uncertainty factor of 200, and an absorption of 7%.

Organic mercury

IARC (1993) classified the carcinogenicity of methyl mercury to humans in group 2B: *possibly carcinogenic to humans*.

US-EPA derived an oral RfD for methyl-mercury of 0.1 μg/kg bw/day. This value was based on a benchmark dose of 1.1 μg/kg bw/day from human neurotoxic data with an extrapolation factor of 10 (IRIS, revision 1995).

For oral exposure to methyl mercury a chronic MRL of 0.3 μg/kg bw/day was derived by ATSDR. This value is based on the epidemiological study addressing human neurodevelopment of humans exposed through fish with a NOAEL of 1.3 μg/kg bw/day. An uncertainty factor of 3 was used for kinetic variability, and a factor of 1.5 for "domain specific findings" (ATSDR 1999).

Hassauer et al. (1993) advised the UBA (Germany) for methyl-mercury a long term oral "Orientierungswert" of 0.05 µg/kg.d. This was based on neurotoxicity in humans with a LOAEL of 0.7 µg/kg bw/day with an uncertainty factor of 15, and an absorption of 100%.
The JECFA-WHO concluded that the present epidemiological studies do not provide the appropriate data for an adjustment of the PTWI for methylmercury of 200 µg/week. It was recommended that it should be re-evaluated in 2002 when relevant data may become available (WHO final draft 10/6/99)
Mercury vapours
US-EPA derived a RfC for inorganic mercury of 0.3 µg/m^3. It is based on the LOAEC of 0.026 mg/m^3 with neurotoxic effects (tremors) in humans that was adjusted to a LOAEC of 0.009 mg/m^3 for time and inhalation rate. It was noted that an uncertainty factor of 10 was considered needed for the use of a LOAEL and the protection of sensitive humans, and an uncertainty factor of 3 for lack of data of developmental and reproductive studies (IRIS, revision 1995).
ATSDR presented a MRL for mercury vapours of 0.2 µg/m^3 for chronic inhalation, based on occupational exposed humans. Here the LOAEC of 0.026 mg/m^3 for neurotoxic effects (tremors) was corrected for continuous exposure to 0.006 mg/m^3. An extrapolation factor of 3 for the use of a minimal LOAEC and a factor of 10 for human variability was used.
Hassauer et al. (1993) advised the UBA (Germany) an inhalation "Orientierungswert" of 0.3 µg/m^3 that was based on a LOAEC of circa 25 µg/m^3 for neurotoxic effects in humans, and an absorption of 80%.

1.9.5. BACKGROUND EXPOSURE

According to Vermeire et al (1991) the total daily intake of mercury in The Netherlands amounts to 5 up to 10 µg/day.
According to IPCS (1991) and ATSDR (1999) the major contributors to mercury exposure of the population are foods and dental amalgams. The contribution from air and water is negligible. Data reported since 1991 indicate a median weekly intake of 14 µg of total mercury from a series of duplicate diets in The Netherlands (Council of Europe 1994). Thus the intake of total mercury from food is 2 µg/day. According to IPCS (1991) the oral intake of organic -mercury from food is about half of the total intake of mercury. If so, the intake in The Netherlands is 1 µg inorganic mercury and 1 µg organic mercury per day per person. This is similar to an intake of 0.02 µg inorganic mercury/kg bw/day, and of 0.02 µg organic mercury/kg bw/day from food.
The estimates of the mean daily intake of elemental mercury (vapours) from dental amalgams are very diverse. In ATSDR (1999) it is concluded that the best estimate is in the range of 1 to 5 µg/day. Consequently, the exposure to elemental mercury vapours from dental amalgams can be estimated 5 µg/day at maximum. This equals to a daily intake of 0.08 µg elemental mercury/kg bw/day.
It is therefore estimated that the intake of inorganic and elemental mercury in The Netherlands from foods and inhalation of vapours, is 0.1 µg/kg bw/day. For organic mercury the exposure is estimated to be 0.02 µg/kg bw/day.

1.9.6. CONCLUSION

Compound	TDI	TCA	Background exposure
Mercury, metallic	-	0.2	0.1
Mercury, inorganic	2	-	
Mercury, organic	0.1	-	0.02

TDI: tolerable daily intake (oral exposure); µg/kg bw/day
TCA: tolerable concentration in air (inhalation exposure); µg/m^3
Background exposure; µg/kg bw/day

1.9.7. REFERENCES

ATSDR (1999):
Toxicological profile for mercury (update).
Agency for Toxic Substances and Disease Registry, US Public Health Service, Atlanta (Georgia), USA.

Council of Europe (1994):
Lead, cadmium and mercury in food: assessment of dietary intakes and summary of heavy metal limits of food-stuffs.
Council of Europe Press, Strasbourg, France.

Hassauer M, Kalberlah F, Oltmans J & Schneider K (1993):
Basisdate Toxikologie für umweltrelevante Stoffe zur Gefahrenbeurteilung bei Altlasten.
Umwelt Bundes Amt, Berichte 4/93, Erich Schmidt Verlag, Berlin, Germany.

IARC (1993):
Monograph vol. 58: beryllium, cadmium, mercury, and exposures in the glass manufacturing industry.
International Agency for Research on Cancer, Lyon, France.

IPCS (1991):
Environmental Health Criteria 118: inorganic mercury.
World Health Organization, Geneva, Switzerland.

NTP (1993)
Toxicology and carcinogenesis studies of mercuric chloride in F344/N rats and B6C3F1 mice (gavage studies).
US Dept. of Health & Human Services, NIH Publication no. 91-3139; USA

Vermeire TG, Apeldoorn ME van, Fouw JC de & Janssen PJCM (1991):
Voorstel voor de humaan-toxicologische onderbouwing van C-toetsingswaarden.
National Institute of Public Health and the Environment, RIVM-report no. 725201005, February 1991; Bilthoven, The Netherlands.

WHO (1996):
Guidelines for drinking-water quality, 2nd ed. Volume 2, Health criteria and other supporting information.
World Health Organization, Geneva, Switzerland.

WHO, final draft (1999)
Methylmercury
53rd Joint FAO/WHO expert committee on food additives, Rome (Italy), 1-10 june 1999, PCS/FA 99.15

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1.10 MOLYBDENUM

1.10.1. INTRODUCTION

Molybdenum was evaluated within the scope of this project by Vermeire et al in 1991. They derived a TDI of 10 µg/kg bw/day for oral intake. The value was based on an (indicative) NOAEL of 1 mg/kg bw/day in rats. It was noted that this value is almost equal to the upper limit of the daily requirements of molybdenum. A TCA was not suggested.
For the update additional literature was reviewed. This included a review of the US EPA (1989), an inhalation study of the NTP (1997), and a review of the WHO (1996).
Molybdenum is obtained from molybdenite (molybdenum sulphide). The natural occurrence of molybdenite in soil varies from 0.1 to 10 mg/kg. In mining areas the concentrations will be substantially higher (HSDB 1999/10). High concentrations (up to 16 mg/L) can also be found in seawater, whereas in surface water concentrations up to 1500 µg/L are reported (WHO 1996).
Molybdenum is used in the manufacturing of steels and alloys, electronic devices, and pigments. Molybdenum disulphide is used as a lubricant additive. In agricultural areas molybdenum is used in fertilisers to prevent molybdenum deficiency.
As a consequence, molybdenum can be expected in industrial metal waste and at petrochemical sites or activities, leading to local contamination of topsoil. Soluble molybdates will lead to contamination of superficial or deeper groundwater. The use in fertilisers could lead to a more diffuse contamination of topsoil of agricultural areas (WHO 1996).

1.10.2. TOXICOLOGY

Toxicokinetics

Absorption
Gastrointestinal absorption depends on the chemical form. Water-soluble forms are well absorbed; absorption of dietary molybdenum is 30 to 70% (WHO 1996). The aerosols of water-soluble forms are also well absorbed after inhalation exposure (NTP 1997).
Distribution
Molybdenum appears rapidly in blood and most organs. High concentrations can be found in the liver, kidneys, and bones. It passes the placental barrier.
Metabolism
In mammals, including humans, molybdenum interacts with copper and sulphate. High concentrations of molybdenum produce copper deficiency by depleting the copper storage in the liver. This disturbs the synthesis of copper containing proteins.
Excretion
Molybdenum compounds are excreted in urine, and to a lesser extend through the faeces (NTP 1997).

Toxicity

Essentiality
Molybdenum is considered an essential element. There are, however, only a few studies on deficiency of molybdenum in humans; deficiency is most often identified in domestic cattle. As reported by Vermeire et al (1991) an intake of 150 to 500 µg/day is adequate and safe for humans. According to WHO (1996) the daily requirement is 0.015 to 0.15 mg per day for children, and 0.075 to 0.25 mg per day for adults. This equals to about 1 to 5 µg/kg bw/day.
Acute toxicity
There are no data of acute toxicity of molybdenum in humans. For cattle it is reported that excess molybdenum in soils and pastures will cause a disease that is characterised by diarrhoea, anaemia, and a harsh discoloured coat (Shell 1982).
Genotoxicity and carcinogenicity
There is little information on the genotoxicity of molybdenum. According to WHO (1996) some positive results are reported for ammonium molybdate, but other compounds such as molybdenum triox-

ide, molybdenum chloride, and sodium molybdate were neither mutagenic nor recombinogenic in various assays.
There are no indications that oral intake of molybdenum in drinking water causes tumours. Some data suggest that molybdenum may act to prevent certain forms of cancer induced by N-nitroso compounds in laboratory animals (WHO 1996, NTP 1997).
In the NTP study (1997) rats and mice were exposed to molybdenum trioxide by chronic inhalation. It was concluded that there was no evidence of carcinogenic activity in rats, but in mice a small increased incidence of carcinomas in the respiratory tract was observed at 100 mg/m^3.
Subchronic and chronic toxicity
Toxicity data from oral intake of molybdenum was reported for humans exposed to molybdenum in drinking water over a 2-year period. At the level of 0.2 mg/L an increased urinary excretion was seen, but no adverse effects were found. According to the WHO (1996) the intake of 0.2 mg/L can therefore be considered a NOAEL.
There is no information on the toxicity of molybdenum in humans after inhalation. In a semichronic study of inhalation of molybdenum trioxide in rats and mice, only effect on body weight was noticed at 300 mg/m^3. The NOAEC was 100 mg/m^3. After 2-year inhalation exposure of 30 mg molybdenum trioxide/m^3 inflammatory lesions were observed in lungs of rats. It was concluded that these changes are similar to other inhalation studies of particulate compounds and not caused by the molybdenum trioxide (NTP 1997).
There is no information on the toxicity of molybdenum in humans or mammals after dermal exposure.

1.10.3. EVALUATION

The available data suggest that molybdenum is not a genotoxic compound. A TDI can therefore can be derived using a NOAEL and extrapolation factors.
Since the evaluation of 1991 the available new data are restricted to inhalation exposure. This implies that there will be no changes in the initial proposal of the oral TDI of 1991, and the oral TDI of 10 µg/kg bw/day can be maintained. This value does not conflict with the daily requirements of molybdenum for humans.
For the derivation of a TCA for molybdenum compounds the data of the semichronic study of the NTP (1997) can be used. The NOAEC of 100 mg of molybdenum trioxide per m^3 is equivalent to a NOAEC of 12 mg/m^3 for continuous exposure. Using a factor of 100 for inter- and intraspecies extrapolation, and 10 for the extrapolation for semichronic to chronic exposure, the resulting TCA is 12 µg/m^3.

1.10.4. EVALUATIONS BY OTHER ORGANISATIONS

The US-EPA proposed a RfD of 5 µg/kg bw/day. This was based on an epidemiological study in the Soviet Union (of 1961) with estimated intakes with a LOAEL of 0.14 mg/kg bw/day in humans. The critical effect reported was increased uric acid levels. An uncertainty factor of 10 was used for the LOAEL and a factor of 3 for the protection of sensitive humans (IRIS, revision 1993).
The WHO Drinking Water Quality Guideline is 70 µg/L. This value is based on a NOAEL for humans exposed to molybdenum in drinking water of 0.2 mg/L in Denver, Colerado. An uncertainty factor of 3 was considered to be adequate for intrahuman variation. The proposal is consistent with the essential daily requirements of molybdenum (WHO 1996).

1.10.5. BACKGROUND EXPOSURE

Vermeire et al (1991) estimated a maximal daily molybdenum intake of 4 µg/kg bw/day. This estimate is not refuted by more recent data presented in the report of the US-EPA (1989) and the WHO (1996) and can therefore be maintained.

1.10.6. CONCLUSION

Compound	TDI	TCA	Background exposure
Molybdenum	10	12	4

TDI: tolerable daily intake (oral exposure); µg/kg bw/day
TCA: tolerable concentration in air (inhalation exposure); µg/m^3
Background exposure; µg/kg bw/day

The TDI of 10 µg/kg bw/day is similar to the derivation of Vermeire et al. (1991).

1.10.7. REFERENCES

HSDB (1999):
Molybdenum.
CD-ROM database, Silverplatter, London, UK.

NTP (1997):
Toxicology and carcinogenesis studies of molybdenum trioxide in F344/N rats and B6C3F1 mice (inhalation studies).
NIH Publication, NTP.TR 462, US Dept. of Health & Human Services, USA.

Shell (1982):
Toxicology data sheet: molybdenum compounds.
Group Toxicology Division, Shell Internatl Res. Mij. Den Haag, The Netherlands.

US EPA (1989):
Molybdenum hazards to fish, wildlife and invertebrates: a synoptic review.
Biological report 85 (1.19), Fish and Wildlife Service, USA.

Vermeire TG, Apeldoorn ME van, Fouw JC de & Janssen PJCM (1991):
Voorstel voor de humaan-toxicologische onderbouwing van C-toetsingswaarden.
National Institute of Public Health and the Environment, RIVM-report no. 725201005, February 1991; Bilthoven, The Netherlands.

WHO (1996):
Guidelines for drinking-water quality, 2nd ed. Volume 2, Health criteria and other supporting information.
World Health Organization, Geneva, Switzerland.

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1.11 NICKEL

1.11.1. INTRODUCTION

Nickel was evaluated within the scope of this project by Vermeire et al in 1991. They proposed a TDI of 50 µg/kg bw/day for oral intake. The value was derived of a NOAEL of 5 mg/kg bw/day in a semi-chronic experiment with rats exposed to nickel-sulphate in the diet, with an uncertainty factor of 100. A TCA was not suggested.
For the update additional literature was reviewed (published since 1991). This included reviews of IARC (1990), IPCS (1991), WHO (1996), and ATSDR (1997).
Nickel is a ubiquitous element in all parts of the biosphere. It is present in soil in several forms: crystalline minerals, complexed or adsorbed to organic matter, water-soluble free ions, or metal complexes. The background of natural occurring nickel in agricultural soil varies between 3 and 1000 mg/kg (IPCS 1991).
Nickel is mostly used in alloys and stainless steels. As such it is used in various items such as industrial machinery, aeroplanes, cars and ships, and furniture. Another important use of nickel is in batteries and electronic equipment. Of minor importance is its use in ceramics and anti fouling paints.
Due to its production and use, nickel and its compounds are to be expected in household and industrial waste, which leads to soil contamination. This can be both a local and a diffuse type of contamination of soil. Due to the solubility of various salts groundwater contamination can also occur. An indirect soil contamination can exist due to the deposition of emissions of nickel from industrial sources. Finally, contamination is to be expected in sewage sludge.

1.11.2. TOXICOLOGY

Toxicokinetics

Absorption
Studies with experimental animals and human volunteers have demonstrated a low absorption of nickel from food (less than 1 %), whereas absorption is higher from exposure to nickel in drinking water (up to 25%). The gastrointestinal absorption depends on various factors such as chelating agents and pH. Iron also seems to affect the gastrointestinal absorption of nickel. In addition it was demonstrated that absorption is higher for more-soluble nickel compounds.
Absorption of nickel after inhalation increases when particle size decreases, and also soluble nickel compounds are better absorbed.
Nickel is known to cause contact dermatitis in hypersensitive humans. Dermal absorption is, however, not different between normal and hypersensitive persons. Experiments on permeation showed that the rate depends on the type of nickel salt. Highest permeation rates are reported for nickel chloride. After dermal exposure to nickel chloride for 200 hr up to 43% of the amount of nickel applied was present in the skin matrix.
Distribution
After uptake nickel is bound to serum proteins, which apparently facilitates transport. Nickel is concentrated in kidney, liver, lungs, and lymph nodes. In humans 75% of respiratory nickel is retained. In experimental animals also retention in the skin is reported.
Metabolism and excretion
Nickel metabolism seems to depend on the presence of other metals; manganese and magnesium strongly antagonise the binding of nickel to phosphate. In general the clearance of nickel is very slow.
Soluble nickel is cleared and excreted in the urine; a small percentage is excreted in the faeces. Hair is also an excretory tissue for nickel (ATSDR 1997).
Biomarkers
According to IPCS (1991) levels of nickel in urine, serum, or hair increase in humans with occupational or environmental exposure. Background values, however, show large variations under normal conditions.

Toxicity

Essentiality
There is no indication that nickel should be considered to be an essential element.
Acute toxicity
Acute poisonings are known for nickel carbonyl, a volatile liquid of $Ni(CO)_4$. The critical effects are pulmonary haemorrhage and oedema or pneumonitis, leading to death a few days following exposure.
Information about oral poisoning with other nickel compounds is scarce; after ingestion of grams of nickel sulphate and nickel chloride people suffered from nausea, vomiting, and headache for hours up to a few days. These poisonings were not lethal (IPCS 1991).
Genotoxicity and carcinogenicity
The IARC (1990) presented an overview of cytogenic studies in humans after occupational exposure to nickel. Chromosomal aberrations were found, but no sister chromatid exchange. The results of *in vitro* mutagenicity studies are inconclusive; some nickel compounds did demonstrate DNA damage in bacteria while others did not.
The carcinogenic action of nickel and its compounds was investigated in different epidemiological studies of occupational exposed humans due to inhalation. From this it can be concluded that lung and nasal cancer is associated with inhalation exposure of nickel and/or nickel compounds; for metallic nickel and nickel alloys the evidence of carcinogenicity in humans was inadequate.
Subchronic and chronic toxicity
Following oral nickel exposure endocrine effects in the pancreas and thyroid of laboratory animals were reported. Also cardiovascular effects are known, especially regarding myocardial performance. Besides, nickel exposure has shown to lead to effects on the immune system.
Data of chronic human oral exposure to nickel or nickel compounds are not available. Likewise, new data of chronic oral exposure of laboratory animals were also not found. Consequently the NOAEL of 5 mg/kg bw/day in rats as considered pivotal by Vermeire et al (1991) and others (CEPA 1993, WHO 1996, ATSDR 1997) is still applicable.
IARC (1990), CEPA (1994), and ATSDR (1997) have reviewed chronic inhalation laboratory studies. Exposure to nickel by inhalation resulted in prominent effects in lungs of experimental animals. These include pathological changes of the tissue as well as lung function. Alveolar macrophages showed depressed cellular functions demonstrating also effects on the immune system. Less serious lung damage was reported in rats chronically exposed to levels of 0.06 mg nickel per m^3 (5 d/wk, 6 hr/d). An exposure of 0.03 mg/m^3 was considered the NOAEC for this effect. Studies of occupational exposed humans are focused on cancer only. NOAECs for other effects in humans are not reported.
Allergic reactions
Nickel is a well-known human contact allergen. Experiments with human volunteers have demonstrated that a patch with 5 mg/L of nickel sulphate can cause allergic reactions in hypersensitive humans. At 1 mg/L there is no response. The response was somewhat more pronounced after pretreatment of the skin with water and detergents (ECETOC 1992).
Mechanism of action
The toxic mechanism of action of nickel is not well understood. According to IPCS (1991) there might be an indirect mechanism by nickel displacement of iron and copper from intracellular binding sites, reactions with enzymes, and generation of free radicals. Besides, it is suggested that nickel can replace magnesium, leading to the immune-toxic and cardiovascular effects. The replacement of metals by nickel is also suggested by the ATSDR (1997). It was added that enzymes and hormones will get affected by these metal displacements.

1.11.3. EVALUATION

From the available data it is clear that inhalation exposure of nickel leads to tumours in the lungs and the nasal area. Its clastogenic properties have been demonstrated in humans. Mutagenicity data, however, did not demonstrate genotoxic properties, and the mechanism of toxic action suggests a cytotoxic effect. Thus a TDI for nickel can be proposed on the basis of a NOAEL and extrapolation factors.

Since 1990 no new relevant data on the toxicity of nickel and compounds after oral exposure for humans or experimental animals have been identified. Consequently the proposal of Vermeire et al. (1991), i.e., a TDI of 50 μg/kg bw/day is to be maintained.
A TCA of nickel in air can be derived on the basis of the NOAEC of 30 μg/m^3 for the respiratory system of rats, that is equivalent with a continuous exposure of 5 μg/m^3. Using an extrapolation factor of 100 for intra- and interspecies extrapolation, the TCA is 0.05 μg/m^3.

1.11.4. EVALUATIONS BY OTHER ORGANISATIONS

The US-EPA proposed a RfD of 20 μg/kg bw/day for soluble salts of nickel. The proposal was based on a NOAEL of 5 mg/kg bw/day for body and organs weights in a chronic oral rat study. An uncertainty factor of 300 was used for intra- and interspecies variation, and an additional factor of 3 for inadequacies in the reproductive studies (IRIS, revised 1996). For nickel refinery dust the US-EPA presented an inhalation unit risk of 2.4 x 10^{-4} [μg/m^3]$^{-1}$ (IRIS, revised 1991). The corresponding 1:10^{-4} lifetime excess cancer risk level is 0.4 μg/m^3.
The IARC (1990) classified nickel compounds as *carcinogenic to humans* (group 1); metallic nickel and alloys were classified as *possibly carcinogenic to humans* (group 2B).
The ATSDR presented a MRL of 0.2 μg/m^3 for chronic inhalation. This proposal is based on a NOAEC of 0.03 mg/m^3 in rats for lung fibrosis and inflammation (6 hours/day, 5 days/week), adjusted for continuous exposure with an uncertainty factor of 3 for interspecies extrapolation and 10 for intra-human variation (ATSDR 1997).
The WHO Drinking Water Quality Guideline is 20 μg/L. It was derived from a NOAEL of 5 mg/kg bw/day and an uncertainty factor of 100. An additional uncertainty factor of 10 was applied for lack of data (WHO 1996). The proposal was supported by a more recent two-generation study in rats with a NOAEL of 7 mg/kg bw/day, According to the WHO the value provides sufficient protection for nickel sensitive individuals (WHO 1998).
Hassauer et al. (1993) advised the UBA, Germany to an oral "Orientierungswert" of 1 μg/kg bw/day for long-term exposure to nickel and its compounds. This was based on a LOAEL of 0.95 mg/kg bw/day for reproductive effects in rats with an uncertainty factor of 100, and an absorption of 10%. In their proposal an inhalation "Orientierungswert" of 20 ng/m^3 was included that was based on effects in the respiratory tract of rabbits with a LOAEC of 18 μg/m^3 and an uncertainty factor of 1000.

1.11.5. BACKGROUND EXPOSURE

The WHO (1996) estimated the average daily intake of nickel between 100 and 300 μg/day, and on average probably lower than 150 μg. Food is the major contributor to the exposure. Exposure through inhalation in industrial areas is estimated to be 40 μg/day, and somewhat less in urban and rural areas. Cigarette smoking contributes for an additional 20 μg/day (IPCS 1991).
According to Vermeire et al. (1991) the daily intake is 4 μg/kg bw/day in The Netherlands. This value is in good agreement with the estimates of the other available reports, and hence it is to be maintained.

1.11.6. CONCLUSION

Compound	TDI	TCA	Background exposure
Nickel	50	0.05	4

TDI: tolerable daily intake (oral exposure); μg/kg bw/day
TCA: tolerable concentration in air (inhalation exposure); μg/m^3
Background exposure; μg/kg bw/day

Nickel is a human contact allergen. Dermal contact with an aqueous solution of 2 mg Ni^{2+} per liter can cause allergic reactions in hypersensitive humans; the no-effect-level is 0.4 mg/L.

1.11.7. REFERENCES

ATSDR (1997):
Toxicological profile for nickel (update).
Agency for Toxic Substances and Disease Registry, US Public Health Service, Atlanta (Georgia), USA.

CEPA (1994):
Nickel and its compounds, priority substances list assessment report.
Canadian Environmental Protection Act, Government of Canada.

ECETOC (1992):
Nickel, cobalt and chromium in consumer products: allergic contact dermatitis.
Technical report no. 45, European Chemical Industry Ecology and Toxicology Centre, Brussels, Belgium.

Hassauer M, Kalberlah F, Oltmans J & Schneider K (1993):
Basisdate Toxikologie für umweltrelevante Stoffe zur Gefahrenbeurteilung bei Altlasten.
Umwelt Bundes Amt, Berichte 4/93, Erich Schmidt Verlag, Berlin, Germany.

IARC (1990):
Chromium, nickel and welding.
IARC Monographs on the evaluation of carcinogenic risks to humans, volume 49.
International Agency for Research on Cancer, Lyon, France.

IPCS (1991):
Environmental Health Criteria 108: Nickel.
World Health Organization, Geneva, Switzerland.

IRIS (1999):
CD-ROM database, Silverplatter, London, UK.

Vermeire TG, Apeldoorn ME van, Fouw JC de & Janssen PJCM (1991):
Voorstel voor de humaan-toxicologische onderbouwing van C-toetsingswaarden.
National Institute of Public Health and the Environment, RIVM-report no. 725201005, February 1991; Bilthoven, The Netherlands.

WHO (1996):
Guidelines for drinking-water quality, 2nd ed., volume 2, Health criteria and other supporting information.
World Health Organization, Geneva, Switzerland.

WHO (1998):
Guidelines for drinking-water quality, 2nd ed., Addendum to volume 1, Recommendations.
World Health Organization, Geneva, Switzerland.

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1.12 ZINC

1.12.1. INTRODUCTION

Zinc was evaluated within the scope of this project by Vermeire et al in 1991. They proposed a TDI of 1 mg/kg bw/day for oral intake. A TCA was not suggested. The proposal was derived from a provisional TDI of 0.3 to 1 mg zinc/kg bw/day of the JECFA of 1982, that was based on clinical studies of humans exposed to 200 mg of zinc sulphate per day orally for a period of months.
For the update additional literature was reviewed, published since 1991. This included an update of the ATSDR (1994), a review of the WHO (1996), and an evaluation by the Health Council of The Netherlands (1998).
Zinc is widely distributed in nature. The natural concentration of zinc in soils is estimated to be 10 to 300 mg/kg. Zinc ores are mined and concentrated. Nowadays the metal is electro-deposited; in former days it was gained by smelting.
Zinc is used as coating of other metals, in alloys, and in many common goods. Besides it has many applications in wood preservation, catalysts, ceramics, fertilisers, and batteries. Zinc compounds are used in explosives, medical and household applications, and drugs (ATSDR 1994).
The use will lead to soil contamination from household and industrial waste disposal sites, but a more diffuse contamination is to be expected due to historical uses. Aerial depositions will also release zinc to soil. It can therefore be expected that exposure might occur to zinc in topsoil, sludge and sediments.

1.12.2. TOXICOLOGY

Toxicokinetics

Absorption
Gastrointestinal absorption of zinc was studied in humans using dietary zinc supplements. The absorption varied substantially with the dose and the diet, from 8 to 80%. According to the ATSDR (1994) the absorption is 20 to 30% for individuals with adequate nutritional levels. The absorption decreases after ingestion in combination with compounds such as calcium and phosphorus. This phenomenon is caused by precipitation of zinc in the intestines.
Studies regarding absorption of zinc after inhalation exposure are limited. In animals zinc retention in the lungs was rather small, with a maximum of 20% from inhalation of a zinc aerosol.
Dermal absorption of zinc does occur; zinc oxide is commonly used in medical treatment of wounds (dermal application). In wound tissue the absorption can be as high as 65%.
Distribution
Zinc is found in many human organs and tissues. Muscle and bone contain 90% of body burden of zinc; the remainder is found in the other organs, and blood.
Metabolism and excretion
Plasma provides an active transport of zinc. It is complexed to organic ligands, such as albumin and metallothionein.
Zinc is mainly excreted via the gut in the faeces, the remainder is excreted by the urine. Both the excretion in faeces and urine increase with increasing exposure.
Biomarkers
Zinc in serum and urine is sometimes used as a biomarker for exposure. However, relationships between levels and exposure have not been established. Likewise the correlation between long term exposure and zinc levels in hair and nails is poor.
Effects caused by zinc toxicity are diverse; however, according to the ATSDR (1994) a specific combination of gastrointestinal effects and pancreatitis is very indicative for zinc overexposure.

Toxicity

Essentiality
Zinc is an essential element. Zinc deficiencies are known for humans. Most prominent are skin lesions by deficiencies. According to the WHO (1996) the daily requirement of zinc is up to 22 mg per day, which is equivalent to 0.3 mg/kg bw/day.
Acute toxicity
There are limited data of human deaths after inhalation intake of zinc. In most of the cases death was probably not caused by the toxicity of the chemical compound, but side effects such as an explosion of zinc dust.
Serious acute oral poisonings are not known. According to the ATSDR (1994) a lethal oral intake in humans would need a high dose that is intolerable to humans because of gastric discomfort.
Genotoxicity and carcinogenicity
There is no data indicating any genotoxic properties of zinc, neither *in vitro* nor *in vivo*.
In epidemiological studies of occupational exposed humans there is no increased incidence of tumours associated to zinc inhalation exposure. In oral studies an association could also not been found.
Subchronic and chronic toxicity
Serious effects on various organ systems and reproduction were noted in experimental animals at dose levels in the order of 100 to 1000 mg/kg bw/day. In the available datasets of human studies haematological effects were found following intermediate or chronic oral intake of zinc. The ATSDR (1994) presents a LOAEL of 2 mg/kg bw/day for anaemia after chronic exposure of humans. Less serious effects such as a reduction of the ESOD (erythrocyte superoxide dismutase) activity were reported with a LOAEL of 1 mg/kg bw/day.
There is little information on the toxicity of zinc after inhalation exposure, neither for laboratory animals nor for humans. In epidemiological studies of occupational exposed humans no clear adverse effects were noted at dose levels up to 130 mg of zinc per m^3.
Zinc (as zinc oxide in ointment) is topically applied to promote the healing of burns and wounds. This use has generated some data on dermal exposure of humans to zinc. According to the ATSDR (1994) the human NOAEL for acute dermal exposure is 2.9 mg/cm^2.
Mechanism of action
Zinc is an element of which the absorption is homeostatically controlled. An intracellular carrier is suggested to bind zinc. At high concentrations the carrier becomes saturated. In such cases zinc can enter the cell, and it will bind non-specifically to proteins and other ligands. The latter can disturb various enzyme-systems. Consequently the toxic mechanism of action can be very diverse, leading to effects on various organs and systems.

1.12.3. EVALUATION

The available dataset does not indicate any genotoxic action of zinc. Since zinc appears to interact with a carrier, a threshold mechanism of action is indicated, and the TDI of zinc can thus be derived from a NOAEL with extrapolation factors.
Vermeire et al. (1991) derived a TDI of 1 mg/kg bw/day. This value was taken from a proposal of the WHO using a NOAEL of 3 mg/kg bw/day for humans. ATSDR (1994) reported a LOAEL of 1 mg/kg bw/day for humans. To derive a TDI, a conversion of the LOAEL to a NOAEL is needed. A margin of safety of 2 was considered sufficient by the European Commission (1994) and the Health Council of The Netherlands (1998). Accordingly, a TDI of 0.5 mg/kg bw/day is derived. This meets the daily requirement of zinc of 0.3 mg/kg bw/day. Data on appropriate NOAECs after inhalation exposure are not available. Consequently a TCA of zinc is not derived.

1.12.4. EVALUATIONS BY OTHER ORGANISATIONS

The US-EPA proposed a RfD of 0.3 mg/kg bw/day for zinc and zinc compounds. This value is based on a LOAEL of 1 mg/kg bw/day for a decrease of ESOD (erythrocyte superoxide dismutase) activity in females after 10 weeks of oral zinc exposure. An uncertainty factor of 3 for the conversion of a LOAEL to a NOAEL was used, taken into account the daily requirement of zinc (IRIS, revised 1992).

The ATSDR presented a MRL of 0.3 mg/kg bw/day for chronic oral exposure to zinc. The value was based on the LOAEL of 1 mg/kg bw/day day for a decrease of ESOD (erythrocyte superoxide dismutase) activity in females after 10 weeks of oral zinc exposure, but the daily requirement of zinc was taken into account. No MRLs have been derived for inhalation exposure (ATSDR 1994).
The WHO did not feel the need for a Drinking Water Quality Guideline for zinc. In addition it was stated that the daily dietary requirement of zinc is 0.3 mg/kg bw/day, and the provisional maximal TDI is 1 mg/kg bw/day (WHO 1996).
The SCF of the EC (European Commission, 1994) derived a maximal exposure of humans for zinc of 30 mg/day, equal to 0.5 mg/kg bw/day. This value was supported by the Health Council of The Netherlands (1998).
Hassauer et al. (1993) advised the UBA, Germany, an oral "Orientierungswert" of 1 mg/kg bw/day for long term exposure of zinc and its compounds. This value was based on a LOAEL of 1.9 to 2.3 mg/kg bw/day for haematological effects in humans. An uncertainty factor of 2 was applied, by 100% absorption. It their proposal an inhalation "Orientierungswert" of 18 µg/m^3 was included. This value was derived from a NOAEL of 1.8 mg/m^3 for subacute respiratory toxicity in guinea pigs, with an uncertainty factor of 100.

1.12.5. BACKGROUND EXPOSURE

The major source of zinc for the general population is food. Both animals and vegetable products contain zinc. According to the ATSDR (1994) this leads in the US to an average intake of 0.23 mg/kg bw/day. Data for other countries could not be found. The estimate of Vermeire et al. (1991) of 0.3 mg/kg bw/day is in good agreement with the data from the US. Consequently the value of Vermeire et al. of 1991 does not need to be revised.

1.12.6. CONCLUSION

Compound	TDI	TCA	Background exposure
Zinc	500	-	300

TDI: tolerable daily intake (oral exposure); µg/kg bw/day
TCA: tolerable concentration in air (inhalation exposure); µg/m^3
Background exposure; µg/kg bw/day

Due to lack of reliable data a TCA for inhalation exposure to zinc is not derived.

1.12.7. REFERENCES

ATSDR (1994):
Toxicological profile for zinc (update).
ATSDR report no. TP-93/15, Agency for Toxic Substances and Disease Registry, US Public Health Service, Atlanta (Georgia), USA.

European Commission (1994)
Scientific Committee on Food, Zinc. In: Food and energy intakes for the European Union,
Report no. 31, advice 11.12.1992, Dir. General Industry, Brussels, Belgium.

Hassauer M, Kalberlah F, Oltmans J & Schneider K (1993):
Basisdate Toxikologie für umweltrelevante Stoffe zur Gefahrenbeurteilung bei Altlasten.
Umwelt Bundes Amt, Berichte 4/93, Erich Schmidt Verlag, Berlin, Germany.

Health Council of The Netherlands (1998):
Commissie Risico evaluatie stoffen. Zink.
Gezondheidsraad, report 1997/34. Rijswijk, The Netherlands.

Vermeire TG, Apeldoorn ME van, Fouw JC de & Janssen PJCM (1991):
Voorstel voor de humaan-toxicologische onderbouwing van C-toetsingswaarden.
National Institute of Public Health and the Environment, RIVM-report no. 725201005, February 1991; Bilthoven, The Netherlands.

WHO (1996):
Guidelines for drinking-water quality, 2nd ed. Volume 2, Health criteria and other supporting information.
World Health Organization, Geneva, Switzerland.

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Appendix 2 Other inorganic compounds

2.1. CYANIDES
FREE CYANIDE, COMPLEX CYANIDE AND THIOCYANATES

2.1.1. INTRODUCTION

Cyanide occurs in various organic and inorganic compounds containing a cyano-group (-C≡N) as part of their molecule. In this evaluation the toxicological evaluation (i.e., the derivation of a MPR (maximum permissible risk)) as carried out in 1991 (Vermeire et al. 1991) is updated. Three groups of cyanides are distinghuished: (A) free cyanide, (B) complex cyanide, and (C) thiocyanate.
Cyanide is produced and used in various occupational settings where activities include electroplating, some metal mining processes, metallurgy, metal cleaning, certain pesticide applications, tanning, photography and gas works operations. Cyanide is also used in some dye and pharmaceutical industries. The exposure to thiocyanate is in the same way as to cyanide, because cyanide is metabolised to thiocyanate in the body. Thiocyanate is also present in food and as a soil contaminant. Many species of bacteria, fungi, algae and also of plants are able to utilise cyanide and degrade it to less toxic substances like CO_2, NO_3^-, SCN^- and OCN^-. Cyanides do not persist or accumulate in soils under natural conditions.
Much of the cyanide in soil and water comes from industrial processes. Industrial cyanide-bearing wastewater has frequently caused soil contamination. In The Netherlands particularly the sites of electroplating industries are often contaminated with cyanide. Another source of cyanide-contamination, in the form of Prussian blue ($Fe_4Fe(CN)_6)_3$), is the production of coal gas. In fact by far the most prevalent type of soil contamination with complex cyanide is with ferriferrocyanide (Meeussen, 1992).
Remark: Vitamin B12 is a chemical substance containing cyanide that is beneficial to the body because it prevents anaemia. In vitamin B12 the cyanide is bound, so that it does not serve as a source of cyanide exposure and thus is not harmful (ATSDR 1997).

2.1.2. FREE CYANIDE

2.1.2.1. INTRODUCTION

Cyanide (free) can be defined as the sum of cyanide in the form of HCN (aq, g) and CN^--ion; the toxicity data on HCN and on CN^--ion and its salts (i.e. calcium ($Ca(CN)_2$), potassium (KCN) and sodium (NaCN)) are considered.
Relevant exposure routes in the present context are the oral and inhalation ones.
A MPR for free cyanide was established in 1991 (Vermeire et al. 1991). The ADI as derived by the WHO-JMPR (1965) was adopted as the TDI, which was estimated to be 50 µg CN^-/kg bw/day (based on a NOAEL of a chronic rat diet study (1955) of 5 mg/kg bw, using an uncertainty factor (UF) of 100 (Howard & Hanzal 1955, cited in WHO-JMPR 1965).
TDI (1991): 50 µg CN^-/kg bw/day
TCA (1991): 200 µg CN^-/m^3 (odour threshold).
Daily exposure (1991): 0 µg CN^-/kg bw/day.

2.1.2.2. TOXICITY

Oral exposure
The cyanide ion is readily absorbed by the gastro-intestinal (GI) tract in animal species, and its highly poisonous effects are induced rapidly. Absorption of cyanide across the GI mucosa depends on the pH of the gut, and the pKa and lipid solubility of the cyanide compound. Cyanide blocks oxidative processes (by forming complexes with metal ions present in enzymes) in the cells, allowing anaerobic products, i.e., lactic acid, to accumulate in the cells, thus stimulating respiration. This is due to the combination of cyanide with the catalytic iron group of cytochrome oxidase, inhibiting its enzymatic

activity. The absorption of oxygen by the cells is inhibited, i.e., cellular oxidation cannot proceed, and the main supply of energy to the cells ceases. Acute oral toxicity of cyanide for human beings is relatively high, with an immediate lethal dose for an adult of approx. 1-2 mg/kg bw (ATSDR 1997, HSDB 1998).
Following gavage treatment of rats with 2 mg CN^-/kg as radiolabeled potassium cyanide, in 24 h 47% of the dose was excreted in the urine, indicating that at least 53% of the cyanide was absorbed in 24 h (Farooqui et al. 1982, cited in ATSDR 1997).
Low oral exposures to cyanide (2.9-4.7 mg cyanide/day) are not fatal to humans who have an efficient detoxification system whereby the cyanide is converted, through the rhodanese and thiosulphate enzyme system, to thiocyanate ion (metabolite), which is non-toxic at low levels. Following oral exposure, the highest levels have been detected in the stomach, lungs and blood. Animal studies have shown that cyanide does not accumulate in the blood and tissues following chronic oral exposure. In the body, cyanide is transformed into thiocyanate (80%), with a plasma half-life of 20 minutes to one hour. In humans, cyanide metabolites are excreted primarily in the urine (47-89% within 24 hours) with small amounts excreted through the lungs (approx. 4% in the form of HCN or CO_2). Once thiocyanate is formed, it is not converted back to cyanide. The minor pathway (15%) is the conversion of cyanide to 2-aminothiazoline-4-carboxylic acid and 2-iminothiazolidine-4-carboxylic acid (WHO-WQG 1984,1996, ATSDR 1997). Half-life for the conversion of cyanide to thiocyanate from a non-lethal dose in man is between 20 minutes and 1 hour (HSDB 1998).
In a semichronic study carried by out the US-EPA (unpublished study), Sprague-Dawley rats were administered 0, 0.5, 5, 15 or 50 mg CuCN/kg bw/day for 90 days (gavage application; vehicle was carboxymethylcellulose). At 50 mg/kg haematological anaemia was seen, an effect that is considered to be due to copper toxicity. Blood biochemical parameters (ASAT, ALAT, bilirubine) were changed at 50 mg/kg. From 15 mg/kg onwards laboured respiration, prolonged posture and morphological alterations of female liver and kidney tissues were observed. The NOAEL in this study is 5 mg CuCN/kg bw (LOAEL 15 mg/ CuCN/kg bw). Expressed as CN^- the NOAEL is 1.4 mg/kg bw and the LOAEL 4.3 mg/kg bw (IRIS 1999, Gerhart et al. 1987a, cited in ATSDR 1997).
In another semichronic rat study Sprague-Dawley rats were fed daily for 90 days $KAg(CN)_2$ at doses of 0.8, 2.6 and 7.8 mg CN^-/kg bw. At 0.8 mg CN^-/kg hypoactivity and posture hunching were observed (Gerhart et al. 1987b, cited in ATSDR 1997; an unpublished study of which only a very brief summary of results is available).
Fisher 344 rats were fed NaCN for 13 weeks. Doses used were 4.5, 12.5 and 28.8 mg CN^-/kg bw/day. At 12.5 mg/kg no effects (haematological, hepatic, renal, endocrinological, cardio, respiratory, immunological) were observed in females. At 12.5 mg/kg in males decreased epididymal and testis weights and decreased spermatid count were observed. The NOAEL in males is 4.5 mg CN^-/kg bw (NTP study 1993, cited in ATSDR 1997).
In a 6 months oral study in pigs (Jackson et al. 1988, cited in WHO-WQG 1996 and ATSDR 1997) dose levels of 0, 0.4, 0.7 or 1.2 mg cyanide/kg bw were given daily for 6 months (administration as KCN in water by gavage). A reduction in serum thyroxin was noted in all dose levels. Only at the highest dose level clear toxic effects (behavioural, i.e. slower response time) were observed. WHO (WHO-WQG 1996) concluded that the LOAEL in this study is 1.2 mg/kg bw (WHO did not conclude to a NOAEL). The LOAEL from this study was used by the WHO for establishing the drinking water guideline value. A TDI of 0.012 mg/kg bw was derived by applying an uncertainty factor (UF) of 100 to the LOAEL (WHO-WQG 1996).
In a 2-year dietary study from 1955, rats were administered food fumigated with HCN. The average daily concentrations were 73 and 183 mg/CN^-/kg diet. The daily estimated doses were 4.3 and 10.8 mg CN^-/kg bw. No effects (growth rate, signs of toxicity and histopathological lesions) were seen in this study. The NOAEL was 10.8 mg CN^-/kg bw (Howard & Hanzal 1955, cited in IRIS 1999). This study was used by the EPA for establishing RfD-values for a number of cyanide salts, for hydrogen cyanide and for free cyanide. Each of these evaluations was based on the NOAEL of 10.8 mg CN^-/kg bw/day from the Howard & Hanzal study. Thus for free cyanide, EPA derived an RfD (=TDI) of 0.02 mg CN^-/kg bw/day. In this derivation a UF of 100 and a modifying factor (MF) of 5 were used (the MF is used to account for the apparent tolerance to cyanide when it is ingested with food, as it was done in the study used to establish the RfD, compared to when it is administered by gavage or by drinking water). The Howard & Hanzal study was also used by WHO (1965) in its derivation of the ADI for cyanide

(WHO, however, used the dietary dose level of 73 mg/kg diet, taken to be equivalent with 5 mg/kg bw/day, as the basis for the ADI).
In an oral teratogencity study groups of 6 pregnant pigs were fed diets of cassava to which 0, 250 or 500 mg KCN/kg was added until parturition, after which sows and offspring returned to the standard diet for a 56-day lactation period. At the highest dose level a slight increased maternal thyroid weight and pathological changes in the thyroid were observed (WHO-WQG 1996).
No data on carcinogenicity are available.
Cyanide in the form of KCN was tested in a gene mutation assay using bacteria. The substance was negative in *Salmonella typhimurium* strains TA97, TA98, TA100, TA102, TA1535, AT1537 and TA1538, with and without metabolic activation. Negative results for KCN were also noted in the DNA repair assay in *Escherichia coli* WP67, WP2 and CM871. Cyanide in the form of NaCN was negative in the *Salmonella typhimurium* strains TA97, TA98, TA100 and TA1535 with and without metabolic activation. In an in vivo study with KCN, no testicular DNA-synthesis inhibition was noted in mice after a single dose of 1 mg/kg (de Flora et al. 1984, Painter et al. 1982, NTP 1993, cited in ATSDR 1997). The conclusion based on these results is that cyanide is not mutagenic.
Human studies are not available.
Inhalation exposure
In humans a concentration of 200 mg HCN/m^3 is fatal after 10 minutes, while a single exposure to concentrations upto 1 mg/m^3 caused no adverse effects. Concentrations in the range of 5-50 mg HCN/m^3 caused headache, dizziness and nausea after a few hours (Janssen en Heijna 1987).
In a 28-day study (2-day interval 30 min/day) dogs were exposed to HCN. The neurological effects observed were tremors, ataxia, vasodilatation, haemorrhage and atrophy of glial cells. The LOAEL was 43 ppm (Valade 1952, cited in ATSDR 1997). In both rats and monkeys no haematological effects were found when exposed to 50 ppm cyanide for 6 hours/day, 5 days/week during 6 months (Lewis 1984, cited in ATSDR 1997). In both rats and monkeys no (histo)pathological effects were observed when exposed to 50 ppm cyanide for 6 months (Lewis 1984, cited in ATSDR 1997).
No data on chronic toxicity, reproduction/teratogenicity, or carcinogenicity are available.
A thyroid-hormone evaluation of workers working with cyanide compounds in an electroplating process of a cable industry was carried out. Serum thiocyanate (SCN^-) levels of 35 non-smoking copper-ply employees were assayed by a ferric-chloride colour test. The mean SCN^- concentration of these employees was 316 µmol/L, which was significantly higher than that of the controls (90.8 µmol/L). Serum thyroxin (T4), triiodothyronine (T3), and thyroid-stimulating hormone (TSH) concentrations of exposed workers were compared with those of 35 controls. Cyanide exposure resulted in decreased T4 and T3 concentrations and increased TSH concentration, compared with the controls. It was concluded that occupational cyanide exposure impairs thyroid function (Banerjee 1997, cited in MEDLINE).
Thirty-six male workers employed in the electroplating sections of three factories in Egypt were studied. Cyanide exposure was from a plating bath that contained 3% copper cyanide, 3% sodium cyanide and 1% sodium carbonate. Breathing zone air samples were taken to determine the levels of cyanide to which the men were exposed. Twenty normal male volunteers of the same age group and socio-economic status who had no exposure to cyanide were chosen as controls. None of the exposed or control workers smoked cigarettes. Thyroid function (uptake of radiolabeled iodine) was assayed and urinary levels of thiocyanate were recorded. The men were exposed for a duration of 5-10 years, although one man was exposed for 15 years. In the three factories, the breathing zone cyanide concentrations ranged from 4.2-12.4 ppm (4.63-13.69 mg/m^3), with a mean of 6.4-10.4 ppm (7.07-11.45 mg/m^3). Twenty of the exposed workers had thyroid enlargement to a mild-moderate degree, although there was no correlation between the duration of exposure and either incidence or degree of enlargement. The thyroid function test did indicate significant differences in uptake between controls and exposed individuals after 4 and 24 hours. The LOAEL is 6.4 ppm (7.07 mg/m^3) (El Ghawabi 1975, cited in IRIS 1999). This LOAEL is an 8-hour TWA occupational exposure. The corrected LOAEL is 7.07 mg/m^3 × (10 m^3/day ÷ 20 m^3/day) × (5 days ÷ 7 days) = 2.5 mg/m^3. Applying a UF of 1000 (10 for sensitive human subpopulations, 10 for the lack of a NOAEL, and 10 for deficiencies in the data base, i.e., lack of chronic and multigeneration reproduction studies), US-EPA established an RfC of 0.003 mg/m^3. The degree of confidence assigned by the EPA to this RfC was *'low'* [5]).

[5]) US-EPA uses a classification of three confidence levels: *low*, *medium*, and *high*.

2.1.2.3. EVALUATION

Oral exposure

In the 1991 evaluation, the ADI of 0.05 mg/kg bw as derived by the WHO (1965) was adopted as the TDI (MPR) (Vermeire et al. 1991). This TDI was based on the dose level of 5 mg/kg bw/day from the chronic diet study of Howard & Hanzal (1955). In 1965 the WHO expert committee selected this dose level as the basis for the ADI because this dose does not produce an excessive increase in blood thiocyanate. According to the US-EPA, however, the NOAEL from this study is 10.8 mg/kg bw. In the text above several semichronic toxicity studies with cyanide salts are presented. In some of these studies effects were seen at levels lower than the chronic NOAEL of 10.8 mg/kg bw (or, if the WHO evaluation is followed, the NOAEL of 5 mg/kg bw/day). In the 6 months pig study with KCN already at 0.4 mg CN^-/kg bw an effect was observed, and with $KAg(CN)_2$ at 0.8 mg CN^-/kg bw an effect was reported in a rat 90-day study. In the oral 90 days study with CuCN the LOAEL was 4.3 mg CN^-/kg bw/day (NOAEL = 1.4 mg/kg bw/day). In the NTP-study with NaCN the LOAEL was 12.5 mg/kg bw/day (NOAEL = 4.5 mg/kg bw/day). These semichronic studies were gavage studies with compound administration once per day, which constitutes an exposure regimen that is different from the exposure to free cyanide residues in food as was done in the Howard & Hanzal study. This difference may explain to a certain extent the difference in (no)-effect levels noted above. The validity of the low semichronic effect levels of 0.4 and 0.8 mg/kg bw for evaluating free-cyanide toxicity is questionable given the fact that in other studies NOAELs/LOAELs were clearly higher.

Taking the NOAEL of 4.5 mg/kg bw from the 90 days oral rat study with the well-soluble salt NaCN (from which CN^--ions will be readily available after ingestion) and applying a UF of 100 [6]), a TDI of 0.045 mg CN^-/kg bw can be derived. This value is virtually identical to the existing TDI (MPR) of 0.05 mg/kg bw that was based on the chronic dose level of 5 mg/kg bw for free cyanides. Taking this into account, it is concluded that the latter value (i.e., 0.05 mg CN^-/kg bw/day) is to be retained as TDI.

Inhalation exposure

It has been established that in humans chronic exposure to cyanides may interfere with thyroid function. This effect is due to the metabolite thiocyanate. In the study in workers presented above critical effects occurred in the CNS and thyroid. The corrected LOAEL from the occupational study was 2.5 mg/m^3. As is also pointed out in the evaluation of the US-EPA, the study from which this LOAEL was derived was a limited study, and thus the reliability of the LOAEL is low. Route-to-route extrapolation (derivation of a tolerable concentration in air (TCA) from the TDI derived above) is not feasible since there are strong indications for route-specific metabolism of cyanide [7]).

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[6]) This is the standard factor for TDI derivation. Application of an extra factor for limited duration of the pivotal study is considered not necessary because of the rapidity with which cyanide produces its adverse effects.

[7]) Cyanide is metabolised particularly in the liver. After oral intake of cyanide hepatic conversion to thiocyanate will produce a rapid first-pass effect, while after inhalation any cyanide that is absorbed into the body will be distributed to other body compartments before reaching the liver, and thus no first-pass effect occurs. Further evidence for route-specific metabolism comes from in vitro studies. These studies indicate that in several animal species rhodanese levels in nasal tissues are considerably higher (in rats approx. 7 times) than those in liver. The latter data have led the EPA to conclude that it is reasonable to assume that systemic effects would occur at concentrations well below those at which respiratory tract effects would be present.

In view of this the LOAEL of 2.5 mg/m^3 is used as the basis of the derivation of the TCA. Using a UF of 100 (10 for sensitive human subpopulations and 10 for the lack of a NOAEL) a TCA of 25 µg/m^3 is derived [8]).

2.1.2.4. BACKGROUND EXPOSURE

Cyanide occurs naturally in several plants that contain cyanogenic glycosides such as cassava, soybeans, spinach and bamboo shoots. Cyanide concentrations in cereal grains range from 0.001-0.45 µg/g; in soy protein products from 0.07-0.3 µg/g, and in lima beans from 0.1-3 mg/g (ATSDR 1997). The root crop cassava can create a problem in West-Africa, since cassava is the most important food there. If not properly prepared, it can contain very high levels of cyanide. For a group of 73 Liberians consuming cassava, the mean daily intake was calculated to be 0.61 mg CN^-/kg bw (WHO-WQG 1996). Cyanide concentrations in canned unpitted fruits/peaches, apricots, plums and cherries range from 0-4 µg/g, depending on the glycoside content of the raw fruits and conditions of heat processing.
The most likely source of general population exposure to cyanide are levels in inhaled smoke from cigarettes. These are ranging from 10-400 µg/cigarette.
Data regarding the cyanide level in ambient air and drinking water are lacking (probably low). Although the cyanide concentration in several foods are known, the cyanide content of a total diet consumed by an average adult is unknown. Hence the background exposure cannot be estimated.

2.1.2.5. ADDITIONAL DATA

Absorption factors:
- dermal: HCN is absorbed very rapid percutaneously. In a human study exposure to HCN leaded to collapse within 5 minutes; no quantitative value was given (Grandjean 1989).

Guideline values:
- drinking water: 70 µg/L (WHO-WQG 1996)
  200 µg/L (ATSDR 1997)
  50 µg/L (Richtlijn 98/83/EG)
- air (workplace): 11 mg HCN/m^3 (Dutch occupational limit value)

2.1.2.6. CONCLUSION

TDI:	50 µg CN^-/kg bw/day
TCA:	25 µg CN^-/m^3
Background exposure:	not quantifiable
Odour treshold:	200 µg CN^-/m^3

2.1.3. COMPLEX CYANIDE

2.1.3.1. INTRODUCTION

Complex cyanides, especially the ferrocyanide-complex ($[Fe(CN)_6]^{4-}$), can be defined as bound cyanides in which bound cyanide = $cyanide_{total}$ – $cyanide_{free}$.
Relevant exposure route in the present context is the oral one.

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[8]) As already noted in the text, US-EPA in its RfC-derivation divided the LOAEL by a total uncertainty factor of 1000. The present evaluators, however, feel that for free cyanide the additional factors (of 3 each) for limited duration of the study and limitations in the available data base, respectively, are not needed. The mechanism of cyanide toxicity is well known, and based on this knowledge the urgency for introducing additional factors is limited. The evidence indicating route-specific detoxification via rhodanese in the nasal mucosa (in vitro data indicate the rhodanese levels in nasal tissues to be markedly higher than those in liver) also supports the idea that the additional factors used by the EPA are not needed (cf. the result of route-to-route calculation from the TDI for free cyanide: 230 µg/m^3).

The MPR for complex cyanide was estimated in 1991 (Vermeire et al., 1991) at 13 µg CN^-/kg bw/day. This was based on the NOAEL of a 90-day oral rat study (1974) of 0.05% in food (equivalent 25 mg/kg bw/day), and using a UF of 1000, which resulted in an ADI of 0.025 mg/kg bw as $Fe(CN)_6^{4-}$. This is equal to 0.013 mg CN^-/kg bw/day.
TDI (1991): 13 µg CN^-/kg bw/day
Daily exposure (1991): 0.4 µg CN^-/kg bw/day.

2.1.3.2. TOXICITY

Toxicity of ferrocyanides
The JECFA (1974) allocated an ADI of 0.025 mg Na-ferrocyanide/kg bw/day, based on the NOAEL of a 90-day oral rat study. The ADI is equal to 13 µg CN^-/kg bw/day and was adopted as the MPR in the 1991 evaluation in the present scope (Vermeire et al. 1991). No new toxicity data are available on ferrocyanides.
The Ca, K and Na-salts of ferrocyanide are used as food additives (anti-caking agent). Maximum use of K/Na-cyanide salt in the Netherlands is 10 mg/kg K/Na-cyanide salt, which is equal to max. 5 mg CN^-/kg. Daily sodium intake in the Netherlands is maximal 5.6 g, which is equal to 0.028 mg CN^-/day. Assuming an average body weight of 70 kg (adult), the mean intake from background exposure is 0.4 µg CN^-/kg bw/day (Pearce 1994, Vermeire et al. 1991).
Of solubilised iron cyanides (ferrocyanide as well as ferricyanide) only a minimal fraction dissociates into free cyanide (CN^-): experimentally the dissociation constants were estimated to be 10^{-47} and 10^{-52} for the ferrocyanide ion and the ferricyanide ion, respectively.

Toxicity of ferriferrocyanides
The most prevalent types of cyanide compounds found at former manufactured gasplant (MGP) sites are ferriferrocyanides ($Fe_4[Fe(CN)_6]_3$) (approximately 97%). Soil at MGP sites has a low pH (2-4). This enhances cyanide stability and minimises environmental mobility. As pH increases (due to mixing soils or at the edges of the cyanide-containing soils) some dissociation of complexed cyanides can occur. When aqueous ferriferrocyanide solutions are irradiated with light, free cyanide is released, but only to a very small amount (Shifrin et al. 1996).
Ferriferrocyanide is poorly absorbed from the gut, i.e., only 0.3-2.8% was found in the urine of rats given an oral dose of aqueous ferriferrocyanide (Nielsen 1990, cited in Shifrin et al. 1996). In a study of fasting rats given oral doses up to 10 mg radiolabeled aqueous ferriferrocyanide (36-40 mg/kg bw), only 1% of the administered dose was absorbed (Shifrin et al. 1996).
In a human study an oral dose of 500 mg (6.2-7.1 mg/kg bw) of ferriferrocyanide, in a gastric acid-soluble gelatine capsule, was given to three adult male volunteers. The average 7-day body retention was 0.03-0.07% for radioabelled iron and the amount of absorbed free cyanide was estimated to be 0.2-0.4% (= 0.03 mg CN^-/kg bw) of the total cyanide administration, of which 70% will be excreted mainly as thiocyanate (Nielsen 1990, cited in Shifrin et al. 1996). In humans ingestion of a single dose of $Fe_4(Fe(CN)_6)_3$ at a dose level of 6-7 mg/kg bw did not result in toxic effects (Nielsen 1990, cited in Shifrin et al. 1996).
Ferriferrocyanide has also been used therapeutically, i.e. as antidote for thallium poisoning in humans, at a dose of 250 mg/kg/day (Pearce 1994, Shifrin et al. 1996).
There are two reasons for the low toxicity of ferriferrocyanide, i.e., limited absorption from the gut and only fractional dissociation of the absorbed ferriferrocyanide to toxic HCN or CN^-.

2.1.3.3. EVALUATION

In evaluating the toxicity data it must be noted that the TDI as derived in 1991 was a value derived for ferrocyanide. Given the fact that complex cyanides in soil are predominantly present as ferriferro-cyanides (97%), the present update derives a TDI from the available data for this particular compound.
As outlined in the preceeding paragraph, complex cyanides (as compared to free cyanides) are very poorly absorbed in the gastro-intestinal tract, and in addition to this the toxicity of complex cyanides is even further limited due to the low levels of release of free cyanide. The low bioavailability of the complex cyanide (i.e., both the poor absorption and the very limited release of free cyanide from the

absorbed complex cyanide) results in a low toxic potential for these compounds compared with free cyanide. Thus, following oral exposure to ferriferrocyanide:

$Fe_4[Fe(CN)_6]_3$	→	$Fe(CN)_6^{4-}$	→	CN^-
soil and groundwater		absorbed		liberated
(100% of CN^--dose)		(3% of CN^--dose)		(0.4% of CN^--dose)

The TDI derivation as presented here is based on the TDI derivation for free cyanide. The value for free cyanide is corrected for relative gastro-intestinal absorption of complex cyanides compared to free cyanide [9]). In experiments with rats and humans in which aqueous radiolabeled ferriferrocyanide was administered orally, absorption percentages of ≤ 3% were found. When ferriferrocyanide is present in soil the bioavailability is probably even lower due to the binding effect of the soil matrix. The scant data for free cyanide (a limited study in rats) indicate a level of gastrointestinal absorption of at least 50%. Thus, the TDI for ferriferrocyanide can be calculated by multiplying the TDI for free cyanide by the ratio between the absorption percentage for free cyanide and that for ferriferrocyanide, as follows: TDI (free cyanide) = 50 µg/kg bw × (50% ÷ 3%) = 800 µg/kg bw/day.

2.1.3.4. CONCLUSION

TDI (ferriferrocyanide): 800 µg CN^-/kg bw/day (applicable to both solid and dissolved ferriferrocyanide)
Background exposure: 0.4 µg CN^-/kg bw/day

2.1.4. THIOCYANATE

2.1.4.1. INTRODUCTION

Thiocyanate (SCN^-) is the main metabolite of free cyanide. In the present context the relevant exposure route is the oral one.
In 1991 a MPR of 11 µg SCN^-/kg bw/day was established (Vermeire et al. 1991). This was based on the NOAEL of a 90-day human volunteer study of 8 mg SCN^-/day, using a UF of 10, which resulted in a TDI of 11 µg SCN^-/kg bw/day (Dahlberg et al. 1984).
TDI (1991): 11 µg SCN^-/kg bw/day
Daily exposure (1991): 74 µg SCN^-/kg bw/day

2.1.4.2. TOXICITY

Thiocyanate is a goitrogenic substance (produces thyroid enlargement), an effect that is the result of its competition with iodine. For thiocyanate several epidemiological studies are available. Animal data are limited.
A thyroid-hormonal evaluation of thirty-five women consuming commercially packed milk containing thiocyanate was carried out *(dose levels are unknown)*. The mean serum thiocyanate concentration, which was measured by the $FeCl_3$ colour test, was significantly higher than that of control subjects. Serum thyroxin (T4), triiodothyronine (T3) and thyroid-stimulating hormone (TSH) concentrations of exposed women were compared with those of thirty-five controls. Thiocyanate ingestion was associated with lower levels of T4 and higher levels of TSH compared with the controls. T3 was found to be higher in the women consuming thiocyanate-containing milk but the difference was not

[9]) This is typically a worst-case approach, because only the relative gastro-intestinal absorption is considered, and the very limited release of CN^- from absorbed complex cyanide is not taken into account (in other words, the approach assumes that all absorbed complex cyanide is converted into CN^-, while actually this is only a limited fraction). The resulting TDI for complex cyanides might thus be an overestimation of the toxic risks following oral exposure.

significant. It can be concluded that ingestion of milk, with added thiocyanate, impairs the thyroid function (Banerjee 1997, cited in MEDLINE).
Remark: These effects are the same as the effects observed in the occupational study with free cyanide.
The previous evaluation (Vermeire et al. 1991) included already the study of Dahlberg et al. (1984), in which it was concluded that supplementing thiocyanate to milk, resulting in an intake of 8 mg SCN^- per day during three months, had no effects on the thyroid function in humans (examined parameters were thyroxin concentration, triiodothyronin and thyrotropic hormone in blood serum).
The effects of feeding thiocyanate to female rats throughout gestation and lactation on a microtubule assembly of pups during postnatal development were examined. Microtubules, which are important components of the neuronal cell cytoskeleton, may serve as markers of neuron growth. A progressive increase with age in the initial rate of microtubule assembly was apparent in both untreated control and thiocyanate-treated pups in the cerebrum, cerebellum and brainstem. Thiocyanate treatment did not alter the tubulin content at any of the developmental stages studied (7, 14 and 21 days postnatal). However, examination of the microtubule assembly revealed a markedly reduced polymerisation of tubulin into microtubules in brain regions of thiocyanate-treated rats compared with untreated controls. The effect of thiocyanate on microtubule assembly was evident at all three ages (7, 14 and 21 days). Thiocyanate-induced hypothyroidism increased the lag period for initiation of assembly and also altered the initial rate of microtubule formation. This study suggests that a partial suppression of thyroid function by thiocyanate, as evidenced by a decrease in circulating concentrations of thyroxin, could cause alterations in microtubule formation during brain development and suggests the possibility of an impairment in the process of microtubule metabolism (Lakshmy 1997, cited in MEDLINE).

2.1.4.3. EVALUATION

Since no new adequate toxicity data are available for the derivation of a TDI, the conclusion as drawn in 1991 is retained. Thus, the NOAEL from a 90-day human volunteer study of 8 mg SCN^-/day (0.11 mg SCN^-/kg bw/day) is used. Applying (as before) a UF of 10, a TDI of 11 µg SCN^-/kg bw/day is derived.

2.1.4.4. BACKGROUND EXPOSURE

Regarding background exposure it must be noted that thiocyanate occurs naturally in many edible plants containing glucosinolates which are hydrolysed to thiocyanate. Thiocyanate concentrations of <2 µg/g can be detected in a.o. spinach, radishes and celery. Cabbages and kohlrabi contain high levels of thiocyanate ranging from 5-660 µg/g. Thiocyanate concentrations in milk (and other diary products) and in meat range from <1 - 9 µg/g and 0.5 - 0.7 µg/g, respectively (ATSDR 1997).
Data with respect to levels in drinking water and ambient air are lacking.

2.1.4.5. CONCLUSION

TDI: 11 µg SCN^-/kg bw/day
Background exposure: 74 µg SCN^-/kg bw/day

2.1.5. SUMMARY OF HUMAN MPRs

Compound	TDI	TCA	Background exposure	Odour threshold
Cyanide, free (as CN^-)	50	25	NQ	200
Cyanide, complex [1]) (as CN^-)	800 [2])	-	0.4	-
Thiocyanate (as SCN^-)	11	-	74	-

TDI: tolerable daily intake (oral exposure); µg/kg bw/day
TCA: tolerable concentration in air (inhalation exposure); $\mu g/m^3$
Background exposure; µg/kg bw/day
Odour threshold; $\mu g/m^3$
NQ: not quantifiable
- : not applicable
[1]) particularly ferriferrocyanide
[2]) applicable to solid and dissolved ferriferrocyanide

2.1.6. REFERENCES

ATSDR (1997):
Draft toxicological profile for cyanide.
US Dept. of Health & Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta (GA), USA.

Grandjean P (1989):
Identification and description of substances absorbed through the skin and to which workers are exposed at the workplace. Final report to the Commission of the European Communities, February 10, 1989.

HSDB (1998):
Hazardous Substances Database, at http://toxnet.nlm.nih.gov.
National Institutes of Health, Research Triangle Park, USA.

IRIS (Integrated Risk Information System), 1999:
- Summary for free cyanide; oral RfD assessment dated February 1993.
- Summary for calcium cyanide; oral RfD assessment dated January 1990.
- Summary for copper cyanide; oral RfD assessment dated February 1996.
- Summary for chlorine cyanide; oral RfD assessment dated November 1995.
- Summary for hydrogen cyanide; oral RfD assessment dated September 1994.
- Summary for potassium silver cyanide; oral RfD assessment dated February 1996.
- Summary for potassium cyanide; oral RfD assessment dated February 1996.
- Summary for silver cyanide; oral RfD assessment dated February 1996.
- Summary for sodium cyanide; oral RfD assessment dated February 1996.
- Summary for zinc cyanide; oral RfD assessment dated February 1996.

US Environmental Protection Agency, Washington DC, USA.

Janssen PJCM & Heijna E (1987)
Methylbromide, waterstofcyanide, fosforwaterstof en ethyleenoxide - Vergelijking van de toxicologie van vier voor gebruik in de voorraadbescherming in aanmerking komende gassen.
National Institute of Public Health and the Environment, Toxicology Advisory Centre report January 9, 1987; Bilthoven, The Netherlands.

Janssen PJCM & Speijers GJA (1996):
Reactie op standpunt Oranjewoud t.a.v. MTR-waarden voor vrij cyanide en complex gebonden cyanide.
National Institute of Public Health and the Environment, Toxicology Advisory Centre report dated January 11, 1996; Bilthoven, The Netherlands.

Meeussen JCL (1992):
Chemical Speciation and Behaviour of Cyanide in Contaminated Soils.
Doctoral thesis, Wageningen Agricultural University, The Netherlands.

Richtlijn 98/83/EG van de Raad betreffende de kwaliteit van voor menselijke consumptie bestemd water.
Brussel, October 26, 1998.
Vastgesteld door de Raad van Ministers d.d. 03-11-1998.

RIVM (1991):
Toxbank data file: hydrogen cyanide (human toxicology authors: PJCM Janssen, E Heijna, ecotoxicology authors: R Luttik, JBHJ Linders).
National Institute of Public Health and the Environment, Toxicology Advisory Centre; Bilthoven, The Netherlands.

Shifrin NS, Beck BD, Gauthier TD, Chapnick SD & Goodman G. (1996):
Chemistry, toxicology and, human health risk of cyanide compounds in soils at former manufactured gas plants sites.
Regulat Toxicol Pharmacol 23, 106-116.

Vermeire TG, Apeldoorn ME van, Fouw JC de & Janssen PJCM (1991):
Voorstel voor de humaan-toxicologische onderbouwing van C-toetsingswaarden.
National Institute of Public Health and the Environment, RIVM-report no. 725201005, February 1991; Bilthoven, The Netherlands.

WHO-JMPR (1965):
Evaluation of the hazards to consumers resulting from the use of fumigants in the protection of food.
FAO Meeting report no. PL\1965\10\2; WHO Food Add. 28.65.

WHO-WQG (1984):
WHO guidelines for drinking-water quality. Volume 2: Health criteria and other supporting information.
World Health Organization, Geneva, Switzerland.

WHO-WQG (1996):
WHO guidelines for drinking-water quality. Volume 2, 2nd edition: Health criteria and other supporting information.
World Health Organization, Geneva, Switzerland.
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Appendix 3 Aromatic compounds

3.1. BENZENE

3.1.1. INTRODUCTION

Benzene was previously evaluated by the RIVM in 1987 (Integrated Criteria Document), in 1991 and 1993 (derivation of MPR within the scope of the RIVM soil intervention value project), and in 1994 (update of the carcinogenicity evaluation). In 1991 Vermeire et al. derived a 10^{-4} inhalation excess cancer risk level of 1200 μg/m^3 to be used as inhalatory MPR. From this value an oral MPR of 170 μg/kg bw/day was derived via route-to-route extrapolation (Vermeire et al. 1991). Re-evaluation of benzene in 1993 to verify whether an MPR derivation based on noncancer effects might lead to a lower value than 1200 μg/m^3 led to a proposed inhalatory MPR of 30 μg/m^3. This value was based on a LOAEL in animals for the induction of blood toxicity. From this value an oral MPR of 4.3 μg/kg bw/day was derived via route-to-route extrapolation (Vermeire 1993).
Since 1993/1994 several new evaluations have been prepared by other organizations. In 1995 the WHO re-evaluated benzene within the scope of its Air Quality Guidelines programme (publication in press). More recently a Working Group of experts convened by the EU has carried out an in-depth evaluation of benzene literature (published since the WHO Air Quality Guideline evaluation of 1995) aimed at deriving an air quality guideline to be implemented in EU-countries. The report prepared by this Working Group (EU 1999) was an important source for the present evaluation. Other recent evaluations are those by the Health Council of the Netherlands (1997), ATSDR (1997) and the toxicological review prepared by the US-EPA (1998a and 1998b).
Exposure routes considered relevant: oral and inhalation.

3.1.2. TOXICOLOGY

Toxicokinetics

Benzene is rapidly and efficiently (30-50%) absorbed following inhalation. Following ingestion, animal data suggest about 100% absorption form the gastro-intestinal tract. Less than 1% is absorbed through the skin.
After absorption, benzene is widely distributed throughout the body, indepently of the route of exposure. Levels in blood fall rapidly once exposure stops. Following uptake, adipose tissues have been found to contain high levels of benzene metabolites (WHO-WQG 1996). Benzene passes the placental barrier (IPCS 1993).
The metabolism and elimination of absorbed benzene appear to follow similar pathways in laboratory animals and humans. The assumed primary reactive metabolite of benzene is benzene-oxide (EU 1999). Benzene-oxide is converted mainly to phenol by the mixed-function oxidase system, primarily in the liver, but also in the bone marrow. A small amount of phenol is metabolised to hydroquinone and catechol, and an even smaller part is transformed into phenylmercapturic or *trans,trans*-muconic acid. In humans, between 12% and 14% (up to 50% in laboratory animals) of the absorbed dose is excreted unchanged in expired air. In the urine, a small part is excreted unchanged, the remainder being excreted as phenol conjugates (WHO-WQG 1996).

Toxicity

Acute toxicity
Benzene is of low acute toxicity. In experimental animals oral LD50-values range from 1 to 10 g/kg bw and LC50-values range from 15 to 60 g/m^3 (IPCS 1993, WHO-WQG 1996). The single oral acute dose that has been reported to be lethal to humans is 8.8 g/kg bw (IPCS 1993).
Skin/eye irritation and sensibilization
Benzene is a moderate eye irritant and is irritating to rabbit skin after multiple applications of the undiluted chemical. No information is available on the skin-sensitising potential of benzene (IPCS 1993).

Exposure of humans to high levels of benzene vapor in air has resulted in dermal effects (erythema, edema, frank burns and necrosis). Eye irritation has been reported in workers occupationally exposed to high levels of benzene in air (ATSDR 1997).

Short- and long-term exposure

The most significant adverse effects of short- or long-term exposure to benzene are haematotoxicity, i.e., bone marrow suppression, immunotoxicity, genotoxicity and carcinogenicity (IPCS 1993, EU 1999, ATSDR 1997)). Other toxicological endpoints are neurotoxicity and developmental toxicity (IPCS 1993).

A number of clinical reports indicate that people vary greatly in their susceptibility to adverse health outcomes from benzene exposure. One reason for this could be inter-individual variation in metabolic activation and/or detoxification (EU 1999).

Haematotoxicity/immunotoxicity

Haematotoxicity and immunotoxicity have consistently been reported to be the most sensitive indicators of noncancer toxicity in humans and experimental animals. Chronic benzene exposure can result in bone marrow depression expressed as pancytopenia, aplastic anaemia, thrombocytopenia, granulocytopenia, lymphocytopenia, leucocytopenia and leukemia (for leukemia see *carcinogenicity*). Which effect is found will depend on the dose, length of exposure and the stage of stem cell development affected. The immunological manifestations of benzene toxicity are related to effects on the bone marrow, resulting in changes to both humoral and cellular acquired immunity (IPCS 1993).

In experimental animals, decreases in haematological cell counts and in bone marrow cellularity have been demonstrated in mice after inhalation of concentrations as low as 32 mg/m^3 for 25 weeks (6 h/day, 5 days/week). Rats are less sensitive than mice.

Oral administration of benzene to rats and mice to ≥25 mg/kg bw for 2 years resulted in leukopenia and lymphocytopenia in both rats and mice (NTP 1986, cited in ATSDR 1997). The LOAEL for haematological and immunological effects in mice and rats in this chronic study (25 mg/kg bw) is higher than the LOAEL found in a subacute study with mice. Mice exposed to 0, 8, 40 or 180 mg/kg bw in the drinking water for 4 weeks showed dose-dependent haematological effects (erythrocytopenia, leukocytopenia, lymphocytopenia and increased MCV) at all exposure levels. Haematological effects were accompanied by a biphasic response in several immunological tests, i.e. significantly increased responses at the low exposure level and significantly decreased responses at the mid and high doses. The (subacute) LOAEL for haematotoxicity and immunotoxicity in mice is 8 mg/kg bw (Hsieh et al. 1988, cited in ATSDR 1997 and US-EPA 1998b).

In humans, haematological and immunological effects of varying severity have occurred in workers occupationally exposed to high levels of benzene. As in experimental animals, the primary target organ of benzene is the bone marrow (IPCS 1993). Decreased red and white blood cell counts have been reported above median levels of approximately 120 mg/m^3. According to IPCS (1993) there is only weak evidence for bone marrow depression or aplastic anaemia in workers exposed to time-weighted-average (TWA) concentrations of 32 mg/m^3 or less for 10 years (IPCS 1993, EU 1999). In the well-conducted human occupational study of Rothman et al. (1996, cited in US-EPA 1998b) a median 8-hr TWA benzene concentration of 24 mg/m^3 was identified as a LOAEL for decreased absolute lymphocyte counts, considered the earliest and most sensitive indicator of benzene haematotoxicity (EU 1999). According to IPCS bone marrow depression or anaemia would not be expected to occur in workers exposed for 10 years to TWA benzene concentrations of 3.2 mg/m^3 or less (IPCS 1993, EU 1999). This is supported by recent observations by Collins et al. (1997, cited in EU 1999) showing no increase in the prevalence of lymphopenia among workers exposed to an 8-hr TWA benzene concentration of 1.76 mg/m^3 (EU 1999).

No data are available with respect to haematological and/or immunological effects in humans after oral exposure (ATSDR 1997).

Neurotoxicity

Benzene has been shown to produce neurotoxic effects in experimental animals and humans after short-term exposure to relatively high concentrations. Long-term neurotoxicity exposure studies in experimental studies are lacking (US-EPA 1998b). Chronic inhalation exposure has been associated with distal neuropathy in humans, difficulty in sleeping, and memory loss. Oral exposure results in symptoms similar to inhalation exposure (ATSDR 1997).

Developmental effects

There is some evidence of reproductive and developmental effects due to benzene exposure by inhalation from epidemiological studies, but data are not conclusive to link low exposure concentrations to these effects (US-EPA 1998b). There are no data on developmental effects in humans after oral exposure (ATSDR 1997).

After numerous studies in experimental animals there are no data showing that benzene is teratogenic even at maternally toxic doses (IPCS 1993). Embryotoxicity/fetotoxicity was, however, observed in rats and mice at levels as low as 65 mg/m^3 (WHO-WQG 1996). ATSDR reported (less serious) reproductive effects in male and female mice orally exposed to 25 mg/kg bw for 2 years (ATSDR 1997).

Genotoxicity

The genotoxicity of benzene has been studied extensively. Benzene appears to have a peculiar genotoxic profile. Benzene is hardly, if at all, able to induce gene mutations in *in vitro* testsystems, despite its potent clastogenic properties *in vitro* and *in vivo*. Several studies have demonstrated induction of both numerical and structural chromosomal aberrations, sister chromatid exchanges, and micronuclei in experimental animals and humans after *in vivo* benzene exposure (various routes of exposure). After short-term exposure to benzene levels of 3 to 30 mg/m^3 experimental animals showed chromosomal effects (Vermeire et al. 1993) and some studies in humans have demonstrated chromosomal effects at mean workplace exposures as low as 4 to 7 mg/m^3 (EU 1999).

There appears to be a lack of evidence for direct DNA interaction under normal *in vivo* conditions: despite the demonstrated ability of several benzene metabolites to form DNA adducts under *in vitro* conditions, DNA adduct formation in bone marrow cells in experimental animals *in vivo* could only be demonstrated under quite specific and very high exposure regimes (EU 1999, Health Council of the Netherlands 1997).

Carcinogenicity

Benzene is carcinogenic in mice and rats after both inhalation and oral exposure, producing malignant tumours at many sites. Benzene is a well-established human carcinogen and is classified by IARC in Group 1 (*sufficient evidence for carcinogenicity in humans*) (IARC 1982, 1987). Epidemiological studies and case studies provide clear evidence of a causal association between high exposures to benzene and leukemia, especially acute myelogenous (non-lymphocytic) leukemia (AML or ANLL) and, to a lesser extent, chronic nonlymphocytic leukemia as well as lymphocytic leukemia and multiple myeloma.

The so-called 'Pliofilm cohort' is the most thoroughly studied cohort and it is generally accepted as the best dataset to date for evaluating human cancer risks from exposure to benzene. A series of studies analysing the mortality of male workers exposed to relatively high levels of benzene (several hundreds of mg/m^3) at two rubber hydrochloride manufacturing locations in the USA demonstrated an increased risk of leukemia. The most recent Pliofilm study of Rinsky et al. (1987) demonstrated standard mortality ratios (SMRs) of 337 for leukemia (9 cases observed versus 2.7 expected) and 409 for multiple myeloma (4 cases observed versus 1 expected). A strong positive trend in leukemia mortality was obtained with increasing cumulative exposure. Within the four cumulative exposure groups there were 2, 2, 2, and 3 deaths with SMRs of 109, 322, 1186 and 6637, respectively (ATSDR 1997, IPCS 1993).

According to the Dutch Health Council the average exposure concentration in the Pliofilm cohort was 128 mg/m^3. Converting this value to a concentration applicable to the general population with continuous lifetime exposure results in a concentration of 6234 µg/m^3 (128 mg/m^3 × 10/75 years/lifetime × 5/7 days/week × 48/52 weeks/year × 10/18 inhalation volume/day) (cf. Health Council of the Netherlands 1997). In some risk assessment reports slightly different calculations were presented to convert the average exposure in the Pliofilm cohort to a continuous lifetime exposure of the general population. In the present report the calculation method of the Dutch Health Council has been adopted.

According to US-EPA (1998a) other studies failed to confirm an increased risk of multiple myeloma associated with exposure to benzene. Compared to other published studies the 'Pliofilm cohort' has the fewest reported co-exposures in the workplace to other potentially carcinogenic substances. It should also be noted, however, that exposure estimates for this cohort vary considerably, especially with respect to the exposure levels prior to 1950 (EU 1999, ATSDR 1997, US-EPA 1998a). Crump

(1994) calculated unit risks (UR, i.e., the additional lifetime cancer risk due to exposure to 1 $\mu g/m^{-3}$) for benzene using the most recently updated data for the Pliofilm cohort and a variety of models. Using multiplicative risk estimates and a cumulative exposure model, Crump (1994) arrived at a range of UR of 4.4×10^{-6} to 7.5×10^{-6} (EU 1999). Based on these calculations, the WHO derived in 1995 an UR of 6×10^{-6} (geometric mean) (WHO, in press).
A number of recent occupational studies tried to identify risks of benzene exposure in industries working according to present-day practices, with levels of benzene exposure much lower than those estimated for the Pliofilm cohort, namely 0.3-3.2 mg/m^3. Most studies – of which the large scale study of Wong and Raabe is of major importance – concluded that no increased risk of leukemia could be demonstrated at these levels. In their meta-analysis, Wong and Raabe (1995) combined all cohort studies of petroleum workers in the US and the UK. The study is particularly significant because of the size of the group (208000 workers) and the low benzene concentration (estimated average exposure was 0.7 mg/m^3) involved. Using national populations as controls, the SMR for ANLL was estimated to be 96 (148 cases of ANLL identified, where 155 cases were to be expected). Also, no increased risk of other types of leukaemia were observed (EU 1999). The Dutch Health Council converted the average exposure of this cohort (0.7 mg/m^3 for 10 years) to a concentration value applicable for the general population with continuous exposure during the entire lifetime. The resulting value was 35 $\mu g/m^3$ (Dutch Health Council 1997).
No data were available with respect to carcinogenic effects in humans after oral exposure (WHO-WQG 1996, ATSDR 1997).

Dose-response relationship

Because of the carcinogenic and genotoxic properties of benzene, most risk assessments employ non-threshold linear extrapolation methods to estimate risks associated with low exposure levels. However, with benzene the discussion is currently focused on the issue whether carcinogenic mechanisms and processes which occur at high occupational levels, e.g. in the Pliofilm cohort, are also occurring at the much lower environmental exposures. According to the EU Working group the following observations suggest that non-threshold linear extrapolations based on the Pliofilm data may overestimate risks at the substantially lower environmental levels (EU 1999).

1. The UR of 6×10^{-6} of the WHO does not seem to match the results of recent epidemiological studies. In the meta-analysis of Wong and Raabe (1995) 148 cases of ANLL were identified where 155 cases were to be expected. Based on the UR of leukemia (of which 80% is acute myeloid leukaemia) of the WHO, a clear additional number of ANLL cases should have been observed (above the 155 expected cases).
2. The carcinogenic effects observed at occupational levels of benzene may not solely be driven by genotoxic mechanisms: blood and bone marrow toxicity may be involved or even may be conditional. The high exposure conditions in the Pliofilm cohort were found to be associated with haematotoxicity. According to IPCS (1993) bone marrow depression or anaemia would not be expected to occur in workers exposed for 10 years to TWA benzene concentrations of 3.2 mg/m^3 or less. At these exposure levels so far no increased cancer risk has been observed. Also, in experimental animals carcinogenic exposures clearly exceeded those reported to be haematotoxic.
3. Benzene has an unusual genotoxic profile. It is hardly, if at all, able to induce gene mutations, despite its potent clastogenic potency. Benzene does not appear to interact directly with DNA under normal *in vivo* exposure conditions.

According to the EU Working group, one further complicating factor within the field of low dose risk assessment is the fact that at environmental exposure levels of benzene, other exogenous and endogenous sources appear to be major contributors of endogenous levels of phenol, catechol, hydroquinone and *trans*,*trans*-muconic acid (EU 1999). These metabolites (and some other metabolites as well) are thought to contribute to the genotoxic and haematotoxic effects of benzene (ATSDR 1997, Health Council of the Netherlands 1997). The latter finding will not be taken into account in the evaluation because at the moment it is not known how to incorporate these type of data in risk assessment.

3.1.3. LIMIT VALUES DERIVED BY (INTER)NATIONAL ORGANISATIONS BASED ON CARCINOGENIC EFFECTS OF BENZENE

Inhalation exposure

The WHO derived in 1995 a UR for leukaemia of 6×10^{-6} on the basis of risk calculations of Crump (1994). Based on this UR, air quality guidelines corresponding to excess lifetime cancer risks of 10^{-4}, 10^{-5} and 10^{-6} are 17, 1.7 and 0.17 μg/m^3, respectively (WHO, in press).
The EU Working group concluded that it is reasonable to assume that benzene-induced effects at low exposure levels differ quantitatively as well as qualitatively from those induced at high occupational exposures. It is not clear whether the underlying mechanism of benzene carcinogenicity is direct DNA interaction. In view of this uncertainty the EU Working group decided, on precautionary grounds, to hold on to a non-threshold extrapolation method. Though it was not possible to give a precise estimate of the risk associated with benzene it was possible to define a range within which that risk was likely to lie. The UR calculated by the WHO (6×10^{-6}) was considered to result in the highest plausible estimate of risk. The lowest UR which the EU Working group felt was likely to be plausible was in the order of 5×10^{-8}, an estimate which is consistent with the Dutch Health Council's analysis of the Wong and Raabe data. This range of URs means that an excess lifetime risk for leukemia of 10^{-6} is associated with annual average concentrations varying between (rounded) 0.2 and 20 μg/m^3 (EU 1999).
On the basis of the epidemiological data (Rinsky et al. 1981) and using a nonthreshold extrapolation method the RIVM concluded in 1987 that an ambient concentration of 0.12 μg/m^3 corresponds to an excess lifetime cancer risk of 10^{-6} (RIVM 1987). In 1994 the RIVM reviewed literature on benzene published since the Integrated Criteria Document of 1987. It was concluded that there was no reason to deviate from the risk assessment approach presented in 1987 (Hesse and Kroese 1994).
In 1987 the Dutch Health Council arrived at a recommended 'exposure limit' of 12 μg/m^3 (one hundred times greater than the figure derived by the RIVM at that time by using linear extrapolation) for an excess lifetime cancer risk of 10^{-6}. On the basis of the Wong and Raabe (1995) data the Health Council calculated in 1997 that continuous lifelong exposure to 35 μg/m^3 was not associated with an increased risk of leukemia. Because this figure is in agreement with the previously recommended exposure limit of 12 μg/m^3, it was decided to maintain this previously derived value (Health Council of the Netherlands 1997).
The US-EPA is currently in the process of reviewing the evidence relating to the risk of benzene. Their provisional conclusion is that there is insufficient evidence to reject a linear dose-response curve for benzene carcinogenicity at low-dose exposures and that the approach of using a linear dose-response curve is still to be recommended. The US-EPA gives a range of risk estimates for leukemia at 1 ppm [10]) from 7.1×10^{-3} to 2.5×10^{-2}. Converted this means: an excess lifetime risk for leukemia of 1×10^{-6} is associated with average exposures ranging from 0.13 to 0.45 μg/m^3 (US-EPA 1998a).

Oral exposure

As no data on the carcinogenic risk to humans following ingestion of benzene are available, the WHO derived in 1991/1996 a drinking-water guideline on the basis of epidemiological studies involving inhalation exposure. It was calculated that a drinking-water concentration of 1 μg/l was associated with an excess lifetime cancer risk of 10^{-6} (10 and 100 μg/l is associated with an excess cancer risk of 10^{-5} and 10^{-4}, respectively). Risk estimates were also carried out on the basis of a 2-year gavage study in rats and mice. Using the robust linear extrapolation model, the estimated range of concentrations in drinking water corresponding to an excess cancer risk of 10^{-6}, 10^{-5} and 10^{-4} are 1-8, 10-80 and 100-800 μg/l, respectively. These estimates were similar to estimates based on route-to-route extrapolation from epidemiological data, which formed the basis for the previous drinking-water guideline value of 10 μg/l associated with a 10^{-5} excess lifetime cancer risk. Therefore, guidelines values corresponding to excess lifetime cancer risks of 10^{-6}, 10^{-5} and 10^{-4} are 1, 10 and 100 μg/l, respectively (WHO-WQG 1996).

[10]) Conversion factors: 1 ppm = 3,24 mg/m^3; 1 mg/m^3 = 0.31 ppm.

3.1.4. LIMIT VALUES DERIVED BY (INTER)NATIONAL ORGANISATIONS BASED ON NON-CARCINOGENIC EFFECTS OF BENZENE

Inhalation exposure

US-EPA (1998b) selected the well-conducted human occupational study of Rothman et al. (1996) to derive a RfC. Rothman et al. (1996) identified a median 8-hr TWA benzene concentration of 24 mg/m^3 as a LOAEL for the sensitive immunological endpoint, decreased absolute lymphocyte counts. On the basis of the adjusted LOAEL of 8.6 mg/m^3 and using an uncertainty factor of 1000 (10 for intraspecies differences, 10 for the use of a LOAEL, 3 for extrapolation from subchronic to chronic exposure and 3 for database deficiencies), a RfC was calculated of (rounded) 9 $\mu g/m^3$ (US-EPA 1998b).
No chronic-duration MRL was derived by ATSDR because of a lack of appropriate data on effects of chronic exposure by inhalation to benzene (ATSDR 1997).
In a previous report on maximum permissible risk levels for human exposure to soil contaminants, published within the scope of the RIVM intervention value project, a TCL of 30 $\mu g/m^3$ was derived on the basis of a LOAEL of 30 mg/m^3 for haematological effects in experimental studies and using an uncertainty factor of 1000 (Vermeire 1993).

Oral exposure

In a preliminary draft the US-EPA (1998b) derived an oral RfD of 1 µg/kg bw/day by applying route-to-route extrapolation. In calculating the RfD, the oral equivalent dose rate of the inhalatory LOAEL (i.e. 1.2 mg/kg mg/day) was divided by an uncertainty factor of 1000 (10 for intraspecies differences, 10 for the use of a LOAEL, 3 for extrapolation from subchronic to chronic exposure and 3 for database deficiencies). No uncertainty factor was applied for route to route extrapolation because of benzene's well-documented target organ specificity irrespective of the route of administration. There is also little evidence of toxic effects in either the lungs or the gastrointestinal tract. No modifying factor is considered necessary (US-EPA 1998b). This RfD value is supported by an RfD value of 0.8 µg/kg bw/day, which is 1/10000 of the lowest available LOAEL for haematological effects in experimental studies (28-day drinking water study in mice of Hsieh et al. 1988) (US-EPA 1998b).
No chronic-duration oral MRL was derived by ATSDR because of a lack of appropriate data on effects of chronic exposure to benzene (ATSDR 1997).
In the previous report on maximum permissible risk levels for human exposure to soil contaminants, a TDI of 4.3 µg/kg bw a day was calculated from the inhalatory value of 30 $\mu g/m^3$ by applying route-to-route extrapolation (Vermeire 1993).

3.1.5. EVALUATION

The cancer risk estimates resulting from recent non-threshold extrapolations are presented below. The MPR has been defined as the excess lifetime cancer risk of 10^{-4} for continuous exposure during the entire lifetime. Except for the figures of the WHO (WHO, in press; WHO-WQG 1996), the presented excess lifetime cancer risks of 10^{-4} were calculated from the figures as presented in the reports cited (see the addendum for an elucidation on the derivation of these figures).
As can be seen in the table, the recent non-threshold evaluations result in cancer risk estimates for exposure by inhalation which are all in the same range. The lower limit of the cancer risk estimate of the EU Working Group, i.e. 20 $\mu g/m^3$, is chosen as the new MPR (derivation based on carcinogenic effects). In order to check whether this value would also protect the general population from the toxic (non-cancer) effects of benzene, this value is compared with outcomes of the threshold extrapolations.
In 1993 Vermeire et al. arrived at a TVA value of 30 $\mu g/m^3$ on the basis of haematological effects in experimental animals. Recent human data indicate that bone marrow depression or aplastic anaemia are not expected to occur in workers exposed for 10 years to 8-hr TWA benzene concentrations of 3.2 mg/m^3. From this estimated no-effect-level a TCA of 156 $\mu g/m^3$ can be calculated after compensating for intermittent exposure in the working area to continuous exposure for lifetime ($10/75 \times 5/7 \times 48/52 \times 10/18$) and applying the standard uncertainty factor for intraspecies variation (10).

Because this value is higher than the MPR of 20 µg/m^3 for carcinogenic effects, the latter value is considered to be protective for haematotoxic effects of benzene as well. Therefore the value of 20 µg/m^3 is proposed by the RIVM as the new MPR.
The value now proposed as MPR is somewhat higher than the RfC of 9 µg/m^3 derived by US-EPA. The US-EPA risk assessment report for benzene has not been finalised yet and will therefore not be taken into account (current status: preliminary draft). The same applies to the oral RfD derived by the US-EPA.
Applying route-to-route extrapolation, it can be calculated that the MPR of 20 µg/m^3 corresponds to an oral intake of 3.3 µg/kg bw (using the absorption levels as presented above: 50% absorption after exposure by inhalation and 100% absorption after oral exposure). By analogy with inhalation exposure, this value represents the MPR for carcinogenic effects, but it is considered to protect the general population against the toxic (non-cancer) effects of oral exposure to benzene as well.
Therefore 3.3 µg/kg bw is proposed as the new provisional oral MPR This oral MPR is provisional because it was derived using route-to-route extrapolation, a procedure involving considerable uncertainty.
Remark: the present evaluation replaces all previous benzene evaluations of the RIVM (RIVM 1987, RIVM 1994, Vermeire et al. 1991, Vermeire 1993).

Inhalation excess lifetime cancer risk of 10^{-4}		
WHO (in press)	17	µg/m^3
EU Working group (1999) [1)]	20-36 [2)]	µg/m^3
Health Council of the Netherlands (1997)	24 [2)]	µg/m^3
US-EPA (1998a)	13-45 [2)]	µg/m^3
Oral excess lifetime cancer risk of 10^{-4}		
WHO-WQG (1996)	100	µg/l (drinking water)

[1)] On the basis of the risk estimation developed by the Working Group the European Commission has adopted an air quality limit value for benzene of 5 µg/m^3 to be met on 1 January 2010 (EU 1998). This limit value has been proposed by the EU working group taking into account practical considerations; 5 µg/m^3 is as low as reasonably considered achievable in 2010. This value would implement the precautionary approach whilst making allowance for the practicalities of the timescale (EU 1999).
[2)] For an elucidation on how these figures were derived, see the addendum.

3.1.6. BACKGROUND EXPOSURE

Background exposure is greatly varying, depending on the actual living conditions: in cities the exposure is some orders of magnitude higher than in rural areas. Vermeire et al. (1991) estimated the background exposure of the Dutch population at 2.8-6.5 µg/kg bw/day (excluding smoking); smoking increases the background exposure by a factor of 2-6. IPCS (1993) and ATSDR (1997) estimated the background exposure for non-smokers at 3-25 and 2.5-20 µg/kg bw/day, respectively. Hence the current background exposure of the Dutch population (non-smokers) can be estimated at 2.5-6.5 µg/kg bw/day.

3.1.7. CONCLUSION

Compound	CR_{oral}	CR_{inhal}	Background exposure	Odour threshold
Benzene	3.3 *)	20	2.5 - 6.5	100×10^3

CR_{oral}: $1{:}10^{-4}$ excess lifetime cancer risk intake (oral exposure); µg/kg bw/day
CR_{inhal}: $1{:}10^{-4}$ excess lifetime cancer risk air (inhalation exposure); µg/m^3
Background exposure; µg/kg bw/day
Odour threshold; µg/m^3
*) Provisional MPR because it is derived via route-to-route extrapolation

3.1.8. REFERENCES

ATSDR (1997):
Toxicological Profile for Benzene (update).
U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances Disease Registry, Atlanta (Georgia), USA.

EU (1999):
Benzene: Risk Assessment - Chapter 2.
Commission of European Communities, Council Directive on Ambient Air Quality Assessment and Management, *Working group on Benzene*; January 1999.

EU (1998):
Commission proposes ambient air quality limit values for benzene and carbon monoxide.
Brussels, Belgium; 2 December 1998; IP/98/1049.

Health Council of the Netherlands (1997):
Committee on the evaluation of the carcinogenicity of chemical substances - Benzene.
Gezondheidsraad, Rijswijk, The Netherlands; publication no. 1997/29.

IARC (1982):
Some Industrial Chemicals and Dyestuffs.
IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Volume 29, IARC, Lyon, France.

IARC (1987) Overall Evaluations of Carcinogenicity: Un Updating of IARC Monographs volumes 1-42. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Supplement 7. WHO, IARC, Lyon, France.

IPCS (1993):
Environmental Health Criteria 150 – Benzene.
WHO International Programme of Chemical Safety, WHO, Geneva, Switzerland.

RIVM (1987):
Basisdocument Benzeen.
Slooff W et al. (eds.). Rapport nr. 758476001, betreft herziene versie van rapport nr. 840760002.

US-EPA (1998a):
Carcinogenic Effects of Benzene: An Update.
EPA/600/P-97/001F. U.S. Environmental Protection Agency, Washington DC, USA; April 1998.

US-EPA (1998b):
Draft Toxicological Review of Benzene (Noncancer Effects) (CAS No. 71-43-2). In Support of Summary Information on the Integrated Risk Information System (IRIS), US Environmental Protection Agency, Washington DC, USA; September 1998. *Preliminary Draft.*

Vermeire TG (1993):
Voorstel voor de humaan-toxicologische onderbouwing van C-(toetsings)waarden. Betreft addendum op rapport 725201005. RIVM rapportnr. 715801001.

Vermeire TG et al. (1991):
Voorstel voor de humaantoxicologische onderbouwing van C-(toetsings)-waarden. RIVM rapportnr. 725201005.

WHO-WQG (1996):
WHO Guidelines for Drinking-Water Quality, Second Edition – Volume 2: Health Criteria and Other Supporting Information, Chapter 14: Organic Constituents.
WHO, Geneva, Switzerland.

WHO (in press):
Air Quality Guidelines for Europe. WHO regional publications, European series.
WHO, Copenhagen, Denmark.

Addendum Derivation of the 10^{-4} inhalation excess lifetime cancer risk from the risk estimates as presented by the EU Working group (1999), Health Council of the Netherlands (1997), and US EPA (1998a)

As can be seen when comparing these figures with the 10^{-6} excess cancer risk levels, the 10^{-4} excess cancer risk levels cannot be derived by simply multiplying the upper and lower limit of the 10^{-6} range by a factor 100. The explanation why the upper limit of the 10^{-6} range should not be treated in that way is as follows.

EU Working group (1998a)
The excess lifetime cancer risk of 10^{-4} was calculated to be 20 - 36 μg/m^3.
The *lower* limit of this range (20 μg/m^3) was derived by simply multiplying the figure of 0.2 μg/m^3 (10^{-6} excess lifetime cancer risk presented by the EU Working group) by a factor of 100. The figure of 0.2 μg/m^3 was derived by linear extrapolation from the Pliofilm cohort SMR (cancer incidence) and thus the corresponding 10^{-4} excess lifetime cancer risk can be calculated this way.
The *upper* limit of this range (36 μg/m^3) as being associated with an excess lifetime cancer risk of 10^{-4} was extrapolated from the upper limit associated with an excess lifetime cancer risk of 10^{-6} as presented by the EU Working group (20 μg/m^3). Since the latter figure was not arrived at by linear etrapolation from any observed cancer incidence but was estimated based on the consideration of other possible curves - other curves than the linear one, i.e., sublinear curves - as plausible descriptions of the benzene cancer dose response in the low dose range, the corresponding 10^{-4} excess cancer risk can not be calculated by simply multiplying the figure for 10^{-6} excess cancer risk with a factor of 100. According to the EU the estimate of the 10^{-6} excess cancer risk being reached at 20 μg/m^3 is a point on a plausible sublinear dose response curve, the exact course of which at higher exposure levels is unknown (it is some sublinear curve that ends at the Pliofilm cancer incidence point). Departing from the figure of 20 μg/m^3 as being associated with an excess cancer risk of 10^{-6} the corresponding figure for an excess cancer risk of 10^{-4} can be estimated by interpolating linearly between this point on the dose response curve and the Pliofilm cancer incidence (this in itself is a worst case estimate). The appropriate Pliofilm cancer risk incidence to use in this procedure is the 95% upper confidence limit of the cancer risk. All considerations of the EU Working Group were ultimately based on the unit risk as estimated by the WHO (WHO, in press). Such a unit risk is a figure arrived at by extrapolating departing from the 95% upper confidence limit of the cancer risk. The lifetime continuous exposure level derived from the Pliofilm cohort was calculated to be 6,234 μg/m^3 *). In combination with the unit risk of the WHO this gives a 95% upper confidence limit of the cancer risk in the Pliofilm cohort of 0.037 ($6{,}234 \times 6 \times 10^{-6}$). Linear interpolation between the two points on the dose response curve, i.e., [20 μg/m^3, 10^{-6}] and [6234 μg/m^3, 0.037] gives an 10^{-4} excess cancer risk at 36 μg/m^3.

Health Council of the Netherlands
The figure of 24 μg/m^3 was derived from the estimate as presented by the Health Council of 12 μg/m^3 being associated with an excess lifetime cancer risk of 10^{-6}. The explanation as given above also applies to this estimate. The figure of 12 μg/m^3 was based on the unit risk estimate of the US-EPA of 8.3×10^{-6} as presented in the Dutch Integrated Criteria Document on Benzene (RIVM 1987) increased with a factor of 100. In combination with the unit risk of the US EPA the 95% upper confidence limit of the cancer risk in the Pliofilm cohort was calculated to be 0.052 {6,234 **) $\times$ 8.3×10^{-6}}. Linear interpolation between the two points on the dose response curve, i.e. [12 μg/m^3, 10^{-6}] and [6234 μg/m^3, 0.052] gives an 10^{-4} excess cancer risk at 24 μg/m^3.

US EPA (1988a)
The figures as presented in the US-EPA document represent estimates of the unit risk: the risk per ppm of exposure. When using these figures the benzene concentration associated with an excess lifetime cancer risk of 10^{-4} can be derived from the concentration associated with an excess lifetime cancer risk level of 10^{-6} by multiplying the latter with a factor of 100.

*) The average exposure in the Pliofilm cohort was 128 mg/m^3. Converting this value to a continuous lifetime exposure for the general population results in a value of 6234 µg/m^3 (128 mg/m^3 × 10/75 years/lifetime × 5/7 days/week × 48/52 weeks/year × 10/18 inhalation volume/day) (cf. Health Council of the Netherlands 1997).

**) It is noted that the Dutch Health Council also presents another calculation to convert the average exposure in the Pliofilm cohort to a continuous lifetime exposure of the general population, which results in a value of 4570 µg/m^3 (128 mg/m^3 × 10/70 years/lifetime × 5/7 days/week × 8/24 hours/day). In the present report the calculation method mentioned in note (*) has been adopted.

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3.2. ETHYLBENZENE

3.2.1. INTRODUCTION

Ethylbenzene was evaluated within the scope of the present project in 1991. For the inhalatory route a limit value (TCA) of 77 µg/m^3 was derived from a NOAEL of 430 mg/m^3 which was selected based on the results of several short-term inhalation studies in rats. The NOAEL was adjusted for exposure duration in the rat tests (back-calculation from 6 hours/day, 5 days/week to 24 hours/day, 7 days/week) and divided by an uncertainty factor (UF) of 1000 (10 for extrapolation from rats to humans, 10 for sensitive subgroups in the human population and 10 for using a short-term NOAEL instead of a chronic NOAEL). For the oral route a TDI was calculated based on a 6-month rat study from 1956 [11]). The NOAEL of 136 mg/kg bw/day was divided by a total UF of 1000 (10 for extrapolation from rats to humans, 10 for sensitive subgroups in the human population and 10 for limitations in the data base). This led to a TDI of 136 µg/kg bw/day (Vermeire et al. 1991).
The US-EPA derived its chronic limit values for the oral and inhalatory exposure routes in 1985 and 1990, respectively. In the same period that RIVM published its evaluation, FoBiG published a toxicological evaluation for ethylbenzene (FoBiG 1992). In 1993 RIVM again reviewed ethylbenzene within the scope of the project "Setting Integrated Environmental Quality Objectives" [12]). The oral toxicity was evaluated by the WHO in 1996 (scope: the WHO Guidelines for Drinking-Water Quality). More recent reviews that have appeared are those by IPCS (1996) and ATSDR (1999). Ethylbenzene has also been evaluated by IARC recently (IARC 2000).
Ethylbenzene is present in mineral oil and oil products. It is released to soil through the spilling of gasoline and other fuels. Additional sources of soil contamination are the disposal of solvents and household products such as paints, degreasing solvents and pesticides (ATSDR 1999).

3.2.2. TOXICOLOGY

Toxicokinetics

The primary route of metabolism of ethylbenzene is oxidation of the side chain of the molecule. In humans the main metabolites are mandelic acid and phenylglyoxylic acid, both of which are excreted in urine. Excretion of metabolites in urine is complete within 24 hours. Hydroxylation of the aromatic nucleus is a minor pathway only (WHO 1996, IPCS 1996).

Toxicity

The large majority of toxicity experiments with ethylbenzene was carried out using the inhalation route of dosing. Few oral data are available.
Short- and long-term toxicity
In acute and subacute inhalation studies in rats neurological effects were observed at exposure concentrations of ≥1720 mg/m^3 (≥400 ppm). In semichronic inhalation studies in rats and mice (mild) effects on liver and kidneys were seen. In the previous evaluation within the present scope (1991), a NOAEL of 430 mg/m^3 for these effects was used. The result of the 1992 13-week inhalation study in rats and mice carried out within the scope of the US-NTP showed a similar picture (compared to the earlier studies) with slight liver and kidney effects (weight increases without histopathological effects) at concentrations of ≥1075 mg/m^3 (≥250 ppm) (6 hours/day, 5 days/week) and an overall NOAEL of 430 mg/m^3 (100 ppm) (IPCS 1996, ATSDR 1999). The results of the 2-year NTP inhalation study in rats and mice were published in 1996. Test concentrations were 0, 322, 1075 and 3225 mg/m^3 (0, 75, 250 & 750 ppm) (6 hours/day, 5 days/week). The non-neoplastic findings in rats were limited to a slight reduction in growth in males at 3225 mg/m^3 (750 ppm) (with a marginal decrease in the other

[11]) Reference: Wolf et al. (1956).
[12]) This evaluation resulted in a preliminary Maximum Permissible Concentration (limit value for air) of 39 µg per m^3 based on a NOAEL of 220 mg/m^3 from a 16-week study in rats (duration-adjusted NOAEL is 39 mg/m^3).

male groups and all female groups) and an increase in incidence and severity of renal tubular hyperplasia, also at 3225 mg/m^3 only (males and females). High incidences of nephropathy were present in all treatment groups and in control rats (condition more severe in treated rats). No liver effects were seen (including negative blood clinical chemistry). In mice liver effects (eosinophilic foci, hypertrophy, necrosis) and lung effects (alveolar epithelial metaplasia) were found at 3225 mg/m^3. In addition, increased incidences thyroid follicular cell hyperplasia (males and females) were seen at 3225 mg/m^3 with a positive trend at the lower dose levels also. The incidence of pituitary gland hyperplasia was increased among the 1075 and 3225 mg/m^3 females (NTP 1996). The NOAEL for non-neoplastic effects from the rat study is 1075 mg/m^3. In mice the NOAEL for liver effects is 1075 mg/m^3; the biological significance of the slight effects on thyroid and pituitary gland seen at the lower test concentrations in mice cannot readily be established. In the semichronic NTP study in mice (in which very high test concentrations were used) similar effects were not detected. Clearly, the action of ethylbenzene on these endocrine organs (if any) is not a well established health effect, as is for instance the effect on the liver.

Carcinogenicity and genotoxicity

As already remarked above, ethylbenzene was evaluated recently by IARC. The available epidemiological evidence was limited. In two studies, one of which was of insufficient quality, no evidence for a carcinogenic action was found. IARC concluded there to be *inadequate evidence* in humans for the carcinogencity of ethylbenzene. The only oral bioassay available is a rat study by Maltoni et al. (1985). According to the summary of this study as presented by the IARC, in fact two experiments were carried out, one with a dose level of 800 mg/kg bw and one with a dose level of 500 mg/kg bw. At 800 mg/kg increased incidences were seen of nasal cavity tumours (kind of tumours not specified), neuroestesioepitheliomas and a borderline increase in oral cavity cancer. The value of this study is very limited due to poor study design and incomplete reporting of results (IARC 2000, IPCS 1996). In the 1996 NTP inhalation study in rats and mice (test concentrations 322, 1075 and 3225 mg/m^3) the neoplastic findings were as follows. In rats the incidence of renal tubular cell adenomas and carcinomas was increased in the males and females (in females adenomas only) of the 3225 mg/m^3 group. At the same dose level the incidence of interstitial cell adenomas in the testes was increased; the incidence of bilateral testes adenomas was increased also. In mice the incidences of lung alveolar/bronchiolar adenomas was increased among the 3225 mg/m^3 males and the incidence of hepatocellular adenomas was increased among the 3225 mg/m^3 females (NTP 1996). These results show that ethylbenzene induces tumours at very high dose levels. Accordingly IARC (2000) concluded there to be *sufficient evidence* in experimental animals for the carcinogenicity of ethylbenzene. For limit value derivation (MPR-derivation) the tumour findings must be interpreted in order to determine the mode of action of ethylbenzene in producing the tumours. The renal tubular adenomas and carcinomas in rats may be related to the nephropathy/nephrotoxicity also seen in these animals. Ethylbenzene possibly exacerbates the age-related nephropathy development or induces cytotoxicity in the renal epithelium leading to compensatory cell replication. As is also pointed out in the NTP report, the renal tumours in male rats appear not to be caused by α2μ-globulin accumulation since in the semichronic (NTP) studies no evidence for such an effect was found. Elucidating the mechanism of the formation of the rat renal tumours by ethylbenzene, a compound that is not genotoxic in vivo (see below for the genotoxicity information), is needed for a better understanding of the relevance of these tumours for human exposure situations. The rat testes tumours are of a type known to have a very high spontaneous incidence: nearly all male F334/N rats develop this kind of tumour during the latter part of their life. As the bioassay result shows, ethylbenzene increases this high spontaneous incidence. It is not known how the compound does this. The increased incidence of alveolar/bronchiolar adenomas in mice (seen in males only) was within the range of historical controls. The development of these tumours may be related to the alveolar epithelial hyperplasia also seen in the high dose male mice only. The liver tumours in mice (seen in females only and in the presence of liver toxicity) must be viewed against the known high spontaneous incidence of this kind of tumours in this particular strain of mice; increases in these tumours generally are not considered as clear evidence for a carcinogenic potential of the test compound.

Genotoxicity tests carried out with ethylbenzene (summarised in NTP 1996) indicate that the compound lacks genotoxic activity. *In vivo* studies (mouse peripheral blood micronucleus test, evaluation for micronuclei, DNA-adducts & breaks in human peripheral lymphocytes after occupational expo-

sure, Drosophila recessive lethal assay) were negative as were the Ames test (±S9), a test for gene mutations in yeast and a chromosome aberration assay in cultured Chinese hamster ovary cells. The only positive result was seen in mouse lymphoma cells *in vitro* (test for gene mutations) without activation (not tested with activation). This positive response was seen at a concentration that was highly toxic for the cells.
Based on the available evidence the conclusion is that the tumours most likely do not arise via a genotoxic mechanism. Consequently, in the limit value derivation for ethylbenzene a threshold approach is chosen.
Teratogenicity
Developmental toxicity of ethylbenzene was examined in inhalation studies in mice, rats and rabbits. The results of these studies were evaluated by the US-EPA in 1992. Some of the studies were reported very incompletely as a consequence of which no firm conclusions can be drawn from them. In rats the only effect on fetuses was an increased incidence of supernumerary ribs (at 1000 ppm) and/or extra ribs (at 100 and 1000 ppm). This effect is considered marginally adverse, even at the highest test concentration. In rabbits no clear effects were seen in one study. In another study, the result of which was reported incompletely, a reduction in number of fetuses due to abortion was seen; it is doubtful whether this effect is treatment-related (interpretation hampered by high maternal mortality and incomplete reporting of findings). US-EPA concluded that the NOEAL in both rats and rabbits was 430 mg/m^3 (100 ppm).
Reproductive toxicity
No reproduction studies with ethylbenzene are available. The only information for this endpoint is the negative result (no effect) in sperm or vaginal cytology in the NTP 13-week inhalation studies in rats and mice (IPCS 1996).

3.2.3. EVALUATION

The large majority of toxicity studies carried out with ethylbenzene are inhalation studies. Very few oral studies are available. Since the previous evaluation no new oral studies have been published. Thus, the TDI-derivation from 1991 is retained. However, an adjustment to this derivation is made by applying the exposure duration adjustment (back calculation from the NOAEL for 5 days/week to the value for 7 days/week). The adjusted NOAEL is 97 mg/kg bw/day. Applying a UF of 1000 (as was done in 1991) results in a TDI of 100 µg /kg bw/day.
For the inhalation route several data items that were previously lacking have now become available, most notably the NTP carcinogenicity study in rats and mice. Taking, as was previously done in 1991, the effect on the liver and kidneys as the critical effects, again a NOAEL of 430 mg/m^3 is used as the basis for deriving a TCA. This is the NOAEL from the 1992 semichronic NTP study in rats and mice. The NOAEL from the chronic NTP study (1075 mg/m^3) is higher than this semichronic NOAEL. In view of the now more extensive data base and the availability of chronic NOAELs, the previously used extra UF of 10 for the limitations in the data base is deleted. The NOAEL of 430 mg/m^3 was given 6 hours/day, 5 days /week. Back-calculation to continuous exposure (24 hours/day, 7 days/week) gives a concentration of 77 mg/m^3. Using a UF of 100 (10 for interspecies extrapolation and 10 for intraspecies extrapolation) a TCA of 770 µg/m^3 is calculated.

3.2.4. EVALUATIONS BY OTHER ORGANISATIONS

In 1985 US-EPA derived a RfD of 100 µg/kg bw/day based on an NOAEL of 136 mg/kg bw/day. This is the same NOAEL as used by the RIVM in its 1991 evaluation (study by Wolf et al. 1956). To the adjusted NOAEL of 97 mg/kg bw (corrected from 5 days/week to 7 days/week exposure) US-EPA applied a UF factor of 1000 (10 for intraspecies variation, 10 for interspecies variation and 10 for extrapolation of a subchronic NOAEL to a chronic NOAEL) (US-EPA 1985). This same derivation was adopted by the WHO in its Drinking-Water Guideline Programme (WHO 1996) leading to a TDI of 97.1 µg/kg bw/day.

In 1990 US-EPA derived an RfC of 1000 μg/m^3 based on NOAEL of 434 mg/m^3 (100 ppm) from rat and rabbit developmental studies [13]). In this derivation a UF of 300 (10 for sensitive individuals in the human population, 3 for interspecies conversion and 10 to adjust for the absence of multigenerational reproductive and chronic studies) to the NOAEL (no duration adjustment on NOAEL) (US-EPA 1990).
IPCS (1996) proposed a tentative guidance value of 22 mg/m^3 (5 ppm) for the general population. This value was derived from the NOAEL of 500 ppm (2150 mg/m^3) from the NTP semichronic inhalation study in rats. A UF of 100 was applied (10 for interspecies variation, 5 for intraspecies variation and 2 for lack of chronic toxicxity data).
ATSDR in its 1999 evaluation derived no chronic limit values (MRLs) for ethylbenzene because of lack of appropriate data. The only limit value derived was an inhalatory MRL for intermediate duration which was based on the NOAEL from a rat developmental study, the same NOAEL as used by the US-EPA for deriving its RfC. The MRL was 4.34 mg/m^3 (1 ppm) (ATSDR 1999).
The recent evaluation of the carcinogenicity data by the IARC led to classification in Group 2B (*possibly carcinogenic to humans*) (IARC 2000).

3.2.5. BACKGROUND EXPOSURE

The 1991 estimation of background exposure was primarily based on concentration measurements carried out in the Netherlands in the 1980s showing average concentrations of 0.87 to 2.8 μg/m^3 in urban areas. Exposure via air was estimated to result in a daily intake of 40 μg. Intake via food was roughly estimated to contribute 10 μg/day. Thus, a maximum background exposure of 1 μg/kg bw/day was estimated. Because no new data have been published in the intervening period, the 1991 value of 1 μg/kg bw/day is retained.

3.2.6. CONCLUSION

Compound	TDI	TCA	Background exposure
Ethylbenzene	100	770	1

TDI: tolerable daily intake (oral exposure); μg/kg bw/day
TCA: tolerable concentration in air (inhalation exposure); μg/m^3
Background exposure; μg/kg bw/day

3.2.7. REFERENCES

ATSDR (1999):
Toxicological Profile for Ethylbenzene (Update).
Agency of Toxic Substances and Disease Registry, U.S. Department of Health & Human Services, Public Health Service, Atlanta (GA), USA.

FoBiG (1992):
Basisdaten Toxikologie für umweltrelevante Stoffe zur Gefahrenbeurteilung bei Altlasten.
Umweltforschungsplan des Bundesministers für Umwelt, Naturschutz und Reaktorsicherheit, Forschungsbericht nr. 102 03 443/01 (two volumes: Zusammmenfassung & Zusammenfassung der Einzelberichte). Prepared by FoBiG Forschungs- und Beratungsinstitut Gefahrstoffe, Freiburg im Breisgau, Germany.

IARC (2000):
IARC Monographs on the evaluation of carcinogenic risks to humans – volume 77.
Some Industrial Chemicals. IARC, Lyon, France.

IPCS (1996):
Environmental Health Criteria 186 – Ethylbenzene.
International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland.

[13]) References: Andrew et al. (1981) and Hardin et al. (1981).

NTP (1996):
Toxicology and Carcinogenesis studies of ethylbenzene in F344/N rats and B6C3F1 mice (inhalation studies).
Technical Report Series no 466.

US-EPA (1985):
IRIS file on ethylbenzene. Oral RfD Assessment. Agency Work Group Review 05/20/1985.

US-EPA (1990):
IRIS file on ethylbenzene. Inhalation RfC Assessment. Agency Work Group Review 12/20/1990.

Vermeire TG, Apeldoorn ME van, Fouw JC de & Janssen PJCM (1991):
Voorstel voor de humaan-toxicologische onderbouwing van C-toetsingswaarden.
National Institute of Public Health and the Environment, RIVM-report no. 725201005, February 1991; Bilthoven, The Netherlands.

WHO (1996):
Guidelines for drinking-water quality – Second Edition Volume 2: Health criteria and other supporting information.
World Health Organization, Geneva, Switzerland (based on expert meetings held in 1991).

Wolf MA, Rowe VK, McCollister DD, Hollingsworth RL & Oyen F (1956):
Toxicological studies of certain alkylated benzenes and benzene.
Arch Ind Health 14, 387-398 *(cited in US-EPA 1992).*

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3.3. TOLUENE

3.3.1. INTRODUCTION

Toluene (methylbenzene) was evaluated within the scope of the present project in 1991. For the inhalatory route the limit value as originally proposed in the RIVM Criteria Document (1988) was adopted as the tolerable concentration in air (TCA). The 1988 limit value was 3 mg per m^3, based on a NOAEL of 150 mg/m^3 from the short-term inhalation study in human volunteers carried out by Andersen et al. (1983) [14]). For the oral route it was concluded that no adequate oral toxicity studies that could serve as the basis for a tolerable daily intake (TDI) were available for which reason recourse was taken to route-to-route extrapolation based on the inhalatory limit value. This led to a TDI of 0.43 mg per kg body weight (bw) per day (Vermeire et al. 1991, Slooff & Blokzijl 1988).
Relevant routes in case of soil contamination: oral and inhalation.

3.3.2. TOXICOLOGY

Toxicokinetics

Toluene toxicokinetics were studied in experimental animals and humans. Absorption after inhalation in humans was about 50%. Part of the amount absorbed is exhaled unchanged. After oral intake absorption is virtually complete. The primary site of toluene biotransformation is the liver where the compound is metabolised in the microsomes by the cytochrome P-450 enzymes. The major metabolic pathway of toluene is to benzyl alcohol, which is oxidised to benzyl aldehyde and subsequently to benzoic acid. Benzoic acid is converted to hippuric acid and excreted in urine. Conjugation with glucuronide is an alternative route (quantitatively less important) for this last biotransformation step. A small fraction of the toluene dose is converted to ortho-cresol and para-cresol (IARC 1999).

Toxicity

Since the 1991 evaluation several reviews of the toxicology of toluene have been published. The compound was evaluated by FoBiG (1992), Health Canada (CEPA 1994), and US-EPA (1992/1994). The WHO Air Quality Guideline for toluene was updated in 1995 (WHO 1995). ATSDR has published a new draft evaluation (ATSDR 1998). In addition, the compound is under review in the EU Existing Chemicals Programme, within which scope a draft Risk Assessment Report (RAR) [15]) has been prepared. As of yet, the latter document has not been finalised, this risk assessment still being in progress. Recently IARC published an update of its carcinogenicity evaluation for toluene (IARC 1999).
Genotoxicity and carcinogenicity
IARC recently re-evaluated the available evidence concerning the possible carcinogenicity of toluene. Eight studies in humans were identified in which toluene was an exposure, most of which studies were occupational studies. For two of the studies only, it was believed that toluene was the predominant exposure (in all other studies there being considerable concomitant exposures to other chemicals). Significant increases in the incidences of cancers of several sites were seen in several of the studies, but these results lacked consistency. Overall, IARC concluded that the results of these studies are not strong enough to conclude that there is an association between toluene exposure and cancer in humans. Evidence in experimental animals comprised two 2-year inhalation studies in rats and mice respectively (studies carried out by the NTP, results published in 1989) and a skin painting study in mice. None of the studies showed increases in tumour incidences.
Based on these data IARC concluded that there is *inadequate evidence* in humans of the carcinogenicity of toluene and *evidence suggesting lack of carcinogenicity* of toluene in experimental animals.

[14]) Conversion factors: 1 ppm = 3.75 mg/m^3, 1 mg/m^3 = 0.267 ppm.
[15]) In this EU programme draft RARs are prepared by contact points in the individual member states. The RAR for toluene was prepared by experts from Denmark. In the Netherlands the RIVM participates in this risk assessment programme.

Toluene was placed in IARC Group 3, which contains the compounds that are *not classifiable as to their carcinogenicity for humans* (IARC 1999).
Toluene genotoxicity has been studied in a large number of test systems. The weight of evidence indicates that the compound does not produce gene mutations or chromosome aberrations. The result of a recent in vitro experiment in human cells indicates that the compound may have the potential to produce chromosome breaks and numerical chromosome aberrations (CEPA 1994, IARC 1999).
Subchronic and chronic toxicity
The primary target organs for toluene toxicity is the central nervous system. This kind of effect has been observed both in humans and experimental animals. Liver effects were seen in experimental animals after oral dosing.
For the oral route relatively few toxicity studies have been performed (no human data available). No chronic toxicity study is available. Both the WHO (1991/1996) and the US-EPA (1994) used the 13-week studies carried out in rats and mice within the scope of the US National Toxicology Program for deriving limit values. In these studies toluene was administered by gavage on 5 days/week for 13 weeks. In rats the weights of liver and kidneys were increased at dose levels ≥625 mg/kg bw/day with histopathological changes in these organs being present at higher dose levels only. Neurotoxicity including body tremors and histopathological changes in the brain was seen at ≥1250 mg/kg bw/day. The NOAEL for this study is 312 mg/kg bw/day based on increased liver and kidney weights at 625 mg/kg bw/day [16]). In the mouse study neurological symptoms were seen at ≥2500 mg/kg bw/day. Liver weights were increased (without any histopathological changes being reported) at all dose levels including the lowest of 312 mg/kg bw/day (equivalent to 223 mg/kg bw/day on a 7-days/week basis). The latter level may be regarded as a marginal LOAEL. Based on this marginal LOAEL, WHO calculated a TDI of 223 µg/kg bw/day. In this derivation an uncertainty factor of 1000 was used (10 for interspecies extrapolation, 10 for intraspecies extrapolation and an extra factor of 10 for short duration of the study and use of a marginal LOAEL) (WHO 1991/1996).
For the inhalatory route a relatively large number of studies in humans was done. The effect on the CNS appears as the most sensitive effect. In two studies in industrial workers that were chronically exposed to toluene (without significant exposure to other chemicals) such effects have been detected. In the study by Foo et al. (1990) in female workers (n=30) in an electronic assembly plant in Singapore the mean exposure level was 332 mg/m^3 over a period of on average about 5 years. Statistically significant differences with controls were seen in 6 out of 8 neurobehavioural tests. The mean exposure level of 332 mg/m^3 was identified as a LOAEL and used by the US-EPA and the WHO in their limit value derivation. Another study is the one by Ørbaek & Nise (1989) in rotogravure printers (n=30) from two printing-shops in Sweden. Average toluene exposure concentrations were 43 mg/m^3 in one shop and 157 mg/m^3 in the other (exposure for 4-43 years; median 29). Past exposures of the subjects to toluene were higher than these levels. Effects observed were a higher incidence of self-reported complaints (including fatigue, short-term memory problems, concentration difficulties) and poorer performance in psychometric tests. Physical examination and clinical chemistry were normal. The level of 43 mg/m^3 has been identified as the LOAEL from this study and was the basis for the chronic limit value derivation as developed by the ATSDR (1998). CNS effects have also been observed in animals. For example, rat pups exposed to either 375 or 1875 mg/m^3 (1-28 days postnatal) showed histopathological changes in the hippocampus (WHO 1995).
As stated above, the inhalatory limit value as developed in the RIVM Criteria Document (1988) was based on the test by Andersen et al. (1983) who exposed human volunteers to toluene for 6 hours/day for 4 days. At 375 mg/m^3 increased incidence of neurological symptoms, poorer performance in neurological function tests and respiratory irritation were observed, effects which were not seen at 150 mg/m^3.
Other effects known to be produced by toluene after inhalation include damage to the auditory system (found in humans and animals), reduced semen quality in males (seen in rats), reduction of birth

[16]) As is also pointed out by US-EPA (1994), in view of the histopathologic changes in liver and kidneys at the higher dose levels (>625 mg/kg) the organ weight increases probably are toxicologically significant. This is in agreement with the conclusion of WHO (1991/1996) regarding this study. In the draft EU-RAR, however, it is suggested that the organ weight changes be interpreted as toxicologically non-significant signs of metabolic activity.

weight after exposure in utero (humans and rats) and developmental neurotoxicity (rats). These effects have been observed at dose levels clearly exceeding those that have been associated with neurotoxicity in toluene-exposed workers.
A further point that should be considered is toluene's odour. It is known that at sites contaminated with toluene its odour frequently produces a nuisance problem for people residing in the close vicinity of such a site. In the health evaluations within the scope the WHO air quality guideline programme it has been pointed out that the odour threshold for toluene of 1 mg/m^3 should not be exceeded (averaging time 30 minutes) (WHO 1987/1995). Similarly for the WHO drinking-water guideline for toluene of 700 μg/litre it was pointed out that this value is in excess of the lowest known odour threshold in water of 24 μg/litre (WHO 1991/1996).

3.3.3. EVALUATION

The available data indicate that toluene lacks carcinogenic activity; the compound does not produce mutations or structural chromosome aberrations. On the basis of these results the threshold approach is chosen in the limit value derivation for toluene.
No oral studies of more recent date being available, the WHO (1991/1996) TDI of 223 μg/kg bw/day is accepted as the oral limit value to be used within the present scope.
As to the basis for the inhalatory limit value that is to be derived within the present scope, the most obvious choice are the human data concerning neurological effects after chronic exposure to toluene, thus using either the LOAEL of 332 mg/m^3 from the study by Foo et al. (as was done by the US-EPA and the WHO) or the LOAEL of 43 mg/m^3 from the study by Ørbaek & Nise (as was done by the ATSDR). Existing chronic limit values derived based on these studies are 0.26 mg/m^3 (WHO, 1995), 0.4 mg/m^3 (US-EPA) and 1.5 mg/m^3 (ATSDR). The uncertainty in exposure levels from the pivotal studies (fluctuations in toluene concentrations during the exposure periods) [17]) is a factor that should be taken into consideration when judging these figures. In animal studies (in which exposure is controlled) neurotoxicity generally was found at higher concentrations, but in animal studies relatively subtle effects as those observed in humans cannot readily be detected. The minor difference between the limit values of the WHO and the US-EPA (these values are based on the same LOAEL), respectively, arises from a different way of extrapolating working-week exposure conditions to continous exposure conditions [18]). The value of 0.40 mg/m^3 is accepted as the new TCA to be used in the present scope. The odour threshold for toluene as given by the WHO (1995) is 1 mg/m^3 (30-minute average).

3.3.4. EVALUATIONS BY OTHER ORGANISATIONS

The US-EPA derivation of the RfD (≈ TDI) for toluene was carried out in 1994. A value of 0.2 mg/kg bw/day was derived from the NOAEL of 312 mg/kg bw/day form the 13-week rat gavage study carried out by the NTP (US-EPA, 1994). The US-EPA derived a RfC (≈ TCA) for toluene of 0.4 mg/m^3 based on the LOAEL of 332 mg/m^3 from the study by Foo et al. (1990). A LOAEL of 2261 mg/m^3 from the NTP inhalatory carcinogenicity study in rats (extrapolated to a *human equivalent concentration* of 79 mg/m^3) was used as supporting information (US-EPA, 1992).
In its recent draft Toxicological Profile for toluene the US-ATSDR published oral and inhalatory Minimal Risk Levels (MRLs) [19]) for toluene. An acute oral MRL of 0.8 mg/kg bw/day is proposed based on an LOAEL of 250 mg/kg bw/day from a single-dose gavage study in male rats with neuro-

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[17]) Exposure concentrations for the Ørbaek & Nise-study ranged from 4 to 413 mg/m^3 (in one printing-shop) and 23 to 542 mg/m^3 (in the other printing shop). For the study by Foo et al. the range was not reported, but from publications on examinations for other endpoints for the same cohort it can be concluded that exposure concentrations showed considerable fluctuations in this study as well.

[18]) WHO used a factor of 3 for back-calculating the 8-hour/day exposure concentration to 24 hours/day whereas US-EPA corrected using the ventilation volumes (10 m^3 for a working-day and 20 m^3 for a whole day).

[19]) Minimal Risk Levels are advisories intended to be used by health professionals for screening for the likelihood of health effects. MRLs are derived for both the oral and the inhalatory exposure route and for three exposure periods: acute MRLs are to be applied for exposures up to 14 days, intermediate MRLs for exposures lasting 14-365 days and chronic MRLs are intended for exposures lasting longer than one year.

toxicity (flash-evoked potential tests as a measure of nervous system visual information processing) as the critical effect [20]). An intermediate oral MRL of 0.02 mg/kg bw/day was derived based on a LOAEL of 5 mg/kg bw/day from a 28-day mouse drinking-water study with increased brain regional monoamine neurotransmitter levels as the critical effect [21]). No MRL for chronic duration was derived because of lack of an appropriate study. The proposed acute inhalatory MRL is 15 mg/m^3 based on the NOAEL of 150 mg/m^3 from the 4-day inhalatory volunteer study by Andersen et al. (1983). No intermediate inhalatory MRL was derived for toluene because of lack of data. The LOAEL of 43 mg/m^3 from the study by Ørbeck & Nise (1989) was the basis for the chronic inhalatory MRL. In this study a higher incidence of self-reported complaints (including fatigue, short-term memory problems, concentration difficulties) and poorer performance in psychometric tests were found in rotogravure printers. The chronic inhalatory MRL is 1.5 mg/m^3 (ATSDR 1998).

In its Drinking-Water Guidelines the WHO derived a TDI of 223 µg/kg bw/day based on the marginal LOAEL of 312 mg/kg bw/day from the 13-week study in mice carried out in 1989 within the scope of the US-NTP (WHO 1991/1996).

Health Canada derived a TDI of 1250 µg/kg bw/day based on the lowest LOAEL of 375 mg/m^3 from the available adequate inhalation bioassays (this was the LOAEL from the 1989/1990 NTP subchronic mouse inhalation study carried out by the NTP). In addition a Tolerable Daily Concentration of 3.75 mg/m^3 was derived based on the NOAEL of 150 mg/m^3 from the study of Andersen et al. (1983) (CEPA 1994).

FoBiG (1992) derived limit values to be incorporated in the German method for dealing with soil contamination. A short-term inhalatory limit value (for exposure periods up to 30 days) of 0.7 mg/m^3 was derived from a fetotoxicity study in rats [22]). The same value was proposed as the long-term inhalatory limit value. For the oral route the short-term limit value (for exposure periods up to 30 days) is 0.3 mg/kg bw/day based on a fetotoxicity study in mice [23]). The long-term oral limit value is 0.2 mg/kg bw/day based on hepatotoxicity and nephrotoxicity in rats after subchronic administration [24]) (FoBiG 1992).

3.3.5. BACKGROUND EXPOSURE

In the 1988 RIVM Criteria Document it was concluded there are only few data. The main source of general population background exposure is indoor air. For Canada toluene exposure has been determined via all routes. The estimated daily exposure was 9-18 µg/kg bw/day, about 70% of which was the result of exposure via indoor air (CEPA 1994). This figure agrees well with the estimate presented in Vermeire et al. (1991) of 10 µg/kg bw/day (based on measured concentrations in air in the Netherlands and assuming air to be the major exposure route). Based on these data the estimate of the general population background exposure to toluene as previously presented in Vermeire et al. (1991) is retained.

3.3.6. CONCLUSION

Compound	TDI	TCA	Background exposure	Odour threshold
Toluene	223	400	10	1000

TDI: tolerable daily intake (oral exposure); µg/kg bw/day
TCA: tolerable concentration in air (inhalation exposure); µg/m^3
Background exposure; µg/kg bw/day

Relevant routes in case of soil contamination: oral and inhalation.

[20]) Reference: Dyer et al. (1988)
[21]) Reference: Hsieh et al. (1990)
[22]) Reference: Hudak & Ungvary (1978)
[23]) Reference: Nawrot & Staples (1979)
[24]) References: Wolf et al. (1956) and NTP (1990).

3.3.7. REFERENCES

Andersen I, Lundqvist GR, Mølhave L et al. (1983):
Human response to controlled levels of toluene in six-hour exposures.
Scand J Work Environm Health 9, 405-418 *(cited in Slooff & Blokzijl 1988, and CEPA 1994).*

ATSDR (1998):
Toxicological Profile for Toluene – Draft for Public Comments.
Agency of Toxic Substances and Disease Registry, U.S. Department of Health & Human Services, Public Health Service; Atlanta (Georgia), USA.

CEPA (1994):
The Assessment of Risk to Human Health for Priority Substances under the Canadian Environmental Protection Act.
Environmental Carcinogenesis & Ecotoxicology Reviews – Part C of Journal of Environmental Science and Health (special issue) 12 (no. 2), 507-517.

FoBiG (1992):
Basisdaten Toxikologie für umweltrelevante Stoffe zur Gefahrenbeurteilung bei Altlasten. Umweltforschungsplan des Bundesministers für Umwelt, Naturschutz und Reaktorsicherheit, Forschungsbericht nr. 102 03 443/01 (two volumes: Zusammmenfassung & Zusammenfassung der Einzelberichte). Prepared by FoBiG Forschungs- und Beratungsinstitut Gefahrstoffe, Freiburg im Breisgau, Germany.

Foo S, Jeyaratnam J & Koh D (1990):
Chronic neurobehavioral effects of toluene.
Br J Ind Med 47, 480-484 *(cited in US-EPA 1992, and WHO 1995).*

IARC (1999):
IARC Monographs on the Evaluation of Carcinogenic Risks to Humans – Volume 71: Re-evaluation of some organic chemicals, hydrazine and hydrogen peroxide.
WHO International Agency for Research on Cancer, Lyon, France.

NTP (1989):
Toxicology and Carcinogenesis studies of toluene in F344/N rats and B6C3F1 mice.
Technical Report Series no 371 *(cited in US-EPA 1994, WHO 1991/1996, and IARC 1999).*

Ørbaek P & Nise G (1989):
Neurasthenic complaints and psychometric function of toluene-exposed rotogravure printers.
Am J Ind Med 16, 67-77 *(cited in ATSDR 1998).*

Slooff W & Blokzijl PJ, eds (1988):
Integrated Criteria Document Toluene.
RIVM-report no. 758473010 d.d. July 1988 (+ Appendix: Effects).

US-EPA (1992):
IRIS file on toluene. Inhalation RfC Assessment dated 08/01/1992.

US-EPA (1994):
IRIS file on toluene. Oral RfD Assessment dated 04/01/1994.

Vermeire TG, Apeldoorn ME van, Fouw JC de & Janssen PJCM (1991):
Voorstel voor de humaan-toxicologische onderbouwing van C-toetsingswaarden.
RIVM-rapport nr. 725201005, dated February 1991.

WHO (1987):
Air Quality Guidelines for Europe.
WHO Regional Publications, European Series No. 23; World Health Organization, Regional Office for Europe, Copenhagen, Denmark.

WHO (1991/1996):
Guidelines for drinking-water quality – Second Edition Volume 2: Health criteria and other supporting information.
World Health Organization, Geneva, Switzerland; 1996, based on expert meetings held in 1991.

WHO (1995):
WHO Updating and Revision of the Air Quality Guidelines for Europe: Meeting of the Working Group on Volatile Organic Compounds, Brussels, Belgium, 2-6 October, 1995. Draft Summary Report.

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Date: *21-12-1999*

3.4. XYLENES

3.4.1. INTRODUCTION

Xylenes (dimethylbenzene, three isomers: *ortho*-, *meta*- and *para*-) were evaluated within the scope of the present project in 1991. It was noted in this evaluation that the available data base for the xylenes was incomplete. For the inhalatory route a limit value of 54 μg/m^3 (tolerable concentration in air: TCA) was derived based on a LOAEL of 217 mg per m^3 taken from short-term inhalation studies in rats (critical effect: liver enzyme induction) [25]). A tentative oral tolerable daily intake (TDI) of 10 μg per kg body weight (bw) per day was derived based on a LOAEL of 200 mg/kg diet (equivalent with 10 mg/kg bw/day) from a short-term feeding study in rats by Bowers et al. (1982) in which ultrastructural liver changes were the critical effect. At this LOAEL the effect was considered marginal.
In the 1991 evaluation the three isomers of xylene were not distinguished and the limit values derived are applicable for each of the isomers or, where they occur together (as is often the case in practice), to the sum of the isomers (Vermeire et al. 1991).
Relevant routes in case of soil contamination: oral and inhalation.

3.4.2. TOXICOLOGY

Toxicokinetics

Xylene toxicokinetics were studied in experimental animals and humans. Absorption after inhalation in humans was about 60%. Limited data indicate that xylenes are absorbed well via the oral route (absorption percentage unknown). The primary site of biotransformation is the liver where the compound is converted by the microsomal enzymes (mixed function oxidases). The major metabolic pathway of xylene is to methylbenzyl alcohol, subsequently to methylbenzoic acid and finally to methylhippuric acid which is excreted in urine (ATSDR 1995, IPCS 1997).

Toxicity

Since the 1991 evaluation several reviews of the toxicology of xylenes have been published. The compound was evaluated by FoBiG in 1992. In 1993 RIVM evaluated the inhalatory toxicity of the xylenes within the scope of a project for developing (preliminary) limit values for volatile organic compounds in air (Rademaker et al. 1993, Rademaker & vd Plassche 1993). In addition, Health Canada (CEPA 1994), ATSDR (1995) and IPCS (1997) have published toxicological evaluations for xylenes in the period since 1991. Recently WHO/IARC has updated its carcinogenicity evaluation for xylenes (IARC 1999).
The three isomers of xylene (ortho, meta, para) are usually taken together in the toxicological evaluation an approach that implies that the toxicological properties of the different isomers are taken to be similar. Indeed, as is pointed out in IPCS (1997) some differences in action between the isomers are known to exist but there is no evidence that they (or mixtures of them) have totally different effects. Nevertheless in some instances (i.e., RIVM and ATSDR in their 1993 and 1995 evaluations, respectively) limit values for individual isomers have been derived. There is, however, limited justification for such an approach [26]) and the resulting differences in numerical values of the individual limit values probably reflect the differences in the data available for the different isomers rather than any real differences in toxicological properties.

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[25] Conversion factors: 1 ppm = 4.35 mg/m^3, 1 mg/m^3 = 0.23 ppm.

[26]) ATSDR for instance points out that *"both animal and human data suggest that mixed xylene, m-xylene, o-xylene, and p-xylene all produce similar effects"* while adding *"that individual isomers are not necessarily equal in potency with regard to a given effect"*.

Therefore, the approach of "pooled evaluation" of xylene-isomers, already used in 1991, is also chosen in the present evaluation [27]).

Genotoxicity and carcinogenicity

Xylene genotoxicity has been studied in a number of test systems, *in vitro* assays as well *in vivo* assays. Overall, the results indicate that xylene isomers are non-genotoxic (ATSDR 1995, IPCS 1997, IARC 1999).

IARC recently re-evaluated the available evidence concerning the possible carcinogenicity of xylenes. Four studies were identified in which humans were exposed to xylene; in none of these, however, xylene was the sole or predominant compound of exposure (in all studies there was considerable concomitant exposure to other chemicals). Significant increases in the incidences of cancers of several sites were seen in individual studies, but these results lacked consistency. Overall, IARC concluded that the results of these studies are not strong enough to conclude that there is an association between xylene exposure and cancer in humans.

Evidence in experimental animals comprised gavage studies with mixed xylenes in mice (one study) and rats (two studies). One of the rat studies was considered inadequate for evaluation. In rats nor mice increases in tumour incidence were seen (IARC, 1999).

Based on these data IARC concluded that there is *inadequate evidence* in humans for the carcinogenicity of xylene and *inadequate evidence* in experimental animals for the carcinogenicity of xylene. Xylene was placed in IARC Group 3 in which compounds are placed that are *not classifiable as to their carcinogenicity for humans*.

Subchronic and chronic toxicity

The main toxicological effects observed for xylene are induction of biotransformation enzymes in liver and other organs (seen in experimental animals), neurotoxicity (seen in animals and humans), and fetotoxicity and maternal toxicity (animals). In addition there are data indicating that the kidney is a target organ for xylene toxicity.

In short-term animal studies induction of biotransformation enzymes in different organs has been observed. Liver en kidney enzyme induction was observed at ≥217 mg/m^3 (NOAEL not determined) (WHO 1991/1996, IPCS 1997).

For the oral route relatively few toxicity studies have been performed (no human data available). No adequate chronic toxicity study is available. In the 1991 RIVM evaluation the LOAEL of 200 mg/kg diet (10 mg/kg bw/day) from the limited 6-month study in rats reported by Bowers et al. (1982) was used to derive a TDI. In this study only one dose level was studied and histopathology was incomplete. The toxicological significance of the effect in this study (ultrastructural liver changes) is questionable given the limited nature of this study and the absence of liver histopathological effects in the oral studies carried out under the US National Toxicology Program in which much higher dose levels were tested (up to 500 mg/kg bw/day in rats).

A study not included in the 1991 RIVM evaluation is the oral 90-day study in rats carried out by Condie et al. (1988) using both mixed xylenes and individual xylene isomers as test compounds. Dose levels of 150, 750 and 1500 mg/kg bw/day of mixed xylenes were administered by gavage once per day for 90 days. A number of effects were observed. Increased aggressiveness, mild polycythemia and leukocytosis, increased spleen weight, increased serum transaminase, and increased liver weight were seen at 750 and/or 1500 mg/kg bw/day. In addition in females the incidence of minimal chronic nephropathy was increased at all dose levels. In males renal hyaline droplet formation was present in all treatment groups. The latter effect is generally recognised as a species- and sex-specific effect in male rats and is not considered relevant for humans. Based on increased incidences of mild chronic nephropathy in female rats the LOAEL in this study is 150 mg/bw/day (Condie et al. 1988, ATSDR 1995).

The only chronic (2-year) studies available are the oral carcinogenicity studies in rats and mice carried out under the US-NTP in which two dose levels of mixed xylenes were administered by gavage on 5

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[27]) This implies that the approach of deriving preliminary MPCs (maximum permissible concentrations) for the individual xylene-isomers as presented in the RIVM report by Rademaker et al. (1993) is not followed in the present report. Note that the present evaluation updates this 1993 evaluation (that was done within the scope of the project *Setting Integrated Environmental Quality Objectives*, in Dutch *Integrale Normstelling Stoffen*, INS) as well as it updates the previous RIVM evaluation reported in Vermeire et al. (1991).

days/week for 103 weeks. Very few toxic effects were seen in these studies: in rats growth retardation at 500 mg bw/day without compound-related histological lesions (NOAEL 250 mg/kg bw/day) and in mice hyperactivity at 1000 mg/kg bw/day (NOAEL 500 mg/kg bw/day). The NOAEL of 250 mg/kg bw/day was used by the WHO in its derivation of a TDI within the scope of the drinking-water guidelines programme (WHO 1991/1996). The absence of renal effects (as observed in the study by Condie et al. with Sprague-Dawley rats) in the chronic NTP studies probably is due to a lower sensitivity of the strain of rats used in these latter studies (F344/N).
Studies on developmental toxicity are mainly inhalation studies. Two oral studies in mice showed fetotoxicity in combination with maternal toxicity and teratogenicity at high dose levels (LOAEL 640 mg/kg bw/day; NOAEL 255 mg/kg bw/day) (WHO 1991/1996).
For the inhalatory route more data are available. A number of short-term studies in human volunteers have been performed. From these studies the NOAEL for acute CNS effects was concluded to be 304 mg/m^3 (IPCS, 1997). In several industrial studies workers that were exposed to xylene for periods of several years were evaluated for neurological symptoms. Only in one study, reported by Uchida et al. (1993), exposure was predominantly to xylene (>70% of total exposure). In this study in Chinese factory workers (n=175) exposed to xylenes for an average period of 7 years reported an increase in subjective symptoms (including anxiety, forgetfulness, inability to concentrate). Xylene exposure was at a time-weighted geometric mean of 61 mg/m^3. This level has been identified as a chronic LOAEL by the ATSDR and used in the derivation of a chronic limit value (ATSDR 1995). Neurological effects have also been observed in experimental animals with exposures lasting several months. The LOAEL from these studies is 696 mg/m^3 (IPCS 1997).
For semichronic toxicity, teratogenicity and reproduction toxicity after inhalation only animal data are available (no usable human data). In teratogenicity studies in rats xylenes produced fetotoxicity (reduced fetal weight and delayed ossification) at doses at which there was no or only slight maternal toxicity. LOAEL-values of 500-2175 mg/m^3 have been reported for these effects (NOAEL not determined) (IPCS 1997). In a further study in rats, exposure to xylene during pregnancy resulted in behavioural impairment in the offspring, indicating an adverse effect on CNS development. The LOAEL for this study was 870 mg/m^3 (NOAEL not determined) (Hass & Jakobsen 1993, IPCS 1997).

3.4.3. EVALUATION

The available data base for xylenes does not show the compound to possess carcinogenic or genotoxic activity. Consequently a threshold approach is chosen in the limit value derivation for xylenes.
For the limit value derivation for the oral route the LOAEL of 150 mg kg bw/day of the study by Condie et al. (1988) is the most appropriate basis. The response observed at this LOAEL was marginal only and thus it is resonable to assume that the NOAEL will be only slightly lower than this LOAEL. In agreement with the derivation of the chronic reference value as developed by FoBiG (1992) this LOAEL is divided by an uncertainty factor (UF) of 1000, giving a TDI of 150 µg/kg bw/day. This UF includes an interspecies factor of 10, an intraspecies factor of 10, and an extra factor of 10 for limited duration of the pivotal study; because of the mild nature of the effect seen at the LOAEL in the pivotal study application of an extra factor the use of a LOAEL is not considered necessary. The alternative derivation as presented by the WHO (1991/1996), based on the NOAEL of 250 mg/kg from 2-year NTP study in rats, resulted in a TDI of 179 µg/kg bw, a value that is only slightly different from the value presented above. Thus, a TDI of 150 µg/kg bw/day is proposed as the new oral limit value to replace the value derived in 1991.
For the limit value derivation for the inhalation route the developmental neurotoxicity study by Hass & Jakobsen (1993) is considered the pivotal one, in agreement with the IPCS approach (1997). The LOAEL in this study (no NOAEL determined) was 870 mg/m^3. Applying a UF of 1000 (10×10×10 for interspecies and intraspecies differences, and the use of a LOAEL) results in a TCA of 0.87 mg/m^3.
The odour threshold for xylenes is about 4.35 mg/m^3 (1 ppm) (IPCS 1997).

3.4.4. EVALUATIONS BY OTHER ORGANISATIONS

The US-EPA derivation of the RfD (reference dose, ≈ TDI) for xylene dates back to 1987. A value of 2 mg/kg bw/day was derived from the NOAEL of 250 mg/kg bw/day of the 103-week gavage study carried out by the NTP (US-EPA 1987). No US-EPA RfC (reference concentration, ≈ TCA) is available for xylene.
In its Toxicological Profile for xylenes the US-ATSDR published oral and inhalatory Minimal Risk Levels (MRLs) [28]) for xylenes. As already noted above, ATSDR evaluated the xylene isomers separately and derived separate MRLs for the different isomers and for mixed xylenes. For p-xylene an acute oral MRL of 1 mg/kg bw/day is proposed based on a NOAEL of 125 mg/kg bw/day from a single-dose gavage study in male rats with neurotoxicity (flash-evoked potential tests as a measure of nervous system visual information processing) as the critical effect [29]). For other xylene-isomers no acute oral MRLs were derivable because of lack of appropriate data. An intermediate oral MRL of 0.2 mg/kg bw/day was derived for mixed xylenes based on the LOAEL of 150 mg/kg bw/day of the 90-day rat study by Condie et al. (1988). In addition, an intermediate oral MRL of 0.6 mg/kg bw/day was derived for m-xylene based on a LOAEL for hepatotoxicity in a 3.5-week study in rats [30]). No oral MRL for chronic duration was derived because of lack of an appropriate study. Inhalatory MRLs have been derived for mixed xylenes only. The proposed acute inhalatory MRL is 4.35 mg/m^3 based on the LOAEL of 435 mg/m^3 of an acute inhalatory volunteer study with increased reaction times as the critical effect [31]). An intermediate inhalatory MRL of 3.0 mg/m^3 was derived from the LOAEL of 870 mg/m^3 of the developmental neurotoxicity study by Hass & Jakobsen (1993). The LOAEL of 61 mg/m^3, being the time-weighted geometric mean concentration in the study of Uchida et al. (1993), was the basis for the chronic inhalatory MRL. In this study a higher incidence of reported subjective symptoms (including anxiety, short-term memory problems, concentration difficulties) was found. Haematology, serum biochemistry and urinalysis were unaffected in this study. The chronic inhalatory MRL is 0.44 mg/m^3 (ATSDR 1995).
Already mentioned in the text above is the TDI derivation as developed by the WHO in its Drinking-Water Guidelines. A TDI of 179 µg/kg bw/day was derived based on a NOAEL of 250 mg/kg bw/day of the 103-week NTP carcinogenicity study in rats (WHO 1991/1996).
Health Canada derived a TDI from an inhalation assay (inhalation was given preference because general population exposure was primarily via that route). Based on a LOAEL of 250 mg/m^3 from a teratogenicity study in rats [32]) with maternal and fetal toxicity as the critical effect, a TDI of 0.144 mg/kg bw/day was calculated. It was added that use of the appropriate NOAEL from the oral bioassays carried out with xylenes would lead to a higher TDI and the use of the value derived is protective as regards the results of the oral toxicity studies (CEPA 1994).
FoBiG (1992) derived limit values to be incorporated in the German method for dealing with soil contamination. A short-term inhalatory limit value (for exposure periods up to 30 days) of 0.3 mg/m^3 was derived from a fetotoxicity study in rats [33]). The same value was proposed as the long-term inhalatory limit value. For the oral route the short-term limit value (for exposure periods up to 30 days) is 1.25 mg/kg bw/day based on a neurotoxicity study in rats [34]) - the same study as used by the ATSDR for deriving its acute oral MRL for p-xylene. The long-term oral limit value is 0.15 mg/kg bw/day based on the LOAEL of 150 mg/kg bw/day for nephrotoxicity in rats after subchronic administration as seen in the study of Condie et al. (1988) (FoBiG 1992).
IPCS (1997) developed inhalatory guidance values for different toxicological endpoints. The developmental neurotoxicity as observed in rats being a serious and possibly long-lasting effect was consid-

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[28]) Minimal Risk Levels are advisories intended to be used by health professionals for screening for the likelihood of health effects. MRLs are derived for both the oral and the inhalatory exposure route and for three exposure periods: acute MRLs are to be applied for exposures up to 14 days, intermediate MRLs for exposures lasting 14-365 days and chronic MRLs are intended for exposures lasting longer than one year.
[29]) Reference: Dyer et al. (1988)
[30]) Reference: Elovaara et al. (1989)
[31]) Reference: Dudek et al. (1990)
[32]) Reference: Ungvary & Tatrai (1985)
[33]) Reference: Ungvary et al. (1980)
[34]) Reference: Dyer et al. (1988)

ered the critical effect for the derivation of a limit value for the general population [35]). Thus, from the LOAEL of 870 mg/m^3 of the developmental neurotoxicity study by Hass & Jakobsen (1993) a guidance value of 0.87 mg/m^3 was derived. A total UF of 1000 was applied, incorporating two factors of 10 for inter- and intraspecies extrapolation, respectively, and an extra factor of 10 for the use of a LOAEL instead of a NOAEL (IPCS 1997).

3.4.5. BACKGROUND EXPOSURE

IPCS reviewed all available data on environmental levels and human exposure, and concluded that inhalation is the main route of exposure. Total daily intake was estimated at 70 µg/person in rural areas and 2000 µg/person in urban areas. For a 70 kg person this is equal to 1 µg/kg bw/day and 28 µg/kg bw/day, respectively (IPCS 1997). CEPA (1994) estimated total xylene exposure for different age groups in the Canadian general population, which led to a maximum range of 5.7-9.0 µg/kg bw/day for the 5-11 year age group, again with inhalation being the major exposure route.
Based on these data background exposure is estimated to be 30 µg/kg bw/day (rounded value).

3.4.6. CONCLUSION

Compound	TDI	TCA	Background exposure	Odour threshold
Xylenes *(ortho-, meta- and para-)*	150	870	30	4×10^3

TDI: tolerable daily intake (oral exposure); µg/kg bw/day
TCA: tolerable concentration in air (inhalation exposure); µg/m^3
CRI: 1:10^{-4} excess lifetime cancer risk intake (oral exposure); µg/kg bw/day
CRA: 1:10^{-4} excess lifetime cancer risk air (inhalation exposure); µg/m^3
Background exposure; µg/kg bw/day
Odour threshold; µg/m^3

Relevant routes in case of soil contamination: oral and inhalation.

3.4.7. REFERENCES

ATSDR (1995):
Toxicological Profile for Xylenes (Update).
Agency of Toxic Substances and Disease Registry, U.S. Department of Health & Human Services, Public Health Service.

Bowers DE, Cannon MS & Jones DH (1982):
Ultrastructural changes in livers of young and aging rats exposed to methylated benzenes.
Am J Vet Res 43, 679-683 *(cited in Vermeire et al. 1991, and WHO 1991/1996).*

CEPA (1994):
The Assessment of Risk to Human Health for Priority Substances under the Canadian Environmental Protection Act.
Environmental Carcinogenesis & Ecotoxicology Reviews – Part C of Journal of Environmental Science and Health (special issue) 12 (no. 2), 545-556.

Condie LW, Hill JR & Borzelleca JF (1988):
Oral toxicity studies with xylene isomers and mixed xylenes.
Drug Chem Toxicol 11, 329-354.

[35]) The IPCS Working-Group attached little weight to the changes in metabolic enzymes and increased liver weight (present at levels exposure lower that the LOAEL for developmental neurotoxicity) stating that these could be taken as indication of metabolic adaptation rather than toxicity.

FoBiG (1992):
Basisdaten Toxikologie für umweltrelevante Stoffe zur Gefahrenbeurteilung bei Altlasten.
Umweltforschungsplan des Bundesministers für Umwelt, Naturschutz und Reaktorsicherheit, Forschungsbericht nr. 102 03 443/01 (two volumes: Zusammenfassung & Zusammenfassung der Einzelberichte). Prepared by FoBiG Forschungs- und Beratungsinstitut Gefahrstoffe, Freiburg im Breisgau, Germany.

Hass U & Jakobsen BM (1993):
Prenatal toxicity of xylene inhalation in the rat: a teratogenicity and postnatal study.
Pharmacol Toxicol 73, 20-23 *(cited in IPCS 1997).*

IARC (1999):
Monographs on the Evaluation of Carcinogenic Risks to Humans – Volume 71: Re-evaluation of some organic chemicals, hydrazine and hydrogen peroxide; pp. 1189-1208
WHO International Agency for Research on Cancer, Lyon, France.

IPCS (1997):
Environmental Health Criteria no. 190 – Xylenes.
International Programme of Chemical Safety, WHO, Geneva.

NTP (1986):
Toxicology and carcinogenesis studies of xylenes (mixed) (60% m-xylene, 14% p-xylene, 9% o-xylene, 17% ethylbenzene) (CAS no. 1330-20-7) in F344/N rats and B6C3F1 mice (gavage studies).
US National Toxicology Program. NTP Technical Report series no. 327 *(cited in WHO 1991/1996).*

Uchida Y, Nakatsuka H, Ukai H, Watanabe T et al. (1993);
Symptoms and signs in workers exposed predominantly to xylene.
Int Arch Occupat Environm Hlth 64, 597-605.

Rademaker BC, Guinée EP & Plassche EJ van de (1993):
The derivation of preliminary maximum permissible concentrations of volatile compounds in air.
RIVM-report no. 679101 009, dated July 1993.

Rademaker BC & Plassche EJ van de (1993):
The derivation of maximum permissible concentrations of volatile compounds in air.
RIVM-report no. 679101 010, dated October 1993.

US-EPA (1987):
IRIS file on xylenes.
Oral RfD Assessment dated 09/30/1987.

Vermeire TG, Apeldoorn ME van, Fouw JC de & Janssen PJCM (1991): Voorstel voor de humaantoxicologische onderbouwing van C-toetsingswaarden.
RIVM-rapport nr. 725201005, dated February 1991.

WHO (1991/1996):
Guidelines for drinking-water quality – Second Edition Volume 2: Health criteria and other supporting information. WHO, Geneva, 1996 (based on expert meetings held in 1991).

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Date: *21-12-1999*

3.5. STYRENE

3.5.1. INTRODUCTION

Styrene was evaluated within the scope of this project by Vermeire et al. in 1991. Decreased growth was noticed with a NOAEL of 7.7 mg/kg bw/day in an chronic oral study, in which male rats were exposed to styrene in drinking water. A TDI (tolerable daily intake) of 77 µg/kg bw/day was derived for oral intake using a UF (uncertainty factor) of 100 for intra- and interspecies extrapolation.
A TCA of 800 µg/m^3 was derived from a marginal effect concentration of 84 mg/m^3 for occupationally exposed humans. A UF of 100 was used for extrapolation to continuous exposure of the general population.
For the update additional literature, published since 1991, was reviewed. This included a review of ATSDR (1992), an IARC monograph (1994), WHO (1996a, 1996b), and a report of the Health Council of The Netherlands (1998).
Styrene is a man-made chemical. Sometimes it is referred to as vinylbenzene, phenylethene or styrol. It is a volatile compound [36]). The background natural occurrence in soil is negligible, but according to IARC (1994) low concentrations of natural occurring styrene, synthesised in plants, can be found.
Styrene is manufactured by the chemical industry on numerous sites and in substantial quantities. It is predominantly used for the production of plastics and resins. The plastics are used in various consumer products, such as electrical materials and insulation, and food packaging.
Styrene is emitted into the atmosphere by the industrial facilities, and from residues of consumer products. Industrial effluents emit into surface waters. Soil may become contaminated by spills and by industrial waste disposal. Consumer products may lead to residues of styrene in household waste disposal.

3.5.2. TOXICOLOGY

Toxicokinetics

Absorption
There are no data regarding absorption after oral exposure of humans to styrene. In laboratory animals it was demonstrated that the gastrointestinal absorption of styrene is rapid and complete when administered in an aqueous solution.
The uptake in humans following inhalation exposure is very rapid. At low doses the uptake ranges from 60 to 70%.
In studies with humans the percutaneous absorption of styrene vapours is less than 2%. Dermal absorption from liquid styrene is also very low, in the order of 1 µg/cm^2/min (ATSDR 1992).
Distribution
Data from humans and experimental animals demonstrate that highest concentrations of styrene are found in the adipose tissue, both after oral and inhalation exposure. Also in the fat parts of blood and organs increased concentrations were reported. The elimination half-life for styrene from adipose tissue of humans is reported to be 24 to 96 hours. Styrene was found to distribute to foetuses of rats after inhalation exposure of the dams, but concentrations in the foetuses were much lower than in maternal tissues.
Metabolism
Most styrene is metabolised by the microsomal P450 mono-oxygenase to styrene oxide (styrene-7,8-epoxide). A minor part of styrene is transformed into phenylethanol and vinylphenol. The latter compound can be detected in the urine of exposed workers. Styrene oxide is biotransformed in styrene glycol and finally to hippuric acid and phenylglyoxylic acid. At low doses the metabolism in humans is very rapid. Pharmacokinetic model calculations, however, show that styrene metabolism becomes saturated at inhaled levels above 200 ppm (860 mg/m^3) in humans.
Excretion

[36]) Conversion factors: 1 mg/m^3 = 0.23 ppm; 1 ppm = 4.33 mg/m^3.

Styrene is almost totally excreted as urinary metabolites both in humans and animals. After inhalation only 2% was found to be exhaled as unchanged styrene.

Biomarkers

Styrene in expired air is not a good marker for exposure, as no correlations with the exposure rate have been found. Blood levels are more suitable for exposure assessments. Levels of metabolites in urine are also good markers for styrene exposure of humans, but there are large individual variations in the rate of metabolism. Reference values have been reported in the literature for styrene in exhaled air and in blood, and for urinary metabolites.

Toxicity

Acute poisoning

There are no documents regarding death of humans after accidental or occupational exposure to styrene. Lethal doses for inhalation and oral exposure of laboratory animals are high, with no specific critical effects or cause of death reported.

Genotoxicity and carcinogenicity

IARC (1994) extensively reviewed the results of studies on the genotoxic properties of styrene. Styrene induced mutations in human lymphocytes, and caused DNA strand breaks and chromosome aberrations. It did, however, not induce DNA adducts in human peripheral granulocytes or Hb-adducts, and it was negative in various tests such as the DNA repair test and the micronucleus test.

Styrene can be metabolised to styrene oxide, and styrene oxide is probably a genotoxic carcinogen. In humans exposed to styrene, however, the styrene oxide metabolite can only be found at very low concentrations. It was concluded by ATSDR (1992) that humans have a very high capacity to metabolise styrene oxide into styrene glycol, since human epoxide hydrolase has a high affinity for styrene oxide. Consequently, styrene oxide concentrations in humans will be very low, thus indicating a very low carcinogenic activity for styrene in humans.

In experimental animals carcinogenic action of styrene is found after both oral and inhalation exposure. An oral LOAEL of 300 mg/kg bw/day is reported in mice for lung tumours as the critical effect. For inhalation a LOAEC of 430 mg/m^3 (100 ppm) is reported in rats. Here mammary tumours were observed (ATSDR 1992).

There are case-control studies with occupational exposed humans investigating styrene exposure and cancer incidence. The results of the different studies are inconclusive; no clear dose response relationships could be established, and diverse types of tumours have been found in the different studies. The incidence ratio of tumours was not or only marginally statistically significant increased. WHO (1996b) concluded that the genotoxic effects are not be considered as critical endpoints for the development of a guideline, in view of the equivocal evidence of carcinogenicity for styrene. On the basis of the data the Health Council of The Netherlands (1998) concluded that the evidence for carcinogenic activity of styrene in humans is weak and inconsistent.

Subchronic and chronic toxicity

There is no information of toxic effects after oral exposure of humans to styrene.

From the available data in various experimental animals the LOAEL is 200 mg/kg bw/day for hepatic effects after subchronic oral exposure. In a 2 years three-generation study rats were exposed to 125 mg/L (equivalent to 7.7 mg/kg bw/day for males and 12 mg/kg bw/day for females) and 250 mg/L in drinking water (equivalent to 14 mg/kg bw/day for males and 21 mg/kg bw/day for females). The body weight of the females was affected at the dose of 21 mg/kg bw/day, but in both males and females organ systems and reproduction were not affected (Van Apeldoorn et al. 1986). So the NOAEL for systemic toxicity was 12 mg/kg bw/day for females, and 14 mg/kg bw/day for males.

After chronic inhalation exposure in occupational exposed humans low dose effects reported concerned liver weight and serum enzyme levels, and neurological effects. A LOAEC for decreased verbal learning skills of 107 mg/m^3 (25 ppm) was reported for intermittent occupational exposure of humans for an average period of 8.6 years. Other neurological effects on visuomotor accuracy and psychomotor performance were observed at concentrations of 235 mg/m^3 (55 ppm) (ATSDR 1992). Also in experimental animals impairments of the neurological development is among the most sensitive effects. In the offspring of rats exposed to 260 mg/m^3 (60 ppm) effects on biochemical parameters in the brain and behaviour were reported (WHO 1996b).

Data of dermal exposure to styrene are very limited. In experimental animals it was demonstrated that dermal effects occur only at very high doses (i.e., grams per kg body weight). Tumours of the skin are not induced (ATSDR 1992).

3.5.3. EVALUATION

From the available data it must be concluded that styrene is not a genotoxic compound. Its carcinogenic potential is related to the metabolite styrene oxide. Concentrations of this metabolite in humans, however, are very low thanks to rapid biotransformation to styrene glycol. WHO (1996b) concluded therefore that the genotoxic effects are not be considered as critical endpoints for the development of a guideline, and the Health Council of The Netherlands (1998) concluded that the evidence for carcinogenic activity of styrene in humans is weak and inconsistent. A TDI can therefore be derived on the basis of a NOAEL and UFs.
A NOAEL of 12 mg/kg bw/day was found for chronic exposure of rats. Using a UF of 100 for intra- and interspecies variation a TDI of 120 μg/kg bw/day is derived.
Minor effects on the central neural system was noticed in humans who were occupationally exposed to 107 mg/m^3 of styrene for a period of several years. This equals a continuous inhalation exposure of 26 mg/m^3. For the extrapolation of a marginal affect to the NOAEC a UF of 3 is applied, and a further UF of 10 is applied for intra-human variation. This results in a TCA of 900 μg/m^3.

3.5.4. EVALUATION OF OTHER ORGANISATIONS

The carcinogenic action of styrene was classified by the IARC (1994) in group 2B: *possibly carcinogenic to humans*. It was concluded that there is inadequate evidence for the carcinogenicity in humans, and limited evidence in experimental animals. The Health Council of The Netherlands (1998) evaluated the carcinogenic action of styrene and classified as a "suspected human carcinogen".
US-EPA derived a RfD of 200 μg/kg bw/day. This value is based on a NOAEL for effects on the haematology and the liver with a LOAEL of 200 mg/kg bw/day in a subchronic oral dog study. A UF of 100 was applied for interspecies extrapolation and intrahuman variability, and an additional UF of 10 was used to extrapolate from subchronic to chronic effects (IRIS, revised 1990).
For inhalation exposure a RfC was derived of 1 mg/m^3. It was based on an LOAEC of 25 ppm (10.8 mg/m^3) for effects on the central neural system in humans (corrected for continuous exposure). A UF of 3 was used for inadequacy of the database, 3 for intrahuman variability, and 3 for extrapolation to chronic exposure (IRIS, revised 1993).
ATDSR derived a MRL of 200 μg/kg bw/day for intermediate oral exposure. The value was derived from a LOAEL of 200 mg/kg bw/day for hepatic effects (changes in enzyme activities) in rats, with a UF of 100 for interspecies extrapolation and intrahuman variability, and an addiotional factor of 10 for extrapolation from subchronic effects.
For chronic inhalation exposure a MRL of 0.06 ppm (260 μg/m^3) was derived, based on a LOAEC of 25 ppm (107 mg/m^3) for effects on the central nervous system in humans, adjusted for continuous exposure, with a UF of 100 for the use of a LOAEC and human variability (ATDSR 1992).
WHO derived a TDI of 7.7 μg/kg bw/day, based on an oral NOAEL of 7.7 mg/kg bw/day for reduced body weight of rats. This was based on the 2-year generation study with rats that were exposed to 125 mg/L in drinking water. A UF of 100 was used for interspecies extrapolation and intrahuman variability, and an additional factor of 10 was applied for carcinogenicity and genotoxicity of the styrene oxide metabolite. From this a Drinking Water Quality Guideline of 20 μg/L was derived. In addition it was noted that this value is equal to the lowest observed odour threshold for styrene in water (WHO 1996a).
WHO (1996b) derived a guideline for inhalation exposure of 0.26 mg/m^3 for styrene, based on subtle effects in humans such as reductions in visuomotor accuracy and verbal learning skills, and subclinical effects on colour vision by concentrations of 108 to 217 mg/m^3. This value was adjusted for continuous exposure; a UF of 10 was used for intrahuman variation, and an additional factor of 10 was applied to extrapolate to a NOAEC. It was noted, however, that the air quality guideline is 70 μg/m^3, based on the odour detection threshold level.

3.5.5. BACKGROUND EXPOSURE

Relevant sources for background exposure of the general population are inhalation of air and intake of foods that are contaminated with styrene from packaging materials. According to Vermeire et al. (1991) the total daily intake is 0.6 µg/kg bw/day. Food was estimated to be responsible for 0.1 µg/kg bw/day. According to IPCS (1983), however, the styrene concentration in foods is 3 to 4 orders of magnitude lower than the package, and it was concluded that the exposure from food is minimal. Consequently the intake in The Netherlands is estimated to be 0.5 µg/kg bw/day.

Odour threshold

According to ATSDR (1992) styrene in air has a sweet and sharp odour, and it reports an odour threshold of perception in air of 1.36 mg/m^3. According to WHO (1996a), however, the odour threshold is 0.1 mg/m^3. The latter value is also reported by Vermeire et al. (1991). WHO (1996b) reported that styrene has a pungent odour with a detection threshold of 70 µg/m^3, and a recognition at concentrations 3 to 4 times the threshold of detection.

3.5.6. CONCLUSION

Compound	TDI	TCA	Background exposure	Odour threshold
Styrene	120	900	0.5	100

TDI: tolerable daily intake (oral exposure); µg/kg bw/day
TCA: tolerable concentration in air (inhalation exposure); µg/m^3
Background exposure; µg/kg bw/day
Odour threshold; µg/m^3

3.5.7. REFERENCES

ATSDR (1992):
Toxicological Profile for Styrene.
Agency for Toxic Substances and Disease Registry, US Public Health Service, Atlanta (GA), USA.

Dutch Health Council (1998):
Styrene, evaluation of the carcinogenicity and genotoxicity.
Report 1998/07 WGD, Rijswijk, The Netherlands.

IPCS (1983):
Styrene, Environmental Health Criteria 26.

IARC (1994):
Some industrial chemicals. IARC Monographs on the evaluation of carcinogenic risks to humans. Volume 60.
International Agency for Research on Cancer, Lyon, France.

Van Apeldoorn ME et al. (1986):
Criteriadocument Styreen.
National Institute of Public Health and the Environment, RIVM-report no. 738513003, July 1986; Bilthoven, The Netherlands.

Vermeire TG, Apeldoorn ME van, Fouw JC de & Janssen PJCM (1991):
Voorstel voor de humaan-toxicologische onderbouwing van C-toetsingswaarden.
National Institute of Public Health and the Environment, RIVM-report no. 725201005, February 1991; Bilthoven, The Netherlands.

WHO (1996a):
Guidelines for drinking-water quality, 2nd ed. volume 2, Health criteria and other supporting information.
World Health Organization, Geneva, Switzerland.

WHO (1996b):
Updating and revision of the air quality guidelines for Europe. Report of a working group on volatile compounds, Brussels 2-6 October 1995.
WHO Regional Office for Europe, Copenhagen, Denmark.

Profile compilation: *R.M.C. Theelen*
Profile review: *A.J. Baars*
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3.6. PHENOL

3.6.1. INTRODUCTION

Phenol was evaluated within the scope of this project by Vermeire et al in 1991. A NOAEL of 60 mg/kg bw/day was identified for effects on the body weight of the offspring of rats. A UF (uncertainty factor) of 1000 was used to derive a TDI (tolerable daily intake) of 60 µg/kg bw/day for oral intake.
It was stated that available data were inappropriate to set a NOAEC for inhalation exposure. The odour threshold for humans was proposed as the TCA (tolerable concentration in air), leading to a TCA of 100 µg/m^3.
For the update additional literature, published since 1991, was reviewed. This included reviews of IPCS (1994) and ATSDR (1998).
Phenol is not an abundant naturally occurring chemical in soil. It can be formed during natural decomposition of organic materials, but the natural background concentration in soil will be very low. Phenol is obtained by distillation from petroleum, or synthesised from cumene or toluene. The chemical industry will be a major source of phenol atmospheric emissions. Exhaust gases of cars, cigarettes, incinerators and home fires are known as minor sources of emissions.
Phenol is used as a basic chemical for the synthesis of a number of materials like resins, bisphenol A, caprolactam and chlorophenols (including pentachlorophenol). Phenol is also used in medicinal preparations, and in the production of paints, rubber, ink and dyes (IPCS 1994, ATSDR 1998).
It can be expected that phenol might occur in industrial and in household spills, and waste disposal. Besides aerial emissions of the various sources can contribute to the environmental load. Based on the partition coefficient it can be predicted that phenol is very mobile in soil, and will leach to the ground water. Consequently phenol concentrations will be detectable in top-soil but also in deeper soil layers, and the ground water. Due to its volatility [37]) human exposure to phenol from contaminated soils and ground water can also occur by inhalation of vapours.

3.6.2. TOXICOLOGY

Toxicokinetics

Absorption
Results of human studies indicate that phenol is readily absorbed after oral and inhalation exposure. Retention reported after inhalation vary between 60 and 88%. Tracer studies showed that in humans following oral intake about 90% is absorbed.
Studies with humans exposed to phenol in air have demonstrated that percutaneous absorption of vapours is also rather high; it was estimated to be about half of the absorption through the lungs. Studies with high doses have shown that phenol concentrations may destroy the diffusion barrier normally provided by the skin, thus substantially increasing the percutaneous permeability.
Distribution
According to ATSDR (1998) there are no data on the distribution of phenol after inhalation, oral, or dermal exposure of humans. In laboratory animals the dose of phenol is fairly uniformly distributed in all tissues and organs. More than 90% of the administered dose is eliminated within 24 hours.
Metabolism
Prior to excretion, phenol is largely metabolised, primarily by cytochrome P450 2E1 into 1,2- and 1,4-dihydroxybenzenes, and 1,2,4-trihydroxybenzenes. The hydroxybenzenes in turn are conjugated with sulphate or glucuronide. (ATSDR 1998).
Excretion
Phenol and its conjugated metabolites are rapidly excreted in the urine, both after oral, inhalation as well as dermal exposure. The highest concentration of the parent compound is found in the urine about 2 hours after exposure.
For inhalation by humans a half-life of 3.5 hours is reported. Accidental dermal exposure demonstrated almost 100% excretion within one day; clothing did not appear to provide protection.

[37]) Conversion factors: 1 mg/m^3 = 0.255 ppm; 1 ppm = 3.92 mg/m^3.

Toxicity

Acute poisoning
Fatal intoxications of humans due to inhalation of phenol have not been reported. However, suicides by ingestion of large amounts of phenol are known. Death in these cases occurred by respiratory failure.
Accidental deaths have been reported after dermal exposure of humans to phenol, both after acute exposure and continuous exposure to phenol solutions. The cause of death was reported to be cardiac and respiratory depression.
Phenol is therefore considered highly toxic.
Genotoxicity and carcinogenicity
IPCS (1994) present an overview of the results of mutagenicity studies with phenol. In virtually all bacterial test systems mutagenic effects could not be detected. Experiments with Drosophila, however, showed phenol to be highly mutagenic, but the induction of sex-linked recessive lethals in Drosophila phenol, tested by injection or feeding, was negative. According to ATSDR (1998) results were also negative or inconclusive in other *in vitro* and *in vivo* test systems, stating that positive effects are found at high doses only.
Phenol showed strong promoting activity for tumour formation in mice after initiation with 9,10-dimethyl-1,-2,-benzanthracene (DMBA) followed by repeated skin applications of phenol. In a two years study (cited in the Hazardous Substances Database, 2000) an increased incidence of leukaemia and lymphomas was detected in male rats exposed to 2500 ppm phenol in drinking water.
In epidemiological studies of occupationally exposed humans an excess of various cancers was found, but there were no statistically significant dose-response relationships. Based on the available data IARC (1989) concluded that there is inadequate evidence for the carcinogenicity of phenol in humans, and inadequate evidence for the carcinogenicity of phenol in experimental animals.
Subchronic and chronic toxicity
For oral intake of phenol in humans during 6 months a LOAEL for less serious effects (nausea, dark urine, mouth sores) of 0.14 mg/kg bw/day was reported (ATSDR 1998). ATSDR (1998) also reported a NOAEL of 721 mg/kg bw/day for effects on various organ systems in rats after chronic oral exposure. In a more recent (1995) developmental study with rats (dams exposed to phenol during gestation days 6 to 19) a decrease in the number of pups was observed. The LOAEL and NOAEL in this study were 53 mg/kg bw/day and 40 mg/kg bw/day, respectively.
There are no toxicity data on chronic exposure of humans by inhalation. For laboratory animals only subchronic studies are reported. Effects on liver enzymes, lungs, kidneys, and the cardiovascular system in rats were noticeable at 100 mg/m^3 (26 ppm). In ATSDR (1998) a NOAEC of 20 mg/m^3 (5 ppm) is reported for rhesus monkeys, rats and mice for semichronic inhalation. However, the database is restricted as the concentration of 5 ppm was the only dose tested.
There are no data for dermal exposure of humans that can be used to establish permissible exposure levels. Only for mice ATSDR (1998) reported a NOAEL for dermal effects of 12 mg/cm^2/kg bw.

3.6.3. EVALUATION

Data on the genotoxic activity and the carcinogenic potential of phenol are inconclusive. Available data in experimental animals suggest that phenol can act as a tumour promotor. Hence phenol is considered not to be genotoxic, and consequently a TDI for phenol can be derived from NOAELs and extrapolation factors.
The lowest oral LOAEL reported is 53 mg/kg bw/day for developmental effects in rats, with a NOAEL of 40 mg/kg bw/day. For the estimation of a tolerable daily intake an inter- and intraspecies UF of 100 is to be used. In addition a UF of 3 is applied for the limited duration of exposure (this UF is sufficient because phenol is rapidly eliminated), and a further UF of 3 is applied to correct for the limited database. Thus a TDI of 40 µg/kg bw/day is derived.
A NOAEC of 20 mg/m^3 is reported for various experimental animals after semichronic inhalation exposure. Using a UF of 100 for intra- and interspecies extrapolation, and an additional UF of 10 for ex-

trapolation of a semichronic study to lifetime exposure, a TCA of 20 μg/m^3 for phenol is derived. However, because the NOAEC is based on a very poor database, the TCA is provisional (pTCA).

3.6.4. EVALUATIONS BY OTHER ORGANISATIONS

IARC (1989) classified phenol in group 3: *not classifiableas to its carcinogenicity to humans.*
US-EPA derived an oral RfD of 600 μg/kg bw/day. The value is based on a rat developmental study with a NOAEL of 60 mg/kg, and UFs of 10 for inter- and 10 for intraspecies extrapolation (IRIS, revised 1990). A RfC was not derived because the available data were considered insufficient.
IPCS (1994) proposed a TDI in the range of 60 up to 200 μg/kg bw/day as the upper limit. This was based on NOAELs in the range of 12 to 40 mg/kg bw/day. A UF of 100 was used for intra-and interspecies extrapolation, and an additional UF of 2 for the lack of information in the database.
Hassauer et al. (1993) advised the UBA (Germany) an oral "Orientierungswert" of 36 μg/kg bw/day for long term exposure of phenol. The value was derived from a LOAEL of 36 mg/kg bw/day for renal effects in rats (in a study of 1945) with a UF of 1000, and 100% resorption. An inhalation "Orientierungswert" of 14 μg/m^3 was included for chronic inhalation on the basis of a NOAEL of 4 mg/kg bw/day for systemic toxicity in rats using a UF of 1000, assuming 100% resorption and applying route-to-route extrapolation.

3.6.5. BACKGROUND EXPOSURE

Vermeire et al. (1991) estimated a maximal daily exposure of 0.4 μg/kg bw/day, on the basis of a phenol concentration in air of 0.01 μg/m^3. IPCS (1994) estimated the daily intake for the general population to be 100 μg/kg bw/day at maximum. About 70% of the total intake is caused by phenol intake from air, using a concentration of 200 μg phenol/m^3 in air. Based on more recent data this air concentration must be considered rather high. The remaining exposure results from the intake of drinking water and smoked food items. ATSDR (1998) stated that it is not possible to estimate the daily exposure, they concluded that the data of ambient air and food are insufficient.
More recent data from Finland reported an average concentration in ambient air of 0.23 ppb (ATSDR 1998), which equals 0.9 μg/m^3. Using this value the intake from air can be calculated to be approximately 20 μg/day. According to Vermeire et al. (1991) the intake from food can be estimated to be 30 μg/day. Consequently, the background exposure in The Netherlands is in the order of magnitude of 1 μg/kg bw/day.

Odour threshold
Vermeire et al. (1991) reported an odour perception threshold of 100 μg phenol per m^3. ATSDR (1998), however, reported the odour threshold of perception of phenol in air to be 0.04 to 1 ppm at 20 °C, which equals 160 to 4000 μg/m^3.

3.6.6. CONCLUSION

Compound	TDI	TCA	Background exposure	Odour threshold
Phenol	40	20 *)	1	100 - 400

TDI: tolerable daily intake (oral exposure); μg/kg bw/day
TCA: tolerable concentration in air (inhalation exposure); μg/m^3
Background exposure; μg/kg bw/day
Odour threshold; μg/m^3
*) Provisional MPR because of the poor database

3.6.7. REFERENCES

ATSDR (1998):
Toxicological Profile for Phenol (update).
Agency for Toxic Substances and Disease Registry, US Public Health Service, Atlanta (GA), USA.

Hassauer, M., Kalberlah, F., Oltmans, J. and Schneider, K. (1993):
Basisdate Toxikologie für umweltrelevante Stoffe zur Gefahrenbeurteilung bei Altlasten.
Umwelt Bundes Amt, Berichte 4/93, Erich Schmidt Verlag, Berlin, Germany

IPCS (1994):
Phenol, Environmental Health Criteria 161.
World Health Organization, Geneva, Switzerland.

Vermeire TG, Apeldoorn ME van, Fouw JC de & Janssen PJCM (1991):
Voorstel voor de humaan-toxicologische onderbouwing van C-toetsingswaarden.
National Institute of Public Health and the Environment, RIVM-report no. 725201005, February 1991; Bilthoven, The Netherlands.

WHO (1996):
Guidelines for drinking-water quality, 2nd ed. volume 2, Health criteria and other supporting information.
World Health Organization, Geneva, Switzerland.

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3.7. DIHYDROXYBENZENES 1,2-DIHYDROXYBENZENE (CATECHOL), 1,3-DIHYDROXYBENZENE (RESORCINOL) AND 1,4-DIHYDROXYBENZENE (HYDROQUINONE)

3.7.1. EVALUATION

For the re-evaluation of the dihydroxybenzenes, the following national and international reviews were consulted:

- Toxicological profiles of the US Agency for Toxic Substances and Disease Registry;
- IRIS files of the US Environmental Protection Agency;
- Environmental Health Criteria of the WHO's International Programme on Chemical Safety;
- Evaluations of carcinogenicity of the WHO's International Agency for Research on Cancer;
- Criteria documents of the RIVM;
- Other relevant information available in the compounds database of the library of the RIVM's Centre for Substances & Risk Assessment.

New relevant information regarding dihydroxybenzenes could not be located. Consequently the MPRs as derived by Vermeire et al. in 1991 are to be maintained. In 1991 only TDIs were derived since inhalation exposure in cases of soil contamination was considered not relevant.

Compound	TDI	Background exposure
1,2-Dihydroxybenzene	40	*)
1,3-Dihydroxybenzene	20	*)
1,4-Dihydroxybenzene	25	*)
Dihydroxybenzenes (total)	25	*)

TDI: tolerable daily intake (oral exposure); µg/kg bw/day
Background exposure; µg/kg bw/day
*) No data available; assumed to be negligible

3.7.2. REFERENCES

Vermeire TG, Apeldoorn ME van, Fouw JC de & Janssen PJCM (1991):
Voorstel voor de humaan-toxicologische onderbouwing van C-toetsingswaarden.
National Institute of Public Health and the Environment, RIVM-report no. 725201005, February 1991; Bilthoven, The Netherlands.

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Date: 01-06-2000

3.8. CRESOLS

3.8.1. EVALUATION

For the re-evaluation of the cresols, the following national and international reviews were consulted:
- Toxicological profiles of the US Agency for Toxic Substances and Disease Registry;
- IRIS files of the US Environmental Protection Agency;
- Environmental Health Criteria of the WHO's International Programme on Chemical Safety;
- Evaluations of carcinogenicity of the WHO's International Agency for Research on Cancer;
- Criteria documents of the RIVM;
- Other relevant information available in the compounds database of the library of the RIVM's Centre for Substances & Risk Assessment.

New relevant information regarding cresols could not be located. Consequently the MPRs as derived by Vermeire et al. in 1991 are to be maintained.

Compound	TDI	TCA	Background exposure
Cresols	50	170	*)

TDI: tolerable daily intake (oral exposure); µg/kg bw/day
TCA: tolerable concentration in air (inhalation exposure); µg/m^3
Background exposure; µg/kg bw/day
*) No data available; assumed to be negligible

3.8.2. REFERENCES

Vermeire TG, Apeldoorn ME van, Fouw JC de & Janssen PJCM (1991):
Voorstel voor de humaan-toxicologische onderbouwing van C-toetsingswaarden.
National Institute of Public Health and the Environment, RIVM-report no. 725201005, February 1991; Bilthoven, The Netherlands.

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Date: 01-06-2000

3.9. PHTHALATES
BIS(2-ETHYLHEXYL) PHTHALATE, DIBUTYL PHTHALATE, DIETHYL PHTHALATE AND BUTYLBENZYL PHTHALATE

3.9.1. INTRODUCTION

Phthalates were evaluated within the scope of this project by Vermeire et al in 1991. They derived a TDI for oral intake of all phthalates of 25 µg/kg bw/day. This was based on the TDI for bis(2-ethylhexyl)phthalate (DEHP), and it was stated that other phthalate-esters are equally or less toxic than DEHP. The TDI of DEHP was derived of a NOAEL for rats of 2.5 mg/kg bw/day for peroxisomal proliferation in the liver, with an uncertainty factor (UF) of 100. A TCA was not derived.
For the update additional literature published since 1991 was reviewed. This included various reports of the RIVM, reviews of WHO (1996), ATSDR (1994, 1999), and CICAD (1999), and draft reviews of the European Union (in this evaluation referred to as RIVM 2000a, 2000b, and 2000c).
Phthalates (actually phthalate esters) are a wide group of related compounds. They are synthesised by esterification of phthalic acid with an organic component. Examples are bis(2-ethylhexyl)phthalate, diisononyl and diisodecyl phthalate, butylbenzyl phthalate, dibutyl and diisobutyl phthalate, and diethyl phthalate. The different phthalate-esters are mainly used as (intermediate) plasticizers. Phthalates can be found in a broad range of consumer products like packaging materials, glues and dyes and resins, but also in toys and cosmetics. In addition they are used in propellants, explosives, insecticides, and emulsions.
Phthalates are man made chemicals, produced by large scale industrial processes, and thus the natural concentrations of phthalates in soil will be negligible. Sources of phthalates are emissions into the atmosphere by the chemical industry, industrial waste disposal and household waste. Consequently, soil contamination can exist due to waste dumps and from aerial depositions (ATSDR 1994, 1999, CICAD 1999). It can therefore be expected that phthalates are to be found both at dumping sites and on a more diffuse scale.
Due to their physiochemical properties phthalates will not volatilise into the atmosphere but adsorb to soil. According to Peijnenburg et al. (1991) there is a relationship between the octanol-water partition coefficient (K_{ow}) and the degradation rate of phthalate esters, and biodegradation will be less when the K_{ow} increases. Consequently the phthalates with long and branched alkyl chains will persist longest in soil and sediment. There is some information about concentrations of phthalates in soil or sediment in The Netherlands at present. According to the Hazardous Substances Database (HSD 2000) the concentrations of phthalates found in Dutch soil or river sediments are highest for bis(2-ethylhexyl)-phthalate, with levels of 1 to 70 mg/kg. Sediment concentrations for dibutyl phthalate varied from 0.5 to 2 mg/kg, whereas for diethyl phthalate concentrations ranged from 0.2 to 0.8 mg/kg. For butylbenzyl phthalate the sediment concentrations in Dutch rivers reported were between 0.01 and 0.05 mg/kg. For other phthalate esters no data about concentrations in soil or sediment could be found. Therefore MPRs are derived for these four phthalate esters:

A. Bis(2-ethylhexyl)phthalate: DEHP (CAS 117-81-7)
B. Dibutyl phthalate: DBP (CAS 84-74-2)
C. Diethyl phthalate: DEP (CAS 84-66-2)
D. Butylbenzyl phthalate: BBP (CAS 85-68-7)

3.9.2. BIS(2-ETHYLHEXYL)PHTHALATE (DEHP)

3.9.2.1. TOXICOLOGY

Toxicokinetics

DEHP is readily absorbed from the gastrointestinal tract after oral administration in rats. Oral absorption in humans is substantially lower. Both DEHP and its metabolites are distributed throughout the

body, but the highest concentrations are being found in adipose tissue and in the liver. Estimated half-lives in rats are 1 to 5 days for fat and other tissues.
DEHP is hydrolysed to mono(2-ethylhexyl)phthalate. The mono-ester can form conjugates with glucuronide or oxidation products like keto-acids. The main route of excretion differs for experimental animals and humans. In rats 90% is excreted in the urine, but in marmosets only 1, and in humans 11 to 25% is excreted in the urine (WHO 1996).

Toxicity

Acute poisoning
Mild gastric disturbances and catharsis was noticed at low oral single doses of DEHP in human volunteers. Data of acute lethal toxicity of DEHP are restricted to animals, in which it has a low acute toxicity.
Genotoxicity and carcinogenicity
DEHP showed negative results in most *in vitro* and *in vivo* mutagenicity test systems. No evidence was found for interaction with DNA. However, DEHP induced aneuploidy in eukaryotic cells, and cell transformation in mammalian cells *in vitro* and *in vivo*. There was no increase of chromosomal aberrations in leukocytes in occupationally exposed humans who were exposed to DEHP by inhalation for a period of 10 to 34 years.
In an oral study with mice increased incidences of hepatocellular carcinomas were seen at dose levels of 3000 and 6000 mg/kg in the diet. In mice no tumour initiating activity was found, but promoting activity indicated by an increase of hepatocellular proliferative lesions was observed in the liver.
In a small cohort study pancreas and bladder tumours were reported in industrial workers, but this study was considered to be inadequate to prove "a causal association" (WHO 1996). At present DEHP is classified by IARC as *possibly carcinogenic to humans* (group 2B) (IARC 1987).
Subchronic and chronic toxicity
Peroxisomal proliferation in the liver can be considered a low dose toxic effect of DEHP exposure. In a short-term oral study of the RIVM a NOAEL of 5 mg/kg bw/day was established in rats for this effect (Jansen et al. 1992). In a chronic study with rats this effect was found with a LOAEL of 10 mg/kg bw/day; the NOAEL was 2.5 mg/kg bw/day. The NOAEL for other low dose effects such as liver and kidney enlargement, microscopic changes in the liver, and testicular atrophy was 50 mg/kg bw/day in this study. In a more recent 2 years oral study reviewed by the EU (in draft, RIVM 2000c) effects on kidney weight were reported with a NOAEL of 29 mg/kg bw/day.
In a reproduction study and some teratogenicity studies with mice the oral NOAEL was 35 mg/kg bw/day for a series of effects such as reduced fertility, decreased foetal weight, neural tube effects, and skeletal disorders. However, the most prominent effects found in a repeated dose study are testicular effects based on Sertoli cell vacuolation. A dose of 50 ppm DEHP in the diet, which equals to 3.7 mg/kg bw/day for 13 weeks, was the NOAEL.
Data about inhalation exposure of DEHP in humans indicate no effects of occupational exposure to 0.010 to 0.016 mg/m^3 over a period of 10 to 34 years (WHO 1996).

3.9.2.2. EVALUATION

There are no indications that DEHP is a genotoxic compound. Consequently a TDI can be derived from a NOAEL with UFs.
Testicular effects were found DEHP in the diet with a NOAEL of 3.7 mg/kg bw/day for 13 weeks. The results of this study is considered relevant for both young and adult males (RIVM 2000c). Consequently a UF of 10 is to be used for extrapolation to life time exposure. With a UF of 100 for inter- and intraspecies variation a TDI of 4 μg/kg bw/day can be derived. Due to the low volatility of DEHP, inhalation exposure is considered not relevant.

3.9.2.3. EVALUATIONS BY OTHER ORGANISATIONS

IARC (1987) has concluded that DEHP is possible carcinogenic to humans, and has classified it in group 2B.
US-EPA derived a RfD for DEHP of 0.02 mg/kg bw/day on the basis of a LOAEL of 0.04 % in the diet (19 mg/kg bw/day), based on an increase of relative liver weights in a subchronic guinea pig oral bioassay. A UF of 100 was used for intra- and interspecies variability. As the effect was considered minimally adverse, an additional factor of 10 was used for extrapolation from a subchronic LOAEL to a chronic NOAEL (IRIS 2000).
An oral slope factor of 0.014 $[mg/kg\ bw/day]^{-1}$ was derived for carcinogenic risk, by means of a linearised multistage procedure. Dose response was derived using data of hepatocellular carcinomas and adenomas in male B6C3F1 mice (IRIS 2000).
The WHO proposed a Drinking Water Quality Guideline of 8 µg/L for DEHP, allocating 1% of the TDI. A TDI of 25 µg/kg bw/day was derived, based on a NOAEL for peroxisomal proliferation in the liver of rats, with a UF of 100 for inter- and intraspecies variation (WHO 1996).
The EC presented a TDI of 50 µg/kg bw/day (EC 1997).
Hassauer et al. (1993) advised the UBA, Germany, an oral "Orientierungswert" of 20 µg/kg bw/day for long term exposure of DEHP. It was based on a NOAEL of 19 mg/kg bw/day for hepatotoxicity in guinea pig, with a UF of 1000 and 100% absorption. In their proposal an inhalation "Orientierungswert" of 0.7 $\mu g/m^3$ was included for chronic inhalation. This value was based on a NOAEC of 1.4 mg/m^3 for systemic toxicity in rats, with a UF of 1000 and 100% absorption.

3.9.3. DIBUTYL PHTHALATE (DBP)

3.9.3.1. TOXICOLOGY

Toxicokinetics

DBP is rapidly and extensively absorbed after oral intake, data from rats indicate a complete absorption. Rapid absorption was also seen after inhalation exposure. Animal data suggest that DBP is widely distributed throughout the body. It does not accumulate. After inhalation exposure DBP was consistently detected in brains of rats.
From animal studies it is known that DBP is transformed into monobutyl-phthalate. After conjugation with glucuronic acid monobutyl-phthalate-glucuronide is formed. In addition small amounts of other metabolites such as phthalic acid and carboxypropyl phthalate can be formed. Both the parent compound and the metabolites of DBP are excreted in urine. Excretion is complete within 48 hours after a single dose (ATSDR 1999).

Toxicity

Acute poisoning
Data of acute oral toxicity of DBP are restricted to animals, in which its acute toxicity is low. Associated effects and causes of death were not reported.
Genotoxicity and carcinogenicity
DBP was negative in most of the *in vitro* test systems. No genotoxic effects were observed in *in vivo* studies for gene-mutations with Drosophila, and in the micronucleus assay in mice.
There are no long-term studies regarding carcinogenic effects of DBP, neither in humans nor in laboratory animals.
Subchronic and chronic toxicity
Human studies of oral exposure to DBP have not been reported. For laboratory animals only semi-chronic studies are reported that can be used to derived NOAELs. Peroxisomal proliferation was most prominent, and the NOAEL for this effect was 152 mg/kg bw/day for rats after 3 months of exposure. At higher doses also haematological and endocrine parameters were affected. In studies in rats with

special attention to testicular effects as demonstrated for DEHP a LOAEL of 250 mg/kg bw/day was reported.
A NOAEL of 50 mg/kg bw/day was established based on embryotoxicity in a one-generation reproduction study in rats with exposure of females only. However, a LOAEL of 52 mg/kg bw/day was be derived based on embryotoxic effects in rats in the absence of maternal toxicity in a two-generation reproduction study: both the number of pups and the body weight of the pups were decreased.
For repeated inhalation exposure a NOAEC of 509 mg DBP per m^3 for systemic effects was reported in a 28-day inhalation study in rats. In this study the lowest exposure concentration of 1.18 mg/m^3 was the LOAEC for local histopathological changes in the respiratory tract (RIVM 2000a).

3.9.3.2. EVALUATION

There are no indications that DBP is a genotoxic compound. Consequently a TDI can be derived from a NOAEL with UFs.
A LOAEL of 52 mg/kg bw/day was found for reproductive effects in a two-generation study. A UF of 10 is to be used for extrapolation of the LOAEL to a NOAEL. In combination with a UF of 100 for inter- and intraspecies variation a TDI of 52 µg/kg bw/day can be derived.
Due to the low volatility of DBP, inhalation exposure is considered not relevant.

3.9.3.3. EVALUATIONS BY OTHER ORGANISATIONS

US-EPA derived a RfD for DBP of 0.1 mg/kg bw/day on the basis of a NOAEL of 0.25% in the diet (125 mg/kg bw/day). It was based on increased mortality in an oral subchronic rat study, with a UF of 100 for inter- and intraspecies variability. An additional factor of 10 was used for extrapolation from a subchronic NOAEL and deficiencies in the study (IRIS 2000).
A (temporary) TDI of 50 µg/kg bw/day was presented by Peijnenburg et al (1991), based on a NOAEL of 50 mg/kg bw/day with a UF of 100 for intra- and interspecies extrapolation, and 10 for a poor database.
The EC (1997) presented a temporary TDI of 50 µg/kg bw/day.
ATSDR (1999) derived an acute oral MRL of 3 mg/kg bw/day. It was based on a NOAEL of 331 mg/kg bw/day for incidence of internal malformations in the offspring of rats, with a UF of 100 for inter- and intraspecies extrapolation.
Hassauer et al. (1993) advised the UBA, Germany, an oral "Orientierungswert" of 0.6 mg/kg bw/day for long term exposure of DBP. It was based on a NOAEL of 62.5 mg/kg bw/day for hepatotoxicity in rats, with a UF of 100 and 100% absorption. In their proposal an inhalation "Orientierungswert" of 2.8 $\mu g/m^3$ was included for chronic inhalation. This value was based on a NOAEC of 50 mg/m^3 for a decreased body weight of rats using a UF of 10000 and 100% absorption.

3.9.4. DIETHYL PHTHALATE (DEP)

3.9.4.1. TOXICOLOGY

Toxicokinetics

There are not studies regarding absorption of DEP in humans or animals following oral or inhalation exposure; the extend of dermal absorption in human skin was reported to be 4.8% of the applied dose. It was stated that DEP did not produce more skin damage than a dermal application of water. Likewise there are no studies regarding distribution in humans or animals following oral or inhalation exposure. After dermal application, small amounts of labelled DEP were detected in blood and in almost all organs.
From animal studies it is known that DEP is transformed into its mono-ester derivative by the liver and the intestines. The mono-ester can be further hydrolysed to phthalic acid or conjugated with glucuronic acid. Both the parent compound and the metabolites are excreted in urine. Only a small percentage was found in the faces (ATSDR 1994).

Toxicity

Acute poisoning
Data of acute oral toxicity of DEP are restricted to animals. The toxicity is low. Associated effects and causes of death were not reported.
Genotoxicity and carcinogenicity
There are data from *in vitro* studies in prokaryotic and mammalian cells, but *in vivo* studies of genotoxic effects could not be located. In most studies DEP did not demonstrate genotoxic action.
DEP showed no carcinogenic potential in a two years rat study, and also not in an initiation and promotion study with mice
Subchronic and chronic toxicity
Human studies of oral exposure to DEP have not been reported. For laboratory animals only two semichronic studies were reported, in both studies hepatic effects were most prominent. According to ATSDR (1994) the LOAEL with mild peroxisomal proliferation was 1753 mg/kg bw/day for rats after 3 weeks exposure. In a study of the RIVM, however, the LOAEL for peroxisomal proliferation reported was 65 mg/kg bw/day for rats after 2 and 4 weeks exposure, with a NOAEL of 19 mg/kg bw/day [38]). Effects on liver and body weight were not observed (Jansen et al. 1993).
Peijnenburg et al. (1991) cited a rat experiment with oral exposure during 16 weeks, in which effects on the liver (organ weight accompanied by histological and biochemical changes) and the testes (degeneration, atrophy and affected spermatogenesis) were observed, the NOAEL in this study was 100 mg/kg bw/day.

3.9.4.2. EVALUATION

DEP is not considered a genotoxic compound. Accordingly a TDI can be derived from a NOAEL and UFs.
The NOAEL for peroxisomal proliferation effects is 19 mg/kg bw/day in rats after subchronic exposure. This effect, however, is generally considered of less relevance for humans. The only other relevant study is the 16 weeks oral study with rats cited by Peijnenburg et al. (1991), in which a NOAEL of 100 mg/kg bw/day was established on the basis of liver and testes effects. From this NOAEL the EC derived a temporary TDI of 200 μg/kg bw/day (EC 1997; cf. next paragraph); this limit value is adopted here as a provisional TDI.
Due to lack of appropriate data it is not possible to derive a TCA; moreover, due to the low volatility of DEP inhalation exposure is considered not relevant.

3.9.4.3. EVALUATIONS BY OTHER ORGANISATIONS

US-EPA derived a RfD for DEP of 0.8 mg/kg bw/day on the basis of a NOAEL of 1% in the diet (750 mg/kg bw/day). It was based on decreased growth and altered organ weights in an oral subchronic rat study, with a UF of 100 for inter- and intraspecies variability, and 10 for extrapolation from a subchronic NOAEL (IRIS 2000).
A (temporary) TDI of 200 μg/kg bw/day was presented by the Scientific Committee for Food of the EC (EC 1997) based on a NOAEL of 100 mg/kg bw/day of a 16 week oral study with rats (cited by Peijnenburg et al. 1991), with a UF of 500 for intra- and interspecies extrapolation and a poor database.
Hassauer et al. (1993) advised the UBA, Germany an oral ”Orientierungswert” of 0.75 mg/kg bw/day for long term exposure of DEP. It was based on a NOAEL of 750 mg/kg bw/day for decreased body weight of rats, with a UF of 1000 and 100% absorption. In their proposal an inhalation ”Orientierung-

[38]) The NOAELs for peroxisomal proliferation for another phthalate ester (DEHP) in a subchronic and a chronic study differed only by a factor of two (5 mg/kg bw/day versus 2.5 mg/kg bw/day in the subchronic and chronic study, respectively), and thus a factor of 2 would be sufficient to extrapolate the subchronic NOAEL of DEP to a chronic NOAEL.

swert" of 0.7 μg/m^3 was included for chronic inhalation. This value was based on the proposal for DEHP.

3.9.5. BUTYLBENZYL PHTHALATE (BBP)

3.9.5.1. TOXICOLOGY

Toxicokinetics

BBP is readily absorbed from the gastrointestinal tract after oral administration in rats. Dermal absorption is also rapid. In rats 80% was absorbed after a single dose (RIVM 2000b). BBP is mainly found in the liver.
BBP is hydrolysed to its mono-butyl or -benzyl ester. In rats the mono-butyl ester was shown to be the most prominent metabolite. In rats 90% of the absorbed amount of BBP is eliminated within 24 hours; 80% of the phthalate mono-esters are eliminated in the urine, the remaining is found in the faeces (CICAD 1999).

Toxicity

Acute poisoning
Data of acute toxicity of BBP are restricted to animals: the oral toxicity is rather low. Histological examination at lethal doses revealed degenerative lesions of the central nervous system.
Genotoxicity and carcinogenicity
In various *in vitro* assays such as the Ames test, mouse lymphoma assays and transformation of BALBc cells BBP did not demonstrate any genotoxic activity, and it was negative in the mouse dominant lethal assay. It did not induce sex-linked recessive lethals *in Drosophila melanogaster* (RIVM 2000b). In a mouse bone marrow test positive response is reported but it was concluded that BBP demonstrates only weak clastogenic activity (NTP 1997).
In this carcinogenicity bioassay (NTP 1997) no increased incidence of any neoplasm was found. It was concluded that BBP is not carcinogenic for mice. In rats mononuclear cell leukemias were reported in females. In another study benign pancreatic tumours were seen in males, but not after dietary restriction. A marginally increased incidence of pancreatic adenomas and transitional epithelial papillomas of the urinary bladder were found in female rats (RIVM 2000b).
Subchronic and chronic toxicity
There are no data about human exposure to BBP. In different animals studies oral intake was investigated, for both short term and chronic exposure, and reproduction. In a 3 months study with rats effects on kidney weight and urinary pH were noticed by a dose of 382 mg/kg bw/day, the NOAEL was 151 mg/kg bw/day. In a more recent study of the NTP (1997) marginal effects were noticed on haemoglobin concentrations at 550 mg/kg bw/day after 26 weeks. At higher dose levels testicular atrophy was found. The NOAEL was 2800 ppm in the diet, equivalent with 181 mg/kg bw/day.
Peroxisomal proliferation was found in short term oral studies with rats. According to the EU risk assessment (in draft, RIVM 2000b) the NOAEL for this effect was 639 mg/kg bw/day in a 21 day study.
For inhalation exposure a subchronic study with rats was reported. Here a NOAEC of 51 mg/m^3 was found. Effects were reported on kidney and liver weights and decreased serum glucose, and atrophy of the spleen and testes (CICAD 1999, RIVM 2000b).
Regarding the effects on fertility or reproductive organs, decreases in testes weight and histopathological changes in the testes have been reported in rats. These effects were seen at doses equal to or higher than those inducing other effects, such as kidney weight changes. In reproductive studies effects on the offspring were only noticed at dose levels with apparent maternal toxicity. At doses of 250 mg/kg bw/day decreased maternal body weight gain was reported; decreased foetal body weight was seen at 500 mg/kg bw/day (RIVM 2000b).

3.9.5.2. EVALUATION

BBP did not demonstrate genotoxic activity, and thus a TDI is to be derived on the basis of a NOAEL and UFs.
NOAELs of 151 and 181 mg/kg bw/day were reported in a 3 months study and a 6 months study, respectively. Developmental effects and effects on the fertility were only noticed at higher dose levels. Accordingly a TDI can be derived using the NOAEL of 151 mg/kg bw/day. As the NOAELs were approximately similar in both studies a UF of 3 can be used for extrapolation to life time exposure. With a UF of 100 for inter- and intraspecies variation a TDI of 500 µg/kg bw/day is derived.
Due to the low volatility of BBP inhalation exposure is considered not relevant.

3.9.5.3. EVALUATIONS BY OTHER ORGANISATIONS

IARC concluded that BBP is *not classifiable to its carcinogenicity to humans* and classified it in group 3: *evidence for humans and animals in inadequate* (IARC 1999).
A (temporary) TDI of 100 µg/kg bw/day was presented by Peijnenburg et al. (1991), based on a NOAEL of 140 mg/kg bw/day for peroxisomal proliferation in rat liver, with a UF of 1000 for intra- and interspecies extrapolation, and a poor database.
The EC (1997) presented a temporary TDI of 0.1 mg/kg bw/day.
US-EPA derived a RfD for BBP of 0.2 mg/kg bw/day on the basis of a NOAEL of 2800 ppm in the diet (159 mg/kg bw/day). It was based on an increase of the relative liver and brain weight in an oral 6 months rat study, with a UF of 100 for inter- and intraspecies variability, and 10 for extrapolation from a subchronic NOAEL (IRIS 2000).
CICAD (1999) derived a TDI for BBP of 1.3 mg/kg bw/day. It was calculated using the lower 95% confidence limit of 132 mg/kg bw/day of a benchmark dose of 167 mg/kg bw/day for pancreatic lesions in rats in a subchronic study. A UF of 100 was used for inter- and intraspecies variation. An additional factor for extrapolation of a subchronic study was not considered necessary.
Hassauer et al. (1993) advised the UBA, Germany, an oral "Orientierungswert" of 0.2 mg/kg bw/day for long-term exposure of BBP. It was based on a NOAEL of 159 mg/kg bw/day for hepato-, nephro- and haematotoxicity in rats, with a UF of 1000 and 100% absorption. In their proposal an inhalation "Orientierungswert" of 20.3 µg/m^3 was included for chronic inhalation. This value was based on a NOAEC of 51 mg/m^3 for nephrotoxicity in rats, with a UF of 1000 and 100% absorption.

3.9.5.4. BACKGROUND EXPOSURE

There is little information on the daily intake of phthalate esters. Peijnenburg et al. (1991) presented an average total daily intake from food of all phthalate esters of 0.5 mg/kg bw/day for the Dutch situation in 1977. This value was based on the amount of dimethyl phthalate after complete hydrolysis and subsequent esterification of all phthalates. It is not clear how this relates to the different esters.
For the intake of DEHP WHO (1996) presented an estimate of 200 µg/day (equal to 3 µg/kg bw/day). Food was the major contributor; exposure form air and drinking water was demonstrated to be negligible. This estimation was based on data of 1985, but in a recent review of DEHP (RIVM 2000c) also a total exposure for the general population of 3 µg/kg bw/day was calculated.
In the report of ATSDR (1999) it was concluded that fish is the major source of intake of DBP, but an estimate of the daily exposure was not given. It was stated that the existing data of DBP in foods are outdated and can therefore not be used to estimate background exposure.
CICAD (1999) estimated for BBP a background exposure of 2 to 6 µg/kg bw/day, mainly from food. For the other phthalate esters values for background exposure have not been reported.
It can be concluded that the background exposure is at least in the order of magnitude of 3 µg/kg bw/day from DEHP plus 2 to 6 µg/kg bw/day from BBP, based on older data. There are no indications whether the environmental levels of phthalates are increasing or decreasing, thus it is not possible to adjust this estimate of the background exposure to phthalate esters in The Netherlands. It must therefore be concluded that the background exposure in The Netherlands to phthalate esters is to be estimated at least in the order of 5 to 9 µg/kg bw/day.

3.9.6. CONCLUSION

Compound	TDI	Background exposure
Bis(2-ethylhexyl) phthalate (DEHP)	4	5 - 9 [2])
Dibutyl phthalate (DBP)	52	
Diethyl phthalate (DEP)	200 [1])	
Butylbenzyl phthalate (BBP)	500	

TDI: tolerable daily intake (oral exposure); µg/kg bw/day
Background exposure; µg/kg bw/day
[1]) Provisional because of the limited database
[2]) Based on the sum of data for DEHP and BBP; data for the other phthalates are not available

Remark: The available data show that DEHP is probably the most abundant phthalate ester in soil and sediment, and the most toxic compound of the phthalates in the environment. The phthalate esters share peroxisomal proliferation in the liver as a low dose effect. Although this effect is considered less relevant for humans, it does suggests some common mechanism of action. It is advised to evaluate the toxic potency of a mixture of phthalate esters rather than the different compounds individually, and thus for the evaluation of the total concentration of phthalate esters in a mixture the TDI of 4 µg/kg bw/day is to be used.

3.9.7. REFERENCES

ATSDR (1994):
Toxicological profile for diethyl phthalate
Agency for Toxic Substances and Disease Registry, US Public Health Service, Atlanta (GA), USA.

ATSDR (1999):
Toxicological profile for di-n-butyl phthalate (update).
Agency for Toxic Substances and Disease Registry, US Public Health Service, Atlanta (GA), USA.

CICAD (1999):
Butyl benzyl phthalate.
Concise International Chemical Assessment Document No 17, IPCS.
World Health Organization, Geneva, Switzerland.

EC (1997):
Food Science and Techniques, Report of the Scientific Committee for Food, no. 39.
Office of Official Publications of the European Communities, Luxembourg.

Hassauer M, Kalberlah F, Oltmans J & Schneider K (1993):
Basisdate Toxikologie für umweltrelevante Stoffe zur Gefahrenbeurteilung bei Altlasten.
Umwelt Bundes Amt, Berichte 4/93, Erich Schmidt Verlag, Berlin, Germany.

HSD (2000):
Hazardous Substances Database, at http://toxnet.nlm.nih.gov.
National Institutes of Health, Research Triangle Park, USA.

IARC (1987):
Overall Evaluations of Carcinogenicity, Suppl. 7 - an updating of IARC Monographs volumes 1 to 42.
International Agency for Research on Cancer, World Health Organization, Lyon, France.

IARC (1999):
Monographs on the evaluation of carcinogenic risks to humans, vol. 73 - some chemicals that cause tumours of the kidney or urinary bladder in rodents and some other substances.
International Agency for Research on Cancer, World Health Organization, Lyon, France.

IRIS (Integrated Risk Information System), 2000:
- Summary for bis(2-ethylhexyl)phthalate; oral RfD assessment dated May 1991, carcinogenicity assessment dated February 1993.
- Summary for dibutyl phthalate; oral RfD assessment dated August 1990.
- Summary for diethyl phthalate; oral RfD assessment dated February 1993.
- Summary for butylbenzyl phthalate; oral RfD assessment dated February 1993.

US Environmental Protection Agency, Washington DC, USA.

Jansen EHJM, Van der Ham WA, Dormans JA, Van Apeldoorn ME & Van Leeuwen FXR (1992):
Toxicological investigation of di(2-ethylhexyl)phtalate in rats, the determination of a no-observed-effect-level.
National Institute of Public Health and the Environment, RIVM-report no. 618902.007; Bilthoven, The Netherlands.

Jansen EHJM, Van der Ham WA, De Fluiter P & Van Leeuwen F.R (1993):
Toxicological investigation of diethylphtalate in rats.
National Institute of Public Health and the Environment, RIVM-report no. 618902.012; Bilthoven, The Netherlands.

NTP (1997):
Effect of dietary restriction on toxicology and carcinogenisis study in F344/N rats and B6C3F1 mice.
National Toxicology Program technical report no. 460, NIH publication no. 97-3376, National Institutes of Health, Research Triangle Park, USA.

Peijnenburg WJG, Van Ewijk M, De Haan, MWA et al. (1991):
Update of the exploratory report phthalates.
National Institute of Public Health and the Environment, RIVM-report no. 710401.008; Bilthoven, The Netherlands.

RIVM (2000a)
EU document Risk Assessment Dibutyl phthalate, Draft 2000.
National Institute of Public Health and the Environment, Bilthoven, The Netherlands.

RIVM (2000b)
EU document Risk Assessment Benzylbutyl phthalate, Draft 2000.
National Institute of Public Health and the Environment, Bilthoven, The Netherlands.

RIVM (2000c)
EU document Risk Assessment Bis(2-ethylhexyl)phthalate, Draft 2000.
National Institute of Public Health and the Environment, Bilthoven, The Netherlands.

Vermeire TG, Apeldoorn ME van, Fouw JC de & Janssen PJCM (1991):
Voorstel voor de humaan-toxicologische onderbouwing van C-toetsingswaarden.
National Institute of Public Health and the Environment, RIVM-report no. 725201005, February 1991; Bilthoven, The Netherlands.

WHO (1996):
Guidelines for drinking-water quality, 2nd ed. Volume 2, Health criteria and other supporting information.
World Health Organization, Geneva, Switzerland.

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Appendix 4 Polycyclic aromatic hydrocarbons

4.1. POLYCYCLIC AROMATIC HYDROCARBONS

4.1.1. INTRODUCTION

Evaluations of 1991 and 1993

Polycyclic aromatic hydrocarbons (PAHs) are a group of chemicals composed of two or more fused aromatic rings made up of carbon and hydrogen. At ambient temperatures PAHs are solids. Generally, they have high melting and boiling points, low vapour pressure, and very low water solubility. PAHs are very lipophilic, and chemically rather inert. They are used as intermediates in the production of plastics and plasticizers, pigments and dyes, and pesticides. The largest emissions of PAHs, however, result from incomplete combustion of organic materials during industrial processes and other human activities. Most of them are considered genotoxic carcinogens.
In the scope of the present project 11 PAHs have been evaluated in 1991 (Vermeire et al.) and 1993 (Vermeire), see Table 1. In the soil contamination scope these are known as the "PAHs 10" (because all except naphtalene can be analysed in one gaschromatographic run).
In most cases the values were based on limited toxicological data, and partly extrapolated on the basis of estimated carcinogenic potency of individual PAHs.
The relevant route in case of soil contamination was considered to be the oral one.

Table 1 MPR and background values derived in 1991/1993

Compound	MPR type	MPR value	Daily exposure
Anthracene	TDI	50	0.0004
Benz[a]anthracene	oral cancer risk	20	0.002
Benzo[k]fluoroanthene	oral cancer risk	20	0.009
Benzo[g,h,i]perylene	oral cancer risk	20	0.002
Benzo[a]pyrene	oral cancer risk	2	0.0011
Chrysene	oral cancer risk	2	0.017
Fluoroanthene	oral cancer risk	20	0.039
Indeno[1,2,3-c,d]pyrene	oral cancer risk	20	0.002
Naphtalene	TDI	50	0
Phenanthrene	oral cancer risk	20	0.012
Pyrene	oral cancer risk	20	0.023
PAHs total	oral cancer risk	6.3	0.097

TDI: tolerable daily intake (µg/kg bw/day)
Oral cancer risk: $1{:}10^4$ lifetime excess cancer risk, oral exposure (µg/kg bw/day)
Daily exposure: average daily oral exposure (background; µg/kg bw/day)
PAHs total: based on the average composition of PAH mixtures as characterised at a number of soil contaminated sites (industrial areas, coal mines, gas producing plants)

Scope of the current evaluation

US-EPA requires the analysis of 16 specific PAHs in determining the degree of contamination of wastewater with PAHs: acenaphtene, acenaphtylene, anthracene, benz[a]anthracene, benzo[b]fluoranthene, benzo[j]fluoranthene, benzo[k]fluoranthene, benzo[g,h,i]perylene, chrysene, dibenz[a,h]anthracene, fluoranthene, fluorene, indeno[1,2,3,-c,d]pyrene, naphtalene, phenanthrene, and pyrene (EPA 1984). Probably because this list was originally intended to be used for characterisation of municipal and industrial wastewater, benzo(a)pyrene was not included, and the list has become known as the "EPA 16". Outside the USA, this list of compounds is often taken as a reference list for the analysis of various environmental matrices; obviously it has to be extended with benzo(a)pyrene for matrices other than water (IPCS 1998). This EPA list covers the 11 compounds evaluated earlier by Ver-

meire et al. (1991) and Vermeire (1993).
In its 1995 evaluation of the PAHs, ATSDR discussed 17 PAHs, these include the "EPA 16", benzo[a]pyrene, and benzo[e]pyrene, but excludes naphtalene. The ATSDR evaluation covers the 11 compounds evaluated earlier by Vermeire et al. (1991) and Vermeire (1993), with the exception of naphtalene (ATSDR 1995).
In 1998 PAHs were also evaluated by IPCS. They reviewed 33 PAHs: next to the ones already mentioned above, the IPCS evaluation included anthanthrene, benzo[g,h,i]fluoranthene, benzo[a]fluorene, benzo[b]fluorene, benzo[c]phenanthrene, coronene, cyclopenta[c,d]pyrene, dibenzo[a,e]pyrene, dibenzo[a,h]pyrene, dibenzo[a,i]pyrene, 5-methylchrysene, 1-methylphenanthrene, perylene, and triphenylene. The IPCS evaluation covers all compounds evaluated earlier by Vermeire et al. (1991) and Vermeire (1993) (IPCS 1998).
Recently RIVM reported the results of an oral carcinogenicity study of benzo[a]pyrene in rats, evaluated these results, also in terms of exposure to PAH mixtures, and derived a $1{:}10^6$ lifetime excess cancer risk for benzo[a]pyrene as well as for dietary PAHs in general (Kroese et al. 1999, *in draft*).
In the scope of the present project the non-carcinogenic toxic effects of the aromatic hydrocarbons with equivalent carbon numbers 11-16 and 17-35 were evaluated as part of the evaluation of total petroleum hydrocarbons (this report, appendix 7.6).
In view of the increase in chemical-analytical possibilities during the last decade, the importance of PAHs at Dutch contamination sites, the frequency with which particular PAHs are found at these sites, the availibility of information regarding toxicity and carcinogenicity, and the practical benefits of international harmonisation, the current evaluation considers the PAHs required by EPA; of course benzo(a)pyrene was added to this list. This results in an extension of the current "PAHs 10" to "PAHs 17"; these PAHs are summarised in Table 2. Together these cover compounds with two fused (6-membered) aromatic rings (naphtalene) up to compounds with six fused rings (benzo[g,h,i]perylene); some of them have a 5-membered ring in the molecule. Table 2 also depicts the genotoxicity and carcinogenicity of the PAHs selected, these characteristics are further outlined in paragraph 4.1.2.

Table 2 PAHs selected for the current evaluation

Compound	**CAS no.**	**Genotoxicity IPCS (1998)**	**Carcinogenicity IPCS (1998)**	**Carcinogenicity IARC (1983)**
Acenaphtene	83-32-9	(?)	?	n.e.
Acenaphtylene	208-96-8	(?)	no data	n.e.
Anthracene	120-12-7	–	–	3
Benz[a]anthracene	56-55-3	+	+	2A
Benzo[b]fluoroanthene	205-99-2	+	+	2B
Benzo[j]fluoroanthene	205-82-3	+	+	2B
Benzo[k]fluoroanthene	207-08-9	+	+	2B
Benzo[g,h,i]perylene	191-24-2	+	–	3
Benzo[a]pyrene	50-32-8	+	+	2A
Chrysene	218-01-9	+	+	3
Dibenz[a,h]anthracene	53-70-3	+	+	2A
Fluoroanthene	206-44-0	+	(+)	3
Fluorene	86-73-7	–	–	3
Indeno[1,2,3-c,d]pyrene	193-39-5	+	+	2B
Naphtalene	91-20-3	–	(?)	n.e.
Phenanthrene	85-01-8	(?)	(?)	3
Pyrene	129-00-0	(?)	(?)	3

IPCS classification:
+ positive
– negative
? questionable
( ) result derived from small database

IARC classification:
2A compound is probably carcinogenic to humans
2B compound is possibly carcinogenic to humans
3 compound is not classifiable as to its carcinogenicity to humans
n.e. not evaluated

4.1.2. TOXICOLOGY

Toxicokinetics

Studies of humans and experimental animals exposed to some individual PAHs or PAH-mixtures show that these compounds are well absorbed following inhalation, oral or dermal exposure, but data concerning the rate and extent of absorption are limited. Animal studies indicate that in general the extent of absorption is depending on the lipophilicity and molecular size of the compound: increasing lipophilicity tends to increase absorption, whereas increasing molecular weight tends to decrease it. In addition, the extent of oral absorption is enhanced if the PAH is solubilised in a fatty or oily vehicle that is readily absorbed. Generally, absorption after inhalation or oral exposure appears to be ≥ 50%. Data on the oral absorption of PAHs bound to soil particles are not available. Regarding dermal absorption, epidemiology data indicate that approximately 20% of a skin contamination with PAHs is absorbed, but animal data suggest that dermal absorption might be as high as 50% and more. However, when PAHs are bound to soil particles, dermal absorption is much less: in the order of magnitude of 10%.
Following absorption the PAHs and their metabolites are widely distributed to tissues and organs, and are eliminated by urinary (predominant for low molecular weight PAHs) and biliary (predominant for high molecular weight PAHs) excretion of metabolites; metabolites that are excreted through the bile undergo enterohepatic circulation.
Metabolism involves aromatic ring oxidation forming epoxides, alcohols, dihydrodiols, and quinone derivatives, that can be conjugated to glutathione, glucuronic acid or sulfate. Reactive metabolites, particularly stereospecific isomers of arene oxides and dihydrodiol-epoxides, are thought to cause the genotoxic and carcinogenic effects produced by exposure to carcinogenic PAHs (ATSDR 1995, IPCS 1998).

Biochemistry

Both in humans and in experimental animals the most common finding following exposure to PAHs is induction of (liver) enzymes, in particular specific enzymes of the cytochrome P450 (CYP) system. The CYP1A family appears to be the only one with metabolic capacity towards virtually all PAHs. The induction of CYP1A1 and CYP1A2 is regulated by the Ah (aryl hydrocarbon) receptor, a transcription factor that can be activated by several ligands such as 2,3,7,8-tetrachlorodibenzo-p-dioxin and PAHs. Nevertheless, some PAHs are also capable of inducing other CYP enzymes. As stated above, specific reactive electrophilic PAH-metabolites, particularly stereospecific isomers of arene oxides and dihydrodiol-epoxides, are thought to cause the genotoxic and carcinogenic effects produced by exposure to carcinogenic PAHs. Most of the metabolites that have been found to react chemically with nucleic acids were vicinal diol-epoxides. In studies on the relationship between DNA adduct formation and tumour incidence, a linear increase in DNA adduct level was reflected in a linear increase in tumour incidence, strongly suggesting that indeed the covalent interaction of PAH metabolites with DNA is the starting point in the expression of PAH carcinogenicity (ATSDR 1995, IPCS 1998).

Genotoxicity and carcinogenicity

PAHs have been studied extensively in *in vitro* and *in vivo* assays for genotoxicity and cell transformation; the results are summarised in Table 2. The only compounds for which negative results were found in all assays were anthracene, fluorene and naphtalene. In addition, acenaphtene, acenaphtylene, phenanthrene and pyrene could not be reliably classified for genotoxicity owing to inconsistent results. All others are considered to be genotoxic (IPCS 1998).
The carcinogenicity of the PAHs has been the subject of extensive research. In general, however, data on carcinogenicity following oral exposure to PAHs are very scarce. Most experimental data are restricted to the inhalation or dermal route of exposure. Studies on various environmentally relevant matrices, such as coal combustion effluents, vehicle exhaust, used motor lubricating oil, and side-

stream tobacco smoke, showed that PAHs are the agents predominantly responsible for their carcinogenic potential.
In 1998 IPCS extensively evaluated the research on the carcinogenicity of individual PAHs and concluded that 8 of the 17 PAHs presently selected are to be considered carcinogenic beyond reasonable doubt; these are benz[a]anthracene, benzo[b]fluoranthene, benzo[j]fluoranthene, benzo[k]fluoranthene, benzo[a]pyrene, chrysene, dibenz[a,h]anthracene, and indeno[1,2,3-c,d]pyrene. In addition, fluoroanthene is suspected of being carcinogenic. The carcinogenicity of acenaphtene, acenaphtylene, naphtalene, phenanthrene and pyrene is questionable; of these, naphtalene is considered to be not carcinogenic due to its negative genotoxicity, the others (acenaphtene, acenaphtylene, phenanthrene, and pyrene) must considered to be suspected carcinogens. Finally, next to naphtalene, anthracene, benzo-[g,h,i]perylene, and fluorene are considered to be not carcinogenic (IPCS 1998). Thus, out of the 17 PAHs selected, 4 are considered not to be carcinogenic, the others are either accepted or suspected carcinogens (see Table 2 and also paragraph 4.1.3). IPCS reached this conclusion after having reviewed over 400 studies with experimental animals, 278 of which were considered to be valid for evaluation.
The PAH most extensively tested, benzo[a]pyrene, has been shown to be carcinogenic by all routes. Regarding the other PAHs, in carcinogenicity testing the dermal route was the most common mode of administration. In most studies, the site of the tumour development was related to the route of administration, i.e., dermal application induced skin tumours, inhalation and intratracheal installation resulted in lung tumours, subcutaneous injection resulted in sarcomas, and oral administration induced gastric tumours. Tumour induction is, however, not restricted to these sites (ATSDR 1995, IPCS 1998).

Chronic and subchronic toxicity

Data with regard to non-carcinogenic toxic effects are limited. In general, significant toxic effects are manifested at doses at which carcinogenic responses are also triggered.
Upon occupational inhalation exposure to PAH mixtures, respiratory effects were noted in humans, among which were decrement in ventilatory function, bloody vomit, chest pains, throat irritation, cough, and radiographic abnormalities such as bronchiovascular markings and pleural effusions. In another epidemiological study, humoral immunity was shown to be affected: serum IgA and IgG were markedly depressed; IgM tended to decrease, whereas IgE tended to increase. Anthracene and naphtalene vapours caused mild eye irritation. Regarding inhalation exposure to benzo[a]pyrene, 0.1 $\mu g/m^3$ appeared to be a LOAEL for these non-carcinogenic toxic effects.
Following oral exposure, some PAHs induced hematological effects in mice, notably decreased packed cell volume and decreased hemoglobin content, and in Ah-nonresponsive mice also aplastic anemia and pancytopenia. Experiments with several animal species showed increased absolute and/or relative liver and kidney weights, increased incidence of foci of altered hepatocytes and occasionally also renal damage like tubular dilation and interstitial lymphocytic infiltrates and/or fibrosis. In mice and rats, benz[a]anthracene, benzo[a]pyrene, dibenz[a,h]anthracene and naphtalene (the only PAHs properly tested) were embryotoxic. Benzo[a]pyrene also had teratogenic and reproductive effects: reduction of the number of pregnant animals reaching parturition, reduced mean pup weight, and a high incidence of sterility in the progeny, the latter in some studies associated with alterations in gonadal morphology and germ cell development.
When applied dermally, mixtures of carcinogenic PAHs caused hyperkeratosis in humans and experimental animals. It should be noted, however, that PAH mixtures are also used for medical treatment of some skin disorders in humans. In mice, application of PAHs resulted in suppression of sebaceous glands and a pronounced inflammatory response in the dermis. Benzo[a]pyrene induced allergic contact hypersensitity in mice and guinea pigs (ATSDR 1995, IPCS 1998).
LOAELs and NOAELs for toxic effects of the PAHs considered to be non-carcinogenic (see paragraph 4.1.3) are summarised in Table 3.

Table 3 NOAELs and RfDs for toxic effects of non-carcinogenic PAHs

Compound	Study	Effect	NOAEL	RfD
Anthracene	Mouse, oral subchronic	NOAEL is highest dose administered	1000	0.3 (1993)
Benzo[g,h,i]-perylene	No data available	-	-	-
Fluorene	Mouse, oral subchronic	Decreased RBC, packed cell volume and hemoglobin	125	0.04 (1990)
Naphtalene	Rat, oral subchronic	Decreased terminal body weight	71	0.02 (1998)

Data from IPCS 1998 and IRIS 1999

NOAEL and RfD (chronic oral reference dose, ≈ TDI) are expressed in mg/kg bw/day.
For all RfD estimations, a UF (uncertainty factor) of 3000 was applied (10×10 for inter- and intraspecies variation, 10 for using a subchronic study, 3 for lack of data in second species or lack of reproductive/developmental toxicity data).

4.1.3. EVALUATION

The weight of evidence as evaluated by ATSDR (1995) and IPCS (1998) strongly suggest that the 17 PAHs selected for the current evaluation are carcinogenic [39]) with the exception of anthracene, benzo-[g,h,i]perylene, fluorene, and naphtalene. Consequently, the risk estimation of the PAHs selected must be based on the non-threshold linear extrapolation approach (Janssen and Speijers 1997) except the 4 non-carcinogenic PAHs mentioned above: for these compounds the threshold approach can be applied.
The recent chronic oral (gavage) rat study of RIVM with benzo[a]pyrene (dosed 3, 10 and 30 mg/kg bw/day, 5 days/week during 2 years) as reported *(in draft)* by Kroese et al. (1999) is taken as the pivotal study for the derivation of the carcinogenic risk. The study resulted in dose-dependent tumour development in a variety of organs and tissues. The most prominent effects were seen in the liver and forestomach, but also soft tissue sarcomas in oesophagus, skin and mammary gland, and tumours of the auditory canal, skin, oral cavity, small intestine and kidney were observed. Applying the linear non-threshold approach the authors concluded to a $1{:}10^6$ lifetime excess cancer risk of 5 ng benzo[a]-pyrene per kg bw per day. This value corresponds well with the results of the recent two-year carcinogenicity study of benzo[a]pyrene in mice of the US National Center for Toxicologial Research (Culp et al. 1998): according to Kroese et al. (1999, *in draft*), applying the same extrapolation method the results of Culp et al. indicate also a $1{:}10^6$ lifetime excess cancer risk of approximately 5 ng/kg bw/day. Hence the $1{:}10^4$ lifetime excess cancer risk as defined in the scope of the present project is 0.5 µg benzo[a]pyrene per kg bw per day.
With respect to the carcinogenic risk following dietary exposure to mixtures of PAHs, Kroese et al. (1999, *in draft*) discussed the literature and the composition and exposure to such mixtures in the Dutch situation, and suggested that benzo[a]pyrene should be taken as the indicator for dietary exposure to PAH mixtures. This approach, however, can not be used for oral exposure to PAHs at soil contamination sites due to the wide variety in composition of PAH mixtures at such sites. Consequently, the carcinogenic potency approach must be used. In this approach the potency of the PAH relative to that of benzo[a]pyrene is estimated, which results in a benzo[a]pyrene equivalent. The key assumption is that the relative potency of two PAHs in an animal model is similar to that of the same components in humans. Furthermore the approach is based on the assumption of additivity, i.e., in the final risk estimation the individual PAH concentrations are multiplied with their respective potency factors, and the resulting benzo[a]pyrene equivalents are summed. A number of estimations for such carcinogenic potency factors have been made and have been evaluated recently by IPCS (1998) and Kroese et al. (1999, *in draft*). In the scope of the current project the present review considers the estimations of US-EPA (EPA 1993) and Kalberlah et al. (1995) the most appropriate:

[39]) These include acenaphtene, acenaphtylene, phenanthrene and pyrene: although the carcinogenicity as well as the genotoxicity of these PAHs are questionable due to inconsistent test results, at present they should be considered as suspected carcinogens.

- EPA (1993) derived the relative potencies of individual PAHs in increments of order of magnitude by comparison, considering only the results of carcinogenicity bioassays, limited to those in which benzo[a]pyrene and other PAH were assayed by the same protocol and within the same time frame. The studies considered involved various routes of exposure, including skin painting, intraperitoneal and subcutaneous injections, and lung impantations.
- Kalberlah et al. (1995) adopted the EPA-approach: these authors had a panel of experts made independent reviews of the existing data, considering data from studies of skin painting in mice, the induction of lung and liver adenomas in newborn mice, mammary tumours in rats, studies by oral administration, genotoxicity studies, and structure-activity relationships. They scored about 150 PAHs as having high, moderate, marginal, or slight potential carcinogenicity; the results were converted to powers of 10.

These two estimations are listed in Table 4, expressed as the relative potency compared to the potency of benzo[a]pyrene, which is defined as 1.00. Table 4 lists also the resulting carcinogenic risk of the various PAHs that result from the multiplication of the cancer risk of benzo[a]pyrene by the carcinogenic potency of that particular PAH (figures used for the calculation are printed in bold).

Table 4 Carcinogenic risk estimation of selected PAHs

Compound	**Carcinogenic potency [1])**		**Cancer risk [2])**
Acenaphtene	**0.001**	0	500
Acenaphtylene	**0.01**	n.e.[3])	50
Benz[a]anthracene	**0.1**	**0.1**	5
Benzo[b]fluoroanthene	**0.1**	**0.1**	5
Benzo[j]fluoroanthene	**0.1**	n.e.	5
Benzo[k]fluoroanthene	**0.1**	0.01	5
Benzo[a]pyrene	**1.00**		**0.5**
Chrysene	**0.01**	0.001	50
Dibenz[a,h]anthracene	**1.0**	**1.0**	0.5
Fluoroanthene	**0.01**	n.e.	50
Indeno[1,2,3-c,d]pyrene	**0.1**	**0.1**	5
Phenanthrene	**<0.001**	n.e.	negligible
Pyrene	**0.001**	n.e.	500

Data from IPCS 1998

[1]) first figure (left hand column): Kalberlah et al. (1995), second figure (right hand column): US-EPA (EPA 1993).

[2]) $1:10^4$ excess lifetime cancer risk for oral exposure, in µg/kg bw/day; for the risk estimation the largest of the two potency factors (printed in bold) was used.

[3]) n.e.: not evaluated.

Regarding the non-carcinogenic toxic effects of some specific PAHs, the evaluation of total petroleum hydrocarbons (this report, appendix 7.6) concluded to an overall TDI of 40 µg/kg bw/day for the aromatic compounds with equivalent carbon numbers >9 to 16, and 30 µg/kg bw/day for the aromatic compounds with equivalent carbon numbers >16 to 35. It was emphasised that these values are only valid for non-carcinogenic aromatics. Considering this and considering the experimental results as described in paragraph 4.1.2 and Table 3, the TDI for PAHs considered to be non-carcinogenic should be set at 40 and 30 µg/kg bw/day, for the aromatic compounds with equivalent carbon numbers of >9-16 (i.e., anthracene, fluorene and naphtalene) and >16-35 (i.e., benzo[g,h,i]perylene), respectively.
However, in view of these results and in view of the evaluations by other organisations (see paragraph 4.1.4) it must be noted that there is no general agreement regarding the carcinogenicity vs. non-carcinogenicity of a number of PAHs. In the literature this controversy resulted in carcinogenic potency factors for some PAHs considered to be non-carcinogenic, and in TDIs for some PAHs considered to be carcinogenic. In the scope of the current project the choice for the MPR of any PAH is the oral excess quantitative cancer risk for the carcinogenic PAHs as defined above (including the suspected carcinogenic ones), and the TDI for the non-carcinogenic PAHs. The only exception is phe-

nanthrene: this PAH is considered to be carcinogenic, but its carcinogenic potency is extremely low (< 0.001; Table 4), and therefore the TDI of 40 µg/kg bw/day is applied.
The values as derived fom the above evaluation are listed in Table 5.

Table 5 Risk estimation of the PAHs selected for the current evaluation

Compound [1])	**CAS no.**	**MPR [2])**	
		Cancer risk oral	**TDI**
Acenaphtene	83-32-9	500	-
Acenaphtylene	208-96-8	50	-
Anthracene	120-12-7	-	40
Benz[a]anthracene	56-55-3	5	-
Benzo[b]fluoroanthene	205-99-2	5	-
Benzo[j]fluoroanthene	205-82-3	5	-
Benzo[k]fluoroanthene	207-08-9	5	-
Benzo[g,h,i]perylene	191-24-2	-	30
Benzo[a]pyrene	50-32-8	0.5	-
Chrysene	218-01-9	50	-
Dibenz[a,h]anthracene	53-70-3	0.5	-
Fluoroanthene	206-44-0	50	-
Fluorene	86-73-7	-	40
Indeno[1,2,3-c,d]pyrene	193-39-5	5	-
Naphtalene	91-20-3	-	40
Phenanthrene	85-01-8	negligible	40
Pyrene	129-00-0	500	-

[1]) PAHs which are in the current evaluation considered to be *non-carcinogenic* are printed in *italics*.
[2]) Either $1{:}10^4$ excess lifetime cancer risk for oral exposure, or tolerable daily intake, both expressed in µg/kg bw/day

Due to the very large differences in physical-chemical properties of the different PAHs it is not possible to derive a MPR for "PAH total" or "PAH mixtures", because this would lead to erroneous results of calculations using the CSOIL model. Thus, in evaluating the risk of a given, specific soil contamination site, separate calculations need to be made for each of the composing PAHs individually (both carcinogenic and toxic risks). Obviously this requires detailed chemical analysis of this particular contamination site. Only with the results of these individual calculations the specific risk of this given soil contamination site can be assessed.
For oral exposure to a particular mixture of PAHs the cancer risk can be calculated according to the general priciple of toxicity equivalence, as follows:

$$\text{total (oral) cancer risk} = \sum f_i \times MPR_i$$

in which f_i and MPR_i are the fraction ($0 \leq f_i \leq 1$) and the MPR of the i^{th} specific PAH in this mixture, respectively. The (non-carcinogenic) toxic risk of a particular PAH mixture can be calculated accordingly.

4.1.4. EVALUATIONS BY OTHER ORGANISATIONS

ATSDR (1995) adopted the RfDs (reference dose, ≈ TDI) for intermediate duration oral exposure (15-364 days) as developed by US-EPA in 1988 and 1989: 0.6 mg/kg bw/day for acenaphtene, based on a minimal LOAEL of 175 mg/kg bw/day for liver weight in mice; 0.4 mg/kg bw/day for fluoranthene based on a minimal LOAEL of 125 mg/kg bw/day for liver weight in mice; and 0.4 mg/kg bw/day for fluorene, based on a minimal LOAEL of 125 mg/kg bw/day for liver weight in mice. ATSDR did not estimate MRLs (maximum risk level) for chronic oral exposure, nor did this organisation estimate MRLs for carcinogenic risks following oral exposure. Besides the chronic oral RfDs developed by

US-EPA summarised in Table 3 (paragraph 4.1.2), this institute also developed chronic oral RfDs for acenaphtene, fluoranthene, and pyrene of 0.06, 0.04 and 0.03 mg/kg bw/day, respectively (IRIS 1999). US-EPA developed an oral slope factor for carcinogenic risk of benzo[a]pyrene of 7.3 per [mg/kg bw/day] (IRIS 1999). According to Kroese et al. (1999, *in draft*), the $1{:}10^6$ excess lifetime cancer risk (oral) can be calculated from this slope factor via linear extrapolation to be 0.14 ng/kg bw/day, which equals a $1{:}10^4$ excess lifetime cancer risk (oral) of 14 ng/kg bw/day. This value is considerably lower than the cancer risk estimated by Kroese et al. (1999, *in draft*), due to differences in (1) the animal data selected for extrapolation, (2) dose scaling, 93) other concentration factors, and (4) using a 95% confidence limit instead of a mean estimate (IRIS 1999).

4.1.5. BACKGROUND EXPOSURE

Kroese et al. (1999, *in draft*) evaluated recent data regarding the dietary exposure to PAHs of the general Dutch population, and arrived at an estimated median daily intake of approximately 190 ng benzo[a]pyrene per person, which equals 2.7 ng/kg bw/day. This is about twice as much as the intake of 1.1 ng/kg bw/day as estimated by Vermeire et al. (1991) in their earlier evaluation of PAHs (see Table 1), but it should be noted that the currently estimated intake of 190 ng benzo[a]pyrene was derived using median measured concentrations in food items with detectable PAH levels, and half the detection limit in food items with no detectable PAH levels, which might be considered a worst-case approach. If extrapolated to the intake of PAHs total, the value of 97 ng/kg bw/day presented by Vermeire et al. (1991) for total PAHs should be multiplied with the same factor, i.e., [2.7 ÷ 1.1 = 2.45], leading to an estimated background exposure for total PAHs of approximately 240 ng/kg bw/day. Applying the equivalency factors as outlined in table 4, this is equivalent with a background exposure for total PAHs of 7.3 ng benzo[a]pyrene equivalents per kg bw per day.

4.1.6. CONCLUSION

Table 6 Risk estimation of the PAHs selected for the current evaluation

Compound	**CAS no.**	**MPR *)**	
		Type	**Value**
Acenaphtene	83-32-9	CR_{oral}	500
Acenaphtylene	208-96-8	CR_{oral}	50
Anthracene	120-12-7	TDI	40
Benz[a]anthracene	56-55-3	CR_{oral}	5
Benzo[b]fluoroanthene	205-99-2	CR_{oral}	5
Benzo[j]fluoroanthene	205-82-3	CR_{oral}	5
Benzo[k]fluoroanthene	207-08-9	CR_{oral}	5
Benzo[g,h,i]perylene	191-24-2	TDI	30
Benzo[a]pyrene	50-32-8	CR_{oral}	0.5
Chrysene	218-01-9	CR_{oral}	50
Dibenz[a,h]anthracene	53-70-3	CR_{oral}	0.5
Fluoroanthene	206-44-0	CR_{oral}	50
Fluorene	86-73-7	TDI	40
Indeno[1,2,3-c,d]pyrene	193-39-5	CR_{oral}	5
Naphtalene	91-20-3	TDI	40
Phenanthrene	85-01-8	TDI	40
Pyrene	129-00-0	CR_{oral}	500

*) CR_{oral}: $1{:}10^4$ excess lifetime cancer risk for oral exposure; µg/kg bw/day
TDI: tolerable daily intake; µg/kg bw/day

The different risks involved in PAHs-contaminated soils implicate the necessity of two approaches to be applied simultaneously: estimation of the cancer risk as well as estimation of the toxic (non-cancer) risk.

Table 7 Background exposure

Compound	Background exposure (µg/kg bw/day)	
	actual amount	benzo[a]pyrene equivalents
Benzo[a]pyrene	0.0027	0.0027
Total PAHs	0.24	0.0073

Relevant route in case of soil contamination: oral.

4.1.7. REFERENCES

ATSDR (1995): Toxicological profile for polycyclic aromatic hydrocarbons (update).
US Dept. of Health & Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta (GA), USA.

Culp SJ, Gaylor DW, Sheldon WG, Goldstein LS & Beland FA (1998): A comparison of the tumours induced by coal tar and benzo[a]pyrene in a 2-year bioassay.
Carcinogenesis 19, 117-124 *(cited in Kroese et al. 1999, draft)*

EPA (1984): Guidelines establishing test procedures for the analysis of pollutants under the Clean Water Act: Method 610 - polynuclear aromatic hydrocarbons.
Fed. Reg. 49, 43344-43352 [40 CFR Part 136] *(cited in IPCS 1998).*

EPA (1993): Provisional guidance for quantitative risk assessment of polycyclic aromatic hydrocarbons.
EPA/600/R-93/089, US Environmental Protection Agency, Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnatti, Ohio, USA *(cited in IPCS 1998).*

IARC (1983): Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol. 32: polycyclic aromatic compounds, part 1: chemical, environmental and experimental data.
International Agency for Research on Cancer, World Health Organization, Lyon, France.

IPCS (1998): Environmental Health Criteria 202: selected non-heterocyclic polycyclic aromatic hydrocarbons.
International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland.

IRIS (1999): Integrated Risk Information System (IRIS): summaries for acenaphtene (dated 1994), anthracene (dated 1993), fluoranthene (dated 1993), fluorene (dated 1990), naphtalene (dated 1998), pyrene (dated 1993), and benzo[a]pyrene (dated 1994).
US Environmental Protection Agency, Washington DC, USA.

Janssen PJCM & Speijers GJA (1997): Guidance on the derivation of Maximum Permissible Risk levels for human intake of soil contaminants.
National Institute of Public Health and the Environment, RIVM report no. 711701006, January 1997.

Kalberlah F, Frijus-Plessen N & Hassauer M (1995): Toxicological criteria for the risk assessment of polyaromatic hydrocarbons (PAH) in existing chemicals. Part I: the use of equivalency factors.
Altlasten-Spektrum 5, 231-237 *(cited in IPCS 1998).*

Kroese ED, Muller JJA, Mohn GR, Dortant PM & Wester PW (1999): Tumorigenic effects in Wistar rats orally administered benzo[a]pyrene for two years (gavage studies). Implications for human cancer risks associated with oral exposure to polycyclic aromatic hydrocarbons.
National Institute of Public Health and the Environment, RIVM draft report no. 658603010, July 1999.

Vermeire TG (1993): Voorstel voor de humaan-toxicologische onderbouwing van C-(toetsings)waarden - Addendum op RIVM rapport nr. 725201005
National Institute of Public Health and the Environment, RIVM report no. 715801001, May 1993.

Vermeire TG, Apeldoorn ME van, Fouw JC de & Janssen PJCM (1991): Voorstel voor de humaan-toxicologische onderbouwing van C-toetsingswaarden.
National Institute of Public Health and the Environment, RIVM-report no. 725201005, February 1991; Bilthoven, The Netherlands.

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Appendix 5 Chlorinated hydrocarbons

5.1. 1,2-DICHLOROETHANE

5.1.1. INTRODUCTION

1,2-Dichloroethane was evaluated within the scope of this project by Vermeire et al in 1991. They derived an oral risk level for carcinogenic effects of 14 µg/kg bw/day for 1 case of cancer per 10,000 persons for lifetime exposure. This value was calculated by linear extrapolation from an oral study with rats. For inhalation exposure a risk level of 48 µg/m^3 was derived, based on the risk level of oral intake through route to route extrapolation. In this extrapolation an inhalation rate of 20 m^3/day was assumed, and an oral and inhalation bioavailability of 100%.
For the update additional literature, was published since 1991, was reviewed. This included a review of the IPCS (1995), the Health Council of The Netherlands (1997), and ATSDR (1999).
1,2-Dichloroethane is sometimes referred to as ethylene dichloride. It is a synthetic chemical, that has no known natural sources. The natural occurrence in soil will therefore be negligible. It is synthesised and used as a intermediate by the chemical industry. Its most significant use is in the synthesis of vinyl chloride, but also of various other chlorinated solvents such as tri- and tetrachloroethene, and 1,1,1-trichloroethane. Formerly it was also used in products such as fumigants, soap, metal degreasers, and paint and coatings, and in anti-knock formulations for leaded gasoline.
Releases to air will occur from industrial production and use, and in the past also from gasoline emissions. Soil contamination can be expected from industrial waste. 1,2-Dichloroethane is volatile and well soluble in water. It will leach to the groundwater, and volatilise quickly from soil and groundwater (IPCS 1995, ATSDR 1999).

5.1.2. TOXICOLOGY

Toxicokinetics

Absorption
Case studies with humans suggest that 1,2-dichloroethane is rapidly absorbed following oral administration. In rats the absorption is at least 90% within 15 minutes. The vehicle used in oral administration plays a role: the compound is better absorbed in the gastrointestinal tract when administered in water than in corn oil.
Data of humans and experimental animals demonstrate that 1,2-dichloroethane is readily absorbed through the lungs following inhalation exposure. Peak blood levels in rats are found within 1 or 2 hours. The rate of absorption, however, is not reported.
1,2-Dichloroethane is also well absorbed through the skin following dermal exposure of experimental animals. Available data suggest that the absorption is rapid and almost complete (ATSDR 1999).
Distribution
1,2-Dichloroethane is found in the spleen and stomach, kidneys, and liver of humans who died following acute oral poisoning. In experimental animals exposed via inhalation or ingestion the highest concentrations are found in adipose tissue, but it appeared to accumulate also in the liver (IPCS 1995)
Metabolism
The metabolic transformation of 1,2-dichloroethane is extensively studied in laboratory animals; human data are not available. The compound is metabolised to urinary metabolites (i.e. ethene-bis-cysteine) via glutathione S-transferase. The intermediate glutathione episulfonium ion might form cellular macromolecular adducts with DNA and RNA. Another metabolic pathway is through cytochrome P-450, by which 1,2-dichloroethane is transformed into 2-chloroaldehyde. The latter can react with macromolecules, or can be transformed in various urinary metabolites. According to ATSDR (1999) this pathway is the primary oxidation of 1,2-dichloroethane in humans. It involves the P450 2E1 enzyme system.

Excretion
Unmetabolised 1,2-dichloroethane is eliminated in expired air. The metabolites are largely excreted in the urine. As 1,2-dichloroethane may accumulate in adipose tissue, elimination might also occur via breast milk women (IPCS 1995).
Biomarkers
According to ATSDR (1999) breath, blood, and urine might be used to indicate exposure to 1,2-dichloroethane. As the compound is rapidly eliminated it is not possible to establish precise environmental levels to which individuals are exposed. Data on 1,2-dichloroethane in human milk are not sufficient to characterise exposure versus tissue levels.
If exposure to other compounds can be ruled out, thioethers in the urine are well suited as a biomarker for 1,2-dichloroethane exposure. Especially thioglycolic acid is suggested to be a good marker.
Health effects after human exposure to 1,2-dichloroethane are not very specific, and therefore not suited as a biomarker. An exception might be liver damage after exposure, and thus alkylation of hepatocellular macromolecules, increased liver weight, and elevated serum enzyme levels are prominent features.

Toxicity

Acute poisoning
Ingestion of amounts of 1,2-dichloroethane in the order of 10 to 60 mL appeared to be lethal for humans within a period of 28 hours. Circulatory failure, i.e. cardiac arrhythmia is reported to be the cause of death. Other symptoms include bronchitis, haemorrhagic gastritis, liver and renal damage, and central nervous system depression.
In a case study the death of a man was reported one week after half an hour inhalation of 1,2-dichloroethane vapours. The information suggested neurotoxic, nephrotoxic, and hepatotoxic effects. In experimental animals the immune system, central nervous system, liver, and kidneys are the target organs. Besides genotoxic effects are reported in animals exposed by inhalation (ATSDR 1999).
Genotoxicity and carcinogenicity
According to the review of the Health Council of The Netherlands 1,2-dichloroethane is consistently genotoxic in *in vitro* test systems. *In vivo* its genotoxicity is less clear, but it produces somatic and sex-linked recessive lethal mutations in Drosophila. It was positive in DNA binding and DNA damage assays in mice and rats *in vivo* (WHO 1996)
1,2-Dichloroethane is carcinogenic to laboratory animals. Mammary tumours were noticed in rats after chronic inhalation exposure to 20 mg/m^3. Chronic oral exposure of rats and mice to 47 to 149 mg/kg bw/day by gavage resulted in carcinomas of the forestomach and tumours of the mammary gland (IPCS 1995, Health Council of The Netherlands 1997). ATSDR (1999) considered this study limited for a number of reasons. Besides it was added that the results of this study are in conflict with a more recent study in which no signs of carcinogenic effects were found by rats exposed to 50 ppm (250 mg/m^3) for 2 years.
The carcinogenic action of 1,2-dichloroethane to humans was investigated in a series of epidemiological studies of occupationally exposed humans and of a local population exposed through contaminated drinking water. In one study an excess of deaths was observed, but exposure to confounding chemicals could not be excluded. In the other studies there was no clear indication of a carcinogenic action (IPCS 1995). The Health Council of The Netherlands (1997) concluded that none of the studies provide conclusive evidence with respect to the possible carcinogenicity of 1,2-dichloroethane to humans.
IARC has classified 1,2-dichloroethane in group 2B: *possibly carcinogenic to humans*, and *sufficient evidence of carcinogenicity in experimental animals*.
Subchronic and chronic toxicity
In chronic oral studies various systemic effects are reported with a NOAEL of 95 mg/kg bw/day. Tumours in the mammary gland, the forestomach and other organs are found with a LOAEL of 47 mg/kg bw/day.
There is little information on toxic effects in laboratory animals after chronic inhalation exposure. In a chronic study with rats 50 ppm (250 mg/m^3) was the NOAEC for the organ systems and reproductive effects. A LOAEC of 100 to 400 ppm (500 and 2000 mg/m^3, respectively) for less serious effects such as fatty degeneration of the liver is reported for various other experimental animals (ATSDR 1999).

Toxic mechanism of action
Specific mechanisms for 1,2-dichloroethane induced toxicity have not yet been elucidated. Evidence suggests that the toxicity is mediated by the reactive metabolic intermediates, as high levels of gluthatione S-transferase are present in liver, kidneys and other target organs of 1,2-dichloroethane. Besides the conjugates have been identified as nephrotoxic in rats (ATSDR 1999).

5.1.3. EVALUATION

1,2-Dichloroethane is considered a genotoxic compound. Consequently, the MPR for oral and inhalation exposure is to be derived from the acceptable cancer risk level of 1 per 10,000 lifetime exposed humans.
Vermeire et al (1991) presented an oral MPR for carcinogenic action of 14 µg/kg bw/day. The pivotal study was also used by the Health Council of The Netherlands and other institutions to calculate the excess cancer risk. Since 1991 new studies have not been reported, and consequently the value as derived in 1991 is to be maintained.
Appropriate inhalation carcinogenicity studies that allow an estimation of the carcinogenic risk of inhalation exposure are not available. Vermeire et al (1991) used route-to-route extrapolation from the oral MPR to derive the inhalation MPR. This value, i.e., 48 µg/m^3, is to be maintained.

5.1.4. EVALUATION OF OTHER ORGANISATIONS

IARC has classified 1,2-dichloroethane in group 2B: *possibly carcinogenic to humans*, and *sufficient evidence of carcinogenicity in experimental animals*.
US-EPA assessed the carcinogenic action of 1,2-dichloroethane: based on animal carcinogenicity data an oral slope factor of 9.1×10^{-2} [mg/kg bw/day]$^{-1}$ was derived by using a linearised multistage procedure. An inhalation unit risk of 2.6×10^{-5} [µg/m3]$^{-1}$ was derived from the oral data, assuming 100% absorption. This equals to a risk level of 1 per 10^4 at a concentration of 4 µg/m^3 (IRIS, revised 1991).
ATSDR presented a (draft) MRL for intermediate oral intake of 0.2 mg/kg bw/day. This was based on a LOAEL of 58 mg/kg bw/day for kidney effects in rats, using an uncertainty factor of 3 for extrapolation to a NOAEL, and 100 for interspecies extrapolation and human variability. For chronic inhalation a (draft) MRL was derived of 0.6 ppm (3 mg/m^3) from a NOAEC of 50 ppm (250 mg/m^3) for histopathology of the liver and other tissues in rats. An uncertainty factor of 3 for interspecies extrapolation by means of a dosimetric adjustment, 10 for human variability, and 3 for database deficiencies was used (ATSDR 1999).
The WHO presented a Drinking Water Quality Guideline for 1,2-dichloroethane of 3 to 300 µg/L corresponding to excess cancer risks of $1{:}10^6$ to $1{:}10^4$, on the basis of the gavage study in rat that was also used by the US-EPA, applying the linearised multistage model (WHO 1996)
Hassauer et al. (1993) advised the UBA (Germany) an oral "Orientierungswert" of 30 µg/kg bw/day for long-term exposure of 1,2-dichloroethane. It was based on a LOAEL of 33.6 mg/kg bw/day for cardiovascular effects and mortality in rats, with an uncertainty factor of 1000 and 100% absorption. In their proposal an inhalation "Orientierungswert" of 200 µg/m^3 was derived for chronic inhalation, based on a NOAEC of 41 mg/m^3 for hepatotoxic effects in rats, using an uncertainty factor of 100 and 30% absorption.

5.1.5. BACKGROUND EXPOSURE

Exposure to 1,2-dichloroethane by humans is mainly due to inhalation of indoor and outdoor air. Data from 1989 of The Netherlands indicate a background concentration of 2 to 5 µg/m^3 for indoor and outdoor air (IPCS 1995). This leads to an intake of 1 µg/kg bw/day. It should be noted, however, that emissions of leaded gasoline were a significant source in former days. Due to the recent reduction of the use of leaded gasoline the concentrations of 1,2-dichloroethane in air might also be decreased. Consequently, at present the estimate can be expected to be a maximal value.
Food is not considered a significant source for the general population. The contribution of drinking water is only relevant for areas with water with concentrations above 6 µg/L. The latter is not the case for The Netherlands.

It can be concluded that the background exposure in The Netherlands is 1 µg/kg bw/day at maximum, from inhalation of air.

Odour threshold
The WHO (1996) reports an odour threshold for 1,2-dichloroethane of 356 mg/m^3 in air. It has a sweet chloroform like (pleasant) odour. According to ATSDR (1999) the odour threshold in the literature ranges from 12 ppm (60 mg/m^3) up to 100 ppm (500 mg/m^3). From the reports it is not clear whether these thresholds refer to the threshold of detection or recognition.

5.1.6. CONCLUSION

Compound	CR_{oral}	CR_{inhal}	Background exposure	Odour threshold
1,2-Dichloroethane	14	48 *)	1	350×10^3

CR_{oral}: $1{:}10^{-4}$ excess lifetime cancer risk intake (oral exposure); µg/kg bw/day
CR_{inhal}: $1{:}10^{-4}$ excess lifetime cancer risk air (inhalation exposure); µg/m^3
Background exposure; µg/kg bw/day
Odour threshold; µg/m^3
*) Provisional MPR because it is derived via route-to-route extrapolation

5.1.7. REFERENCES

ATSDR (1999):
Toxicological Profile for 1,2-dichloroethane (update), Draft,
Agency for Toxic Substances and Disease Registry, US Public Health Service, Atlanta (GA), USA.

Hassauer M, Kalberlah F, Oltmans J & Schneider K (1993):
Basisdate toxikologie fuer umweltrelevante stoffe zur gefahrenbeurteilung bei altlasten.
Umwelt Bundes Amt, Berichte 4/93, Erich Schmidt Verlag, Berlin, Germany.

Health Council of The Netherlands (1997):
1,2-Dichloroethane, health based calculated occupational cancer risk values
Report of the Dutch Expert Committee on Occupational Standards, 1997/01 WGD; Rijswijk, The Netherlands.

IPCS (1995):
1,2-Dichloroethane (2nd edition), Environmental Health Criteria 176.
World Health Organization, Geneva, Switzerland.

IRIS (1999):
CD-ROM database, Silverplatter, London, UK.

Vermeire TG, Apeldoorn ME van, Fouw JC de & Janssen PJCM (1991):
Voorstel voor de humaan-toxicologische onderbouwing van C-toetsingswaarden.
National Institute of Public Health and the Environment, RIVM-report no. 725201005, February 1991; Bilthoven, The Netherlands.

WHO (1996):
Guidelines for drinking-water quality, 2nd ed. Volume 2, Health criteria and other supporting information.
World Health Organization, Geneva, Switzerland.

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5.2. 1,2-DICHLOROETHENE (*CIS* AND *TRANS* ISOMERS)

5.2.1. INTRODUCTION

1,2-Dichloroethene (ClHC=CHCl; synonyms: dichloroethylene) is the common name for *cis*-1,2-dichloroethene, *trans*-1,2-dichloroethene, and a mixture of the *cis*- and *trans*-isomers. They are synthetic chemicals, which are used as chemical intermediates and industrial solvents. At room temperature they are highly flammable, colourless liquids, with an ethereal, slightly acrid odour; they easily evaporate in air [40]). The *trans*-isomer is more widely used than either the *cis*-isomer or the mixture. The odour threshold (both isomers together) is approximately 0.26 mg/L in water and 68 mg/m^3 in air.
These substances were evaluated within the scope of the present project in 1995 (Janssen et al. 1995). For *cis*-1,2-dichloroethene, a tolerable daily intake (TDI) of 6 µg per kg body weight (bw) per day was estimated, based on the NOAEL of 32 mg/kg bw/day of a 90-day oral study in rats, and using an uncertainty factor (UF) of 5000. For *trans*-1,2-dichloroethene, a TDI of 17 µg/kg bw/day was estimated, based on the NOAEL of 17 mg/kg bw/day of a 90-day oral study in mice, and using a UF of 1000.
Via route-to-route extrapolation provisional TCAs (tolerable concentration in air; pTCAs) of 30 and 80 µG/m^3 were estimated for *cis*- and *trans*-1,2-dichloroethene, respectively, based on the oral TDIs.
Relevant routes in case of soil contamination: oral and inhalation.

5.2.2. TOXICOLOGY

Toxicokinetics

1,2-Dichloroethene appears to be absorbed RAPIDLY by the lungs. The compound is metabolised in the liver by cytochrome P450 to dichloroethanol and dichloroacetic acid, via the epoxide intermediate. Animal studies indicate that the cis-isomer biotransforms more rapidly than the trans-isomer. Moreover, the cis-isomer frequently inhibits or destroys cytochrome P450, while the trans-isomer increases the enzyme level. No information is available on the oral and dermal absorption, on the distribution, or on the excretion of the compound in humans or in animals. The compounds are volatile and lipophilic, move easily through the respiratory and gastrointestinal systems, have high affinity for lipids and blood, but apparently do not accumulate in tissues (ATSDR 1996).

Toxicity [41])

Dichloroethene was evaluated by the US-ATSDR in 1990 and updated in 1996 (ATSDR 1996). The US-EPA evaluated the compounds in 1990 and 1991 (EPA 1998). A toxicity profile aimed at deriving human-toxicological criteria for serious soil contamination was prepared by the RIVM in 1995 (Janssen et al. 1995), mainly based on the ATSDR 1994 draft report. The toxicity data in the ATSDR 1996 update, relevant for this evaluation, were the same as in the ATSDR 1994 draft. Brief evaluations were also published by the German Umweltbundesamt (FoBiG 1992) and the WHO (WHO 1996). Other recent review documents of national and international bodies are not known. In the toxicological literature no publications were found on systemic toxicity.
Genotoxicity and carcinogenicity
1,2-Dichloroethene has not been evaluated by the IARC. Carcinogenicity data are not available.
Cis-1,2-dichloroethene
In vitro studies (tests with and without activation, for gene mutations in bacteria, gene mutations and conversions in yeasts, and chromosome aberrations in mammalian cells) were negative. An *in vivo* cytogenetic study (bone marrow) in mice with intraperitoneal application was positive, producing chromosomal aberrations. Host-mediated assays in mice (test organisms *Salmonella typhimurium* and *Saccharomyces cerevisiae*) were also positive (ATSDR 1996, WHO 1996).

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[40]) Conversion factors: 1 ppm = 3.96 m^3, 1 mg/m^3 = 0.25 ppm (v/v; 25 °C).
[41]) Since there are no relevant new data pertinent to this evaluation, the text of paragraph 2.2 is adopted from the earlier evaluation (Janssen et al. 1995) with slight editorial modifications.

Trans-1,2-dichloroethene
In vitro studies (tests with and without activation, for gene mutations in bacteria, gene mutations and conversions in yeasts, and chromosome aberrations in mammalian cells) were negative. An *in vivo* cytogenetic study (bone marrow) in mice with intraperitoneal application was negative. Host-mediated assays in mice (test organisms *Salmonella typhimurium* and *Saccharomyces cerevisiae*) were also negative (tests described thus far were done by the same authors and with the same study design as the ones reported above for cis-dichloroethene). In an *in vitro* test reported by Önfelt (1987), an increased number of aneuploid V79 Chinese hamster cells was observed (ATSDR 1996, WHO 1996).
Mixture of cis- and trans-1,2-dichloroethene
No data available.
Conclusion
Based on the data above, *cis*-1,2-dichloroethene is considered to be a genotoxic agent *in vivo*, producing gene mutations and chromosome aberrations. For the induction of this kind of genotoxic effect no threshold can be assumed to exist.
Trans-1,2-dichloroethene was negative in the same test systems. This isomer induced aneuploidy in an *in vitro* test (a similar study for *cis*-1,2-dichloroethene is not available). For the induction of this kind of genotoxic effect (i.e., numerical chromosome aberrations) a threshold is assumed to exist. A quantitative evaluation of the aneuploidic effect of *trans*-1,2-dichloroethene is not possible without additional experimental data.
Chronic and subchronic toxicity
Chronic toxicity studies (oral or inhalation) with 1,2-dichloroethene have not been reported. Several oral semichronic studies are available, the results of which have been evaluated by EPA in 1991 (EPA 1998), WHO (1996) and ATSDR (1996).
Cis-1,2-dichloroethene
An oral (gavage) semichronic study in rats by McCauley et al. (1995) showed decreased body weight (in males at 97 and 290 mg/kg bw), decreased hematocrit (in males at 97 and 290 mg/kg bw) and decreased hemoglobin (in both sexes at 290 mg/kg bw). The NOAEL in this study was 32 mg/kg bw/day. Data on dermal and inhalation toxicity are not available.
Trans-1,2-dichloroethene
A 90-day drinking-water study in mice by Barnes et al. (1985) showed increased serum alkaline phosphatase and increased relative liver weight in males at 175 and 387 mg/kg bw/day, and decreased relative thymus weight at 224 and 452 mg/kg bw/day in females. This study included an evaluation for immunotoxicity (reported by Shopp et al. 1985) at day 4-5 after cessation of exposure, the result of which showed a decrease in spleen antibody-forming cells in males (at 175 and 387 mg/kg bw) and enhanced spleen cell response to lipopolysaccharide in females (at 452 mg/kg bw only). The NOAEL from this study is 17 mg/kg bw/day.
The same protocol was used for a 90-day drinking water study in rats (Hayes et al. 1987), that showed decreased kidney weights (without concomitant histological changes) in females as the only detectable change (at 1257 and 2809 mg/kg bw/day, absent at 352 mg/kg bw/day).
In a limited semichronic inhalation study (Freundt et al. 1977), rats were exposed to 780 mg/m^3 for 8 hours/day, 5 days/week during periods of 8 or 16 weeks. Effects were seen in livers (slight to severe fatty degeneration of the liver lobules and Kupffer cells) and lungs (pulmonary hyperaemia, alveolar septal distention and pneumonic infiltration). This study does not yield a NOAEL, the LOAEL is 780 mg/m^3, equivalent with 185 mg/m^3 after adjustment for continuous exposure.
In a teratogenicity inhalation study with rats (Hurtt et al. 1993), maternal body weights and food consumption were decreased at 23760 and 47520 mg/m^3 (exposure for 6 hours/day, day 7-16 of gestation), and foetal body weights were decreased at 47520 mg/m^3 only. The NOAEL in this study was 7900 mg/m^3 (equivalent with continuous exposure to 2000 mg/m^3).
The only dermal tests available showed the undiluted compound to be irritating to skin and eyes. Further information for this route is not available.

5.2.3. EVALUATION

Based on the data presented in paragraph 5.2.2 with respect to carcinogenicity and genotoxicity, it is concluded that *cis*-1,2-dichloroethene should be considered as a genotoxic agent *in vivo,* producing gene mutations and chromosome aberrations. However, carcinogenicity data are not available, and hence the risk estimation has to be based on non-carcinogenic toxicity data (as was done in the 1995 evaluation of Janssen et al.).
The *trans*-isomer was negative in *in vivo* test systems, but induced aneuploidy in an *in vitro* test. For the induction of this kind of genotoxic effect (i.e., numerical chromosome aberrations) the threshold approach is applicable.
From the data presented in paragraph 5.2.2 on the (sub)chronic oral toxicity of the dichloroethene isomers it is concluded that new data (which would warrant new TDI estimations, different from those presented in 1995) are not available. Thus, the earlier values (Janssen et al. 1995) of 6 µg/kg bw/day for *cis*-1,2-dichloroethene based on the study of McCauley et al. (1995) applying a UF of 5000 [42]), and 17 µg/kg bw/day for *trans*-1,2-dichloroethene based on the study of Barnes et al. (1985) applying a UF of 1000 [43]), are to be retained as the TDIs.
In 1995 the TCAs were based on the TDIs and estimated via route-to-route extrapolation. However, the indications for route-specific metabolism make route-to-route extrapolation particularly vulnerable.
Regarding the *trans*-isomer the study of Freundt et al. (1977) is chosen as the pivotal one (which is the same study as chosen in the German risk estimation; FoBiG 1992). In this study a number of effects were noted at 780 mg/m^3 (equivalent with 185 mg/m^3 after adjustment for continuous exposure). Taking this LOAEL and applying a UF of 3000 [44]) results in a provisional TCA (pTCA) of 60 µg/m^3; it is provisional because of the use of the LOAEL from a study of limited duration.
Due to the lack of inhalation data for the *cis*-isomer, the pTCA of 30 µg/m^3 for this isomer as derived by Janssen et al. (1995) was and still has to be extrapolated from the TDI, which was estimated with a UF of 5000; this UF is considered large enough to protect against adverse effects following continuous inhalation exposure, also taking into account the extra uncertainty due to route-to-route extrapolation. Because of this route-to-route extrapolation the tolerable concentration in air of the *cis*-isomer is provisional.

5.2.4. EVALUATIONS BY OTHER ORGANISATIONS

The WHO based its drinking water guideline of 50 µg/L (both isomers; WHO 1996) on a TDI of 17 µg/kg bw/day derived from the NOAEL of 17 mg/kg bw/day in the study of Barnes et al. (1985).
Germany estimated a guideline value of 17 µg/kg bw/day for long-term oral exposure to the *cis*- and/or the *trans*-isomer (based on the NOAEL of 17 mg/kg bw/day from the study of Barnes et al. (1985) of the *trans*-isomer in the mouse, using a safety factor 1000), and a guideline value of 50 µg/m^3 for long-term inhalation exposure to the *cis*- and/or the *trans*-isomer (provisional; based on the LOAEL of 780 mg/m^3 from the study of Freundt et al. (1977) of the *trans*-isomer in the rat, by extrapolating from rat inhalation to rat oral, deriving a human limit value using a safety factor of 10000, and extrapolating from human oral to human inhalation to arrive at the limit concentration in air) (FoBiG 1992).
ATSDR (1996) estimated an intermediate-duration oral MRL for the *cis*-isomer of 0.3 mg/kg bw/day (based on the NOAEL of 32 mg/kg bw/day from the study of McCauley et al. 1995), an intermediate-duration oral MRL for the *trans*-isomer of 0.2 mg/kg bw/day (based on the NOAEL of 17 mg/kg bw/day from the study of Barnes et al. 1985), and an inhalation MRL for the *trans*-isomer (for both acute- and intermediate-duration exposure) of 0.8 mg/m^3 (based on the LOAEL of 780 mg/m^3 from the study of Freundt et al. 1977).

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[42]) 10×10×10×5: interspecies- and intraspecies differences, limited study duration, and severity of endpoint (i.e., no-threshold genotoxic action), respectively.
[43]) 10×10×10: interspecies- and intraspecies differences, and limited study duration, respectively.
[44]) 10×10×10×3: inter- and intraspecies differences, using a LOAEL, and limited study duration, respectively.

EPA (1999) estimated in 1989 only an oral RfD (≈ TDI) for the *trans*-isomer. This RfD was estimated to be 20 µg/kg bw/day, based on the NOAEL of 17 mg/kg bw/day from the study of Barnes et al. (1985).

Exposure limits for 1,2-dichloroethene

	cis-1,2-dichloroethene		*trans*-1,2-dichloroethane	
	oral (µg/kg bw/day)	inhalation (µg/m^3)	oral (µg/kg bw/day)	inhalation (µg/m^3)
Germany	17 *)	50 *)	17 *)	50 *)
US - ATSDR	300	n.e.	200	800
US - EPA	n.e.	n.e.	20	n.e.
Netherlands	6	30	17	60

n.e. not established
*) sum of cis- and trans-isomer by either route

5.2.5. BACKGROUND EXPOSURE

Data for the Netherlands or for other European countries are not available. In urban and suburban areas in the USA average concentrations of *cis*-1,2-dichloroethene varied from 0.04 to 0.30 µg/m^3 (average 0.27 µg/m^3); in rural areas the level of 1,2-dichloroethene was <0.02 µg/m^3. In the USA the compound was not detectable in drinking water prepared from surface water; in drinking water prepared from groundwater, however, the compound was detected in approx. 8% of the systems with maximum concentrations of 2-120 µg/L (ATSDR 1996). Using these data, and in accordance with the estimations of the WHO (1996) the background exposure can be estimated at 0.13 µg/kg bw/day [45]).

5.2.6. CONCLUSION

Compound	TDI	TCA	Background exposure	Odour threshold
cis-1,2-Dichloroethene	6	30 [a])	0.13 [c])	n.a.
trans-1,2-Dichloroethene	17	60 [b])		68 × 10^3

TDI: tolerable daily intake (oral exposure); µg/kg bw/day
TCA: tolerable concentration in air (inhalation exposure); µg/m^3
Background exposure; µg/kg bw/day
Odour threshold; µg/m^3
[a]) Provisional because it is derived via route-to-route extrapolation
[b]) Provisional because of the poor database
[c]) Background exposure for the two isomers together
n.a. No data available

Relevant routes of exposure in case of soil contamination: oral and inhalation.

5.2.7. REFERENCES

ATSDR (1996):
Toxicological profile for 1,2-dichloroethene (update).
Agency for Toxic Substances and Disease Registry
US Department of Health & Human Services, Public Health Service, Agency of Toxic Substances and Disease Registry, Atlanta (GA), USA.

Barnes DW, Sanders VM, White KL, Shopp GM & Munson AE (1985):
Toxicology of trans-1,2-dichloroethylene in the mouse.
Drug Chem Toxicol 8, 373-392 *(cited in WHO 1996 and ATSDR 1996).*

[45]) 0.27×20/70 (from air; adult breathing volume of 20 m^3) + 2×2/70 (from drinking water; adult consumption of 2 L/day) = 0.13 µg/kg bw/day.

EPA (1998):
Integrated Risk Information System (IRIS):
- summary for cis-1,2-dichloroethylene, dated May 5, 1998; last revision December 1990 .
- summary for trans-1,2-dichloroethylene, dated May 5, 1998; last revision March 1991.
US Environmental Protection Agency, Washington DC, USA.

FoBiG (1992):
Basisdaten Toxikologie für umweltrelevante Stoffe zur Gefahrenbeurteilung bei Altlasten - Forschungsbericht 102 03 443/01: 1,2-Dichlorethen.
Umweltbundesamt, Forschungs- und Beratungsinstitut Gefahrstoffe, Freiburg i. Br., Germany.

Freundt KJ, Liebaldt GP & Lieberwirth E (1977):
Toxicity studies on trans-1,2-dichloroethylene.
Toxicology 7, 141-153.

Hayes JR, Condie, LW, Egle JL & Borzelleca JF (1987):
The acute and subchronic toxicity in rats of 1,2-dichloroethylene in drinking water.
J Am Coll Toxicol 6, 471-478 *(cited in WHO 1996).*

Hurtt ME, Valentine, R & Alvarez L (1993):
Developmental toxicity of inhaled trans-1,2-dichloroethylene in the rat.
Fundam Appl Toxicol 29, 225-230 *(cited in ATSDR 1996).*

Janssen PJCM, Apeldoorn ME van, Koten-Vermeulen JEM van & Mennes WC (1995):
Human-toxicological criteria for serious soil contamination - compounds evaluated in 1993 and 1994.
RIVM report no. 715810009, August 1995; National Institute of Public Health and the Environment, Bilthoven, The Netherlands.

Janssen PJCM & Speijers GJA (1997):
Guidance on the derivation of Maximum Permissible Risk levels for human intake of soil contaminants.
RIVM report no. 711701006, January 1997; National Institute of Public Health and the Environment, Bilthoven, The Netherlands.

McCauley PT, Robinson M, Daniel FB & Olson GR (1995):
The effect of subacute and subchronic oral exposure to cis-1,2-dichloroethylene in Sprague-Dawley rats.
Drug Chem Toxicol 18, 171-184.

Önfelt A (1987):
Spindle disturbances in mammalian cells. III. Toxicity, c-mitosis and aneuploidy with 22 different compounds. Specific and unspecific mechanisms.
Mutation Res 182, 135-154.

Shopp GM, Sanders VM, White KL & Munson AE (1985):
Humoral and cell-mediated immune status of mice exposed to trans-1,2-dichloroethylene.
Drug Chem Toxicol 8, 393-407 *(cited in WHO 1996).*

WHO (1996):
Guidelines for drinking-water quality, 2nd. ed., vol. 2: Health criteria and other supporting information - 1,2-dichloroethene; pp 438-444.
World Health Organization, Geneva, Switzerland.

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5.3. TRICHLOROETHENE

5.3.1. INTRODUCTION

Trichloroethene (C_2HCl_3; synonyms: trichloroethylene, tri) is a widely used industrial solvent. It is mainly used for dry cleaning, for the degreasing of fabricated metal parts, as a solvent for fats, waxes, resins, oils, rubber, paints, and varnishes, and as an inhalation analgesis and (in the past) as anaesthetic. Trichloroethene is a readily volatile, colourless liquid with a sweet ethereal smell (chloroform-like) [46]). The odour thresholds in air and water are 546-1092 mg/m^3 and 0.3 mg/l, respectively (WHO 1995, 1996).
The compound was evaluated within the scope of the present project in 1991. The inhalatory limit value as originally proposed for trichloroethene in the RIVM Basisdocument of 1984 was adopted as the tolerable concentration in air (TCA). Thus, a TCA of 1900 µg/m^3 was proposed for trichloroethene based on a NOAEL of 189 mg/m^3 from a 90-day study in five animal species [47]). A tolerable daily intake (TDI) of 540 µg per kg body weight (bw) per day was derived by applying route-to-route extrapolation on the TCA of 1900 µg/m^3. General mean population background exposure was estimated to be 0.3 µg/kg bw/day (Vermeire et al. 1991).
Relevant routes in case of soil contamination: oral and inhalation.

5.3.2. TOXICOLOGY

Toxicokinetics

Trichloroethene is readily absorbed following inhalation and oral exposure. For pulmonary uptake in humans percentages ranging from 37 to 64% have been reported. Via the oral route, absorption is extensive with percentages of 80 to 98% observed in mice and after a single dose. No actual rates of absorption have been measured in humans, but cases of poisoning indicate that the absorption across the gastrointestinal mucosa is extensive (ATSDR 1997, WHO 1995).
Limited data in animals and humans indicate that after absorption trichloroethene is distributed to all body tissues and that it crosses the blood brain barrier and the placenta. Highest concentrations occur in adipose tissues (WHO 1995). Trichloroethene has also been found in breast milk (ATSDR 1997).
Regardless of the route of exposure, humans metabolise between 40 and 75% of the absorbed trichloroethene, mainly in the liver. After inhalation some metabolism also occurs in the Clara cells of the lungs. The major transformation route is oxydation (by cytochrome P450 mixed-function oxygenases) giving trichloroethanol, trichloroethanol-glucuronide and trichloroacetic acid as principal metabolites. An important metabolic intermediate is the reactive epoxide, trichloroethylene oxide, which can alkylate nucleic acids and proteins (ATSDR 1997, WHO 1995). A minor transformation route involves the formation of mercapturic acids. Although all species share common metabolic pathways, differences between species and strains have been identified in the saturability of the trichloroethene metabolism; mice show the highest levels of oxydative biotransformation, resulting in high levels of trichloroacetic acid. The metabolites of trichloroethene are predominantly excreted in the urine, with a small proportion eliminated in the bile and faeces. Most unmetabolised trichloroethene is exhaled (ATSDR 1997, WHO 1995).

Toxicity

Since the 1991 evaluation several reviews of the toxicology of trichloroethene have appeared. The compound was evaluated by the US-ATSDR in 1997 (ATSDR 1997), by Health Canada in 1993 (CEPA 1993) and the WHO/IARC in 1995 (IARC 1995). The WHO Air Quality Guideline for tetra-

[46]) Conversion factors: 1 ppm = 5.46 mg/m^3, 1 mg/m^3 = 0.183 ppm.
[47]) Reference: Prendergast et al. (1967).

chloroethene was updated in 1995 (WHO 1995) [48]). In addition, the compound is under review in the EU Existing Chemicals Programme, in which scope a draft Risk Assessment Report (RAR) has been prepared [49]). As yet, the latter document has not been finalised.
The available toxicological data base for trichloroethene comprises both animal studies and studies in humans. Despite the large data base the number of studies that qualifies as a basis in the derivation of toxicological limit values is very limited.
The main health effects of trichloroethene are cancer, and effects on liver, kidneys and the central nervous system (CNS).

Carcinogenicity and genotoxicity

Carcinogenicity

The carcinogenicity of trichloroethene has been investigated in a number of long-term animal studies, using the oral and inhalation routes, and involving hamsters and a variety of strains of rat and mouse. Several of the studies, however, show limitations when compared to standard protocols for regulatory toxicity testing.
The main findings of the oral studies were increased incidences of hepatocellular adenomas and carcinomas in mice and increased incidences of uncommonly occurring renal tubular-cell adenomas and adenocarcinomas and Leydig-cell (interstitial) testicular tumours in male rats.
The main findings of the inhalation studies were increased incidences of lymphomas, hepatomas (not specified) and pulmonary adenomas and carcinomas in mice and increased incidences of renal tubular-cell tumours and Leydig-cell testicular tumours in male rats. No increase in tumour incidence was found in the hamster study (IARC 1995, WHO 1995).
The significance for humans of these tumours has been evaluated by several groups of experts (CEPA 1994, WHO 1995, RIVM 1999a). The liver tumours are most likely due to the species-specific high trichloroacetic acid levels that are produced in mice because of the higher level of biotransfomation in this species. In the formation of the liver tumours peroxisome proliferation is thought to play a role; probably humans are less sensitive to this effect. The significance of the increase in malignant lymphomas in the study in NMRI mice is questionable in view of the lack of a clear dose-response for the effect, the high spontaneous incidence in this particular strain of mice and the absence of a similar effect in all other studies (WHO 1995, RIVM 1999a).
As to the relevance of the other tumour findings (lung, kidney, testes) interpretation is less straightforward and the scientific issues raised in this discussion in part have not been resolved as yet. The mechanism of the lung tumours in mice was insufficiently known according to the WHO in 1995, but more recent data lend additional support to the hypothesis of the tumours being the endresult of species-specific cytotoxic effects in the Clara cells of the lungs in mice (RIVM 1999a). For the low incidences of renal-cell carcinomas seen in two rat studies the development of these tumours may be related to the toxic effect in this organ (as was concluded by WHO 1995) or, as recently has been put forward, to strongly increased levels of formic acid in urine seen after dosing with trichloroethylene. As to the interpretation of the rat testes tumours, seen in strains of rats with a low spontaneous incidence, WHO (1995) stressed that the mechanism of formation is unknown (and used these tumours for a quantitative cancer risk estimate) whereas a specialized EU Working Group gave litte weight to these tumours (RIVM 1999a). The IARC conluded in 1995 that there is *sufficient evidence* for carcinogenicity in experimental animals (IARC 1995). The EU Working Group arrived at the same conclusion (RIVM 1999a).
A number of epidemiological studies on the occurrence of cancer in trichloroethene exposed populations are available. In its 1995 evaluation the IARC considered three cohort studies (Spiritas et al. 1991, Axelson et al. 1994, Antilla et al. 1994) particularly relevant. The most important observations were the elevated risk for cancer of the liver and biliary tract and the modestly elevated risk for non-Hodgkin's lymphoma in all three studies. Two of these studies reported data for primary liver cancer

[48]) The RIVM contributed to this evaluation through preparation of the trichloroethene working document and by participating in the Working Group in which this document was reviewed and used for developing an updated WHO Air Quality Guideline for the compound.

[49]) In this EU programme draft RARs are prepared by contact points in the individual member states. The RAR for trichloroethene was prepared by experts from the UK. In the Netherlands, the RIVM and TNO participate in this risk assessment programme.

seperately. The IARC also noted the 'suggested marginally increased risk for non-Hodgkin's lymphoma in areas with trichloroethene-contaminated groundwater'. It was concluded that there is *limited evidence* for carcinogenicity in humans. The compound was classified in IARC Group 2A: *'probably carcinogenic to humans'* (IARC 1995).
Within the framework of the Classification and Labelling of trichloroethene (part of the EU Risk Assessment Programme) there is ongoing discussion on the epidemiological data, also because a few recent epidemiologic studies - although debatable - raised some concern for cancer and trichloroethene exposure (mainly renal tumours) (EC 1997).
Genotoxicity
Trichloroethene genotoxicity has been studied in a large number of *in vitro* and *in vivo* test systems. For a great number of these assays the interpretation of the results is difficult due to the presence, in the trichloroethene samples, of impurities with known mutagenic activity, such as the epoxide stabilisers epichlorohydrin and 1,2-epoxybutane. Studies performed with purified trichloroethene do not show a consistent pattern, but indicate that trichloroethene has a weak mutagenic action at the most. Trichloroethene is positive in a number of *in vitro* gene mutation tests. Trichloroethene is not clastogenic *in vitro*. The results of *in vivo* tests indicate that dosing of trichloroethene only (weakly) leads to numerical chromosome aberrations (aneuploidy), which effect may be due to the metabolite chloral hydrate, a known aneugen (WHO 1995, RIVM 1995, 1997). As to the potency of trichloroethylene to produce gene mutations or chromosome aberrations *in vivo* where formerly no firm conclusion could be drawn a recent test for gene mutations in transgenic mice (Douglas et al. 1999) *in vivo* was negative indicating that the compound lacks activity for these endpoints (RIVM 1999b). A few limited studies for genetic effects in occupationally exposed workers have been performed; the results were inconclusive (WHO 1995). According to the ATSDR, data suggest that trichloroethene is a very weak, indirect mutagen (ATSDR 1997).
In conclusion, the available evidence concerning the possible genotoxicity of trichloroethylene shows that *in vivo* the compound produces numerical chromosome aberrations (aneuploidy). For the other genotoxicity endpoints *in vivo*, the activity observed in some *in vitro* studies, according to the available *in vivo* results does not lead to a positive response in intact animals. For the induction of numerical chromosome aberrations by chemical compounds a threshold is assumed to exist.
Chronic and subchronic toxicity
The primary target organs for trichlorothylene non-cancer toxicity in humans and animals after oral and inhalation exposure are the liver, the kidneys and the central nervous system (CNS) (WHO 1995).
For both exposures routes all available experimental toxicity studies show limitations when compared to standard protocols for regulatory toxicity testing. In many of the short-term studies no or very limited histopathology was carried out, thus reducing the value of the study.
For the oral route the human database is limited. From a number of individual case studies it appears that the CNS depression is the main toxic effect after single oral doses of about 450 mg/kg bw and above (ATSDR 1997). The studies involving populations living in areas in which well water was contaminated with trichloroethene (and other contaminants) are considered not suitable for limit value derivation because of several shortcomings (ATSDR 1997).
Since 1991, no new (sub)chronic oral studies with experimental animals according to standard protocol testing have become available. Several international groups of experts have derived limit values for short- or long-term duration on the basis of the following toxicological endpoints: hepatotoxicity, immunotoxicity, carcinogenicity and developmental neurotoxicity *(for the latter see reproductive and developmental toxicity)*). The results of several animals studies also indicate that renal effects might be critical.
The study that has been used by the WHO in its limit value derivation is the 6-week oral study in mice of Buben and O'Flaherty (1985) in which dose-related increases in hepatic DNA, relative liver weight and hypertrophy of the liver were apparent at 100 mg/kg bw and above. The LOAEL from this study was 100 mg/kg bw (Buben and O'Flaherty 1985, cited in WHO 1996). According to ATSDR the lowest dose in this study (100 mg/kg bw) is a NOAEL (ATSDR 1997).
Another oral study that has been used in limit value derivation is the study of Sanders et al. (1982) in which mice received trichloroethene by gavage for 14-days (only males; 0, 24 or 240 mg/kg bw) or through drinking water for 4 to 6 months (both sexes; approx. 18, 200, 400 and 800 mg/kg bw). A significant and dose-related inhibition of cell-mediated immunity of males exposed by gavage was

shown. In the drinking water study a significantly suppressed humoral and cellular response was shown at 400 mg/kg bw and 800 (dose-related). The NOAEL from this study was 200 mg/kg bw (RIVM 1984, ATSDR 1997). FoBiG, however, considered the effects at the lowest dose level (suppressed delayed type hypersensitivity responses and impaired bone marrow stem cell colonisation in females and effects on the recruitability of peritoneal exudate cells from males) toxicologically relevant and thus used a LOAEL of 18 mg/kg bw in its limit value derivation (FoBiG 1992). According to ATSDR limitations of this subchronic study include the lack of a clear dose-response and the transient nature of some of the responses (ATSDR 1997).
In a limited 52-week study of Maltoni et al. (1986) renal toxicity (tubular nucleocytosis) was reported at a dose of 250 mg/kg bw. The NOAEL from this study was 50 mg/kg bw. According to ATSDR this study has numerous limitations because of unusual reporting methods, such as failure to indicate the number of surviving animals and the absence of GLP (ATSDR 1997).
In oral long-term carcinogenicity studies in mice and rats (NCI 1976, NTP 1988, 1990) trichloroethene elicited body weight changes and dermal, ocular or hepatic effects and also renal toxicity (cytomegaly and slight to well marked toxic nephrosis) at doses of 500 mg/kg bw and above. No NOAEL could be derived from these studies (ATSDR 1997).
Taken all data together, the level of 50 mg/kg bw is selected as the overall NOAEL for chronic oral exposure. The total database on oral toxicity, however, shows several limitations and is considered less reliable.
For the inhalation route numerous case studies and studies among occupationally exposed workers are available. The main target organ for acute or short-term trichloroethene toxicity in humans appears to be the CNS. In studies with volunteers decreased psychomotor performance, visual-motor disturbances and mild subjective complaints, such as fatigue and drowsiness, were seen at concentrations $\geq$1080 mg/m^3 (Stewart et al. 1970). At lower exposure levels the results of neurobehavioural tests in humans did not show a consistent pattern (ATSDR 1997). Health surveys carried out among occupationally exposed workers consistently report effects on the CNS and, in some cases, on the liver. Intolerance to alcohol, shown as transient redness affecting mainly the face and the neck, has also been reported frequently. The value of these studies for limit value derivation is limited due to the lack of *detailed* exposure data, simultaneously exposure to other substances (including alcohol) and in many studies, the absence of a control group. Because of the lack of accurate exposure data (of trichloroethene concentrations in air), the WHO attempted to relate human health effects to the urinary excretion of the metabolite trichloroacetic acid. Adverse health effects related mainly to the CNS were reported in the majority of the studies when the urinary excretion of trichloroacetic acid was at a level of over 50 mg/l, which seems to correspond best to the time-weighted average concentration of 135 mg/m^3 (WHO 1987, 1995).
In a recent study of Dutch workers regularly exposed to 189 mg/m^3 (35 ppm; the Dutch MAC value), investigators found a significant association between years of exposure and masseter reflex (a measure of trigeminal nerve function) (ATSDR 1997). In a cross-sectional study in Japanese workers total cholesterol and high-density-lipoprotein cholesterol slightly increased with increasing exposure levels of corresponding to 5.4, 32 and 190 mg/m^3. There was no control group in this study (WHO 1995). In another cross-sectional study no evidence for nephrotoxicity (evaluated by the tubular enzyme N-acetyl-a-D-glucosaminidase in urine) was found in workers exposed to low levels of trichloroethene (average concentration 5 ppm, corresponding to 27 mg/m^3) (WHO 1995).
Since the 1991 evaluation no new subchronic or chronic inhalation studies with experimental animals according to standard protocol testing became available. Several expert groups derived limit values for short- or long-term duration on the basis of the following endpoints: hepatotoxicity, carcinogenicity and neurotoxic/neurobehavioural effects.
The liver, kidneys and central nervous system are the main target organs of trichloroethene inhalation toxicity. With respect to hepatotoxicity, mice are more sensitive than rats. In a series of experiments in mice continuous (24 hours/day) inhalational exposure to trichloroethene for 30 days at concentrations of 200, 405, 810 and 1620 mg/m^3 produced a dose-related increase in liver weight at all dose levels. Plasma butyrylcholinesterase activity, an enzyme produced by the liver, an increased activity of which may indicate early stages of liver toxicity, showed a dose-related increase in males only. Morphological changes in liver (enlarged and vacuolated hepatocytes) were present at 810 mg/m^3 and, as is stated but not fully reported, at all other dose levels as well ("similar morphological picture"). The

histological changes increased in severity when the exposure period was increased to 120 days (this was demonstrated for the 810 mg/m^3 dose concentration only). The liver changes were reversible in that at 120 days after cessation of exposure the weight increase had disappeared and the histological changes were present to a slight degree only (again, this was shown for the 810 mg/m^3 dose level only). The LOAEL from this study is 200 mg/m^3 (Kjellstrand et al. 1983, cited in WHO 1995).
Since trichloroethene toxicity is related to CNS depression, several experiments were performed to study the neurotoxic and neurobehavioural effects using a variety of experimental models with concentrations varying from 270 to 43300 mg/m^3 and exposure times ranging from a few days to 44 weeks. In rats exposed to 270 or 540 mg/m^3 trichloroethene (8 hours/day, 5 days/week for 6 weeks) effects on sleep patterns were observed (altered sleep/wakefulness and heart rate rythms). No NOAEL could be derived from this study (Arito et al. 1994, cited in ATSDR 1997). Gerbils continuosly exposed to trichloroethene for 3 months showed increased brain S100 protein content, consistent with brain astroglial hypertrophy and proliferation, at 324 mg/m^3. In a 30-d study in rats decreased shock avoidance was reported at 675 mg/m^3 trichloroethene (4 hours/day, 5 days/week) and rats exposed to 540 mg/m^3 for 5 weeks (6 hours/day, 5 days /week) showed reduced social behaviour. Inhalation of 1890 to 5400 mg/m^3 for 12 or 13 weeks resulted in altered amplitudes of visual-, auditory- and flash-evoked potential in rabbits and rats. The NOAEL in rats for altered amplitudes of flash-evoked potentials was 1350 mg/m^3 (13-week study). A study that examined the interaction between exposure concentration and time of exposure on CNS function found that concentration, rather than time of exposure, was important in determining effects (ATSDR 1997).
The renal effects produced by trichloroethene are of a mild nature and have been found to occur at higher levels than the liver- and CNS effects. In a limited long-term cancer bioassay kidney tubule meganucleocytosis was seen at 1620 and 3240 mg/m^3 in male rats, but not in female rats or mice of either sex; the NOAEL for kidney toxicity in this study was 540 mg/m^3. The study authors considered that this histopathological change might be a precancerous lesion; however, no kidney tumours were observed (Maltoni et al. 1988). According to the ATSDR this study has serious shortcomings (unusual reporting method, a lack of appropriate pathological data on tumours observed, lack of complete report on methodology and inadequate laboratory operation procedures used). In addition, there was lack of independent pathology reviewers and no GLP statement (ATSDR 1997).
In mice less serious and partly transient, pulmonary effects (vacuolization of Clara cells, reduction of P-450 activity in the lungs) were reported after acute or short-term exposure to 540-2700 mg/m^3. The NOAEL was 108 mg/m^3 (6-hour exposure) (ATSDR 1997). These pulmonary effects in mice are thought to be species-specific due to the high level of oxidative metabolism of trichloroethene in mouse Clara cells, and are thus considered not relevant for humans. In mice exposed to 54 mg/m^3 for 3 hours an increased susceptibility to *Streptococcus zooepidemicus* infection was reported. The NOAEL from this study was 27 mg/m^3. The specific mechanism of the increased susceptibility is unknown. Histopathological changes on the spleen were not observed in other animal species exposed to 3780 mg/m^3 for 6 weeks (8 hours/day, 5 days/week) or continuously to 189 mg/m^3 for 90 days (ATSDR 1997, RIVM 1984).
Because of the very short exposure time and the fact that there are no indications for effects on the immune system after inhalation exposure from other experimental studies, the significance of this result cannot be determined for which reason this study result is left out of consideration.
From the above data, no overall NOAEL could be derived. The available evidence points towards overall LOAELs of 200 and 270 mg/m^3 for hepatotoxicity and CNS depression, respectively. The database with respect to toxicity upon inhalation is more extensive than the database for the oral exposure route. Although several individual studies show limitations, the reliability of the total database is considered sufficient.
The current TCA has been based on the limited study of Prendergast et al. (1967, cited in RIVM 1984), in which five animal species (rats, guinea-pigs, rabbits, monkeys and dogs) were continuously exposed to 189 mg/m^3 for 90 days. In this study no effect on survival, behaviour, macroscopy and microscopy of a number of tissues (among others liver, spleen and kidneys) could be detected in any species. The NOAEL from this study was 189 mg/m^3 (Prendergast et al. 1967, cited in RIVM 1984).

Reproductive and developmental toxicity
In oral reproduction studies in rats and mice adverse effects on reproductive performance were observed only at exposure levels that produce general toxicity in adult animals. Reported NOAELs are 100 mg/kg bw in rats and 375 mg/kg bw in mice (ATSDR 1997).
In developmental inhalation studies in rats and mice there was no evidence of developmental toxicity at doses up to 9720 mg/m^3 (BUA 1995, WHO 1995). In a number of small-scale non-standard oral studies in rats, neurological (decreased myelination of brain neurons, decreased uptake of 2-deoxy-D-glucose in the brain) and neurobehavioural effects (transient changes in rearing open field activity, changes in exploratory behaviour) on developing pups from exposed dams have been reported. The LOAELs from these studies are 37-75 mg/kg bw (Fredriksson et al. 1993, Taylor et al. 1985, Isaacson and Taylor 1989, Noland-Gerbec et al. 1986, cited in ATSDR 1997). Because these studies were of limited scope, further investigations are necessary before conclusions can be drawn on developmental neurotoxicity.
The results of epidemiological studies on the possible effects on reproduction and development in occupationally exposed subjects (exposure by inhalation, and possibly also dermal) are inconclusive (WHO 1995).

5.3.3. EVALUATION

Based on the data presented in paragraph 5.3.2 with respect to carcinogenicity and genotoxicity, it is concluded that trichloroethene is a genotoxic and carcinogenic compound. For the specific type of genotoxicity produced by trichloroethene (only numerical chromosome aberration *in vivo*) a threshold of action is assumed to exist. Therefore it is concluded that it is justified to use a threshold extrapolation method for limit value derivation.
Oral
From the data presented in paragraph 5.3.2 it is obvious that the total database on oral toxicity is limited in that there is a lack of adequate (sub)chronic studies. A provisional tolerable daily intake of 50 µg/kg bw can be calculated on the basis of the overall NOAEL of 50 mg/kg bw using a safety factor of 1,000 (10 for interspecies variation, 10 for intraspecies variation and an extra factor of 10 because of the limitations and less reliability of the database).
Because this value is in line with the TDI derived by the WHO (see paragraph 5.3.4), 50 µg/kg bw is proposed as the new provisional TDI for trichloroethene.
Inhalation
The database on toxicity upon inhalation, presented in paragraph 5.3.2, is more extensive than that for the oral exposure route. Although several individual studies show limitations, the total database is considered sufficient reliable.
Human data indicate that adverse effects related mainly to the CNS occur at 8-hours exposure levels of 135 to 189 mg/m^3 or even maybe lower. These data, however, are not suitable for limit value derivation. The available experimental database is limited; no adequate (sub)chronic inhalation study is available. A number of studies, however, support the lowest-observed-effect level in humans. The available evidence points towards an overall LOAEL for hepatotoxicity and CNS depression at 200 and 270 mg/m^3, respectively [50]). These effect levels are equal to or slightly higher than the NOAEL of 189 mg/m^3 from the study of Prendergast et al. (1967), on which the previous limit value of 1900 µg/m^3 has been based.
On the basis of the overall LOAEL of 200 mg/m^3 a provisional tolerable concentration in air (TCA) of 200 µg/m^3 can be derived using a safety factor of 1000 (10 for interspecies, 10 for intraspecies and an extra factor of 10 for the use of a LOAEL). Because this value is lower than the earlier value, the value of 200 µg/m^3 is taken as the new provisional TCA for trichloroethene.

[50]) Exposure level (8-hours/day) not corrected for continuous exposure, because exposure concentration is more important in determing CNS effects than is exposure time.

5.3.4. EVALUATIONS BY OTHER ORGANISATIONS

Limit values derived by (inter)national organisations based on carcinogenic effects of trichloroethene.
In 1995 the WHO concluded that in the light of the actual data base, the increased tumour incidence in lungs and testes as observed in the animal bioassays are considered to be the best available basis for the risk evaluation. From the available evidence it can not be conclusively established whether a threshold with regard to carcinogenicity in the action of trichloroethene may be assumed. Therefore, linear extrapolation from the animal tumour data is used, providing a conservative approach for estimating human cancer risk. Using the data on the incidence of pulmonary adenomas/carcinomas in mice unit risks of 9.3×10^{-8} and 1.6×10^{-7}, can be calculated by applying the linearized multistage model. Applying the same model on the incidence of Leydig-cell tumours in the testes of rats, a unit risk of 4.3×10^{-7} can be derived. The corresponding ranges of ambient air concentrations of trichloroethene corresponding to excess lifetime cancer risks of $1{:}10^4$, $1{:}10^5$ and $1{:}10^6$ are 230-1100, 23-110 and 2.3-11 µg/m^3, respectively (WHO 1995).
Health Canada derived estimates of carcinogenic potency ($TD_{0.05}$) of 302×10^3 to 597×10^3 µg/kg bw a day using multistage modelling of animal cancer data (pulmonary/carcinomas adenomas in mice and Leydig-cell testicular tumours in rats) (CEPA 1994).
US-EPA has withdrawn the carcinogen assessment summary for trichloroethene following further review (US-EPA 1999).
Limit values derived by (inter)national organisations based on toxic effects of trichloroethene.
ATSDR has published oral and inhalatory Minimal Risk Levels (MRLs) [51]) for trichloroethene in 1997. The acute oral MRL is 0.2 mg/kg bw/day, based on a LOAEL of 50 mg/kg bw/day from a 7-day gavage study in young mice with behavioural changes as the critical effect [52]). For the oral route no MRLs for longer durations were derived due to the lack of appropriate data. The acute inhalatory MRL is 10.8 mg/m^3, based on a LOAEL of 1080 mg/m^3 for mild subjective neurological effects, such as fatigue and drowsiness from an inhalatory volunteer study by Stewart et al. (1970*).* The intermediate MRL is 0.54 mg/m^3, based on a LOAEL of 270 mg/m^3 for decreased wakefulness and, post-exposure, decreased heart rate and slow wave sleep from a 6-week rat study of Arito et al. (1994). For chronic inhalation exposure no MRL was derived due to the lack of appropriate data (ATSDR 1997).
In 1996 the WHO derived a TDI of 23.8 µg/kg bw by applying an uncertainty factor of 3000 to a LOAEL of 100 mg/kg bw per day for minor effects on relative liver weight in a 6-week study in mice [53]). The uncertainty factor components were 100 for inter- en intraspecies variation, 10 for limited evidence of carcinogenicity in humans, and an additional factor of 3 in view of the short duration of the study and the use of a LOAEL rather than a NOAEL. A provisional drinking water guideline value of 70 µg/l (rounded figure) is derived by allocating 10% of the TDI to drinking-water (WHO 1996).
The 'Scientific Advisory Committee to examine the toxicity and ecotoxicity of chemical compounds' (CSTE) of the European Commission concluded in 1997 that the approach adopted in the WHO Guidelines for drinking water (1993/1996) was appropriate but the guideline value proposed there was too high. Reconsideration of the data, including reassessment of the additional potential for respiratory exposure of people shows that a maximum guideline value of 30 µg/l is appropriate. It was also held that there was insufficient reassurance that trichloroethene did not pose a carcinogenic risk to man. For that reason, and because of concern abouts its carcinogenic potential, they felt that an additional tenfold safety factor should be applied to the value proposed by the WHO in 1993. On that basis a provisional guideline value of 3 µg/l was suggested (European Commission 1997).
The German Forschungs- und Beratungsinstitut für Gefahrstoffe (FoBiG) derived limit values to be incorporated in the German method for dealing with soil contamination. A short-term inhalatory limit value (for exposure periods up to 30 days) of 0.6 mg/m^3 was derived from a short-term toxicity study

[51]) Minimal Risk Levels are advisories intended to be used by health professionals for screening for the likelihood of health effects. MRLs are derived for both the oral and the inhalatory exposure route and for three exposure periods: acute MRLs are to be applied for exposures up to 14 days, intermediate MRLs for exposures lasting 14-365 days and chronic MRLs are intended for exposures lasting longer than one year.
[52]) Reference: Frederiksson et al. (1993).
[53]) Reference: Buben and O'Flaherty (1985).

in rats [54]) with hepato- haemato- and neurotoxicity as the critical effects. The long-term inhalatory limit value is 0.07 mg/m^3, based on a 14-w study in rats [55]) with hepatotoxicity as the critical effect. For the oral route the short-term limit value (for exposure periods up to 30 days) is 0.025 mg/kg bw/day, based on a 14-d drinking water study in mice [56]) with immunotoxicity as the critical effect. The long-term oral limit value is 0.01 mg/kg bw/day, based on a subchronic drinking-water study with in mice [10]) with immunotoxicity as critical effect (FoBiG 1992).
The Dutch Expert Committee on Occupational Standards (DECOS) derived a MAC value (maximum acceptable concentration) of 190 mg/m^3 (35 ppm); the 15 minutes time-weighted average MAC value is 538 mg/m^3 (100 ppm) (Chemiekaarten 14e editie 1999).

5.3.5. BACKGROUND EXPOSURE

General population exposure via drinking-water and food is low. In the WHO document of 1995 (WHO 1995) an estimated average total intake via drinking-water of 2 µg/day is given. The estimated daily intake via food is 1 to 7 µg/day. It was noted that in countries where the use of trichloroethene in food production has been banned, the average intake probably is below this range.
Average concentrations in ambient air in urban areas range up to 10 µg/m^3; concentrations in indoor air are typically in this same range. Average concentrations in rural areas are below 1 µg/m^3 (WHO 1995). Higher concentrations may be expected in certain areas, e.g. in proximity to industrial operations. Inhalation of airborne trichloroethene is the major route of exposure for the general population. Based on these data general population background exposure is estimated to equal about 2 µg/kg bw/day (rounded value).

5.3.6. CONCLUSION

Compound	TDI	TCA	Background exposure	Odour threshold
Trichloroethene	50 *)	200 *)	2	800×10^3

TDI: tolerable daily intake (oral exposure); µg/kg bw/day
TCA: tolerable concentration in air (inhalation exposure); µg/m^3
Background exposure; µg/kg bw/day
Odour threshold; µg/m^3
*) Provisional because of limited data.

Relevant routes of exposure in case of soil contamination: oral and inhalation.

5.3.7. REFERENCES

ATSDR (1997):
Toxicological Profile for Trichloroethylene (Update).
US Department of Health & Human Services, Public Health Service, Agency of Toxic Substances and Disease Registry, Atlanta (GA), USA.

CEPA (1994):
Priority Substances List Assessment Report. Trichloroethylene. Canadian Environmental Protection Act, Health Canada.

European Commission (1997):
Opinion on trichloroethene (TCE) and tetrachloroethene (PCE): Proposals for guideline values in drinking water (expressed on 4 September 1997). Scientific Advisory Committee to examine the toxicity and ecotoxicity of chemical compounds. European Commission, Directorate-General XXIV Consumer Policy and Consumer Health Protection, Brussels, XXIV.B.2/JCD/jcd.24n32.D(97).

[54]) Reference: Fujita et al. (1984).
[55]) Reference: Kimmerle and Eben (1973).
[56]) Reference: Sanders et al. (1982).

EC (1997):
Commission Group of Specialised Experts in the fields of Carcinogenicity, Mutagenicity and Reprotoxicity. Meeting at Belgirate, 4-6 juni, 1997. Summary Record ECBI/28/97, 30.6.97. European Commission.

FoBiG (1992):
Basisdaten Toxikologie für umweltrelevante Stoffe zur Gefahrenbeurteilung bei Altlasten. Umweltforschungsplan des Bundesministeriums für Umwelt, Naturschutz und Reaktorsicherheit, Forschunsbericht nr. 102 03 443/01 (two volumes: Zusammmenfassung & Zusammenfassung der Einzelberichte). Prepared by FoBiG Forschungs- und Beratungsinstitut Gefahrstoffe, Freiburg im Breisgau, Germany.

IARC (1995):
Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol. 63: Dry cleaning, some chlorinated solvents and other industrial chemicals.
International Agency for Research on Cancer, World Health Organization, Lyon, France.

US-EPA (1999):
IRIS File Trichloroethylene, 10 November 1999.

RIVM (1995)
Advice to ACT door LCM, J. van Benthem, dated 11-09-1995.

RIVM (1997):
Advice to CSR by LEO/CMG, J. van Benthem dated 13-02-1997.

RIVM (1999a)
Advice to the Ministry of Public Health, Welfare & Sports by LEO/CMG , E.D.Kroese, dated 04-02-1999.

RIVM (1999b)
Personal communication, J. van Benthem (LEO/CMG), November 1999.

Vermeire TG, Apeldoorn ME van, Fouw JC de & Janssen PJCM (1991):
Voorstel voor de humaan-toxicologische onderbouwing van C-toetsingswaarden.
National Institute of Public Health and the Environment, RIVM-report no. 725201005, February 1991; Bilthoven, The Netherlands.

WHO (1993/1996):
Guidelines for drinking-water quality, 2nd. Ed., vol. 2: Health criteria and other supporting information.
World Health Organization, Geneva, Switzerland.

WHO (1995):
WHO Updating and Revision of the Air Quality Guidlines for Europe: Meeting of the Working Group on Volatile Organic Compounds, 2-6 October, 1995; Draft Summary Report and Background Document.
Brussels, Belgium.

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5.4. TETRACHLOROETHENE

5.4.1. INTRODUCTION

Tetrachloroethene ($Cl_2C=CCl_2$; synomyms: tetrachloroethylene, perchloroethylene) is a synthetic chemical widely used for dry cleaning, for metal degreasing, and as a starting material for the synthesis of other chemicals. At room temperature it is a non-flammable colourless liquid which easily evaporates in air. It has a sharp, sweet odour with an odour threshold in humans of about 7 mg/m^3 (≈ 1 ppm) [57]).
The compound was evaluated within the scope of the present project in 1991. A tolerable daily intake (TDI) of 16 µg per kg body weight (bw) per day was proposed, based on a NOAEL of 16 mg/kg bw/day from a subacute gavage study in rats. The inhalatory limit value as originally proposed for tetrachloroethene in the RIVM Basisdocument of 1984 was adopted as the tolerable concentration in air (TCA). Thus, a TCA of 2500 µg/m^3 was proposed for tetrachloroethene based on a NOAEL of 135 mg/m^3 from a study in human volunteers with repeated exposure for 8 hours. General population background exposure was estimated to be 1.8 µg/kg bw/day (Vermeire et al. 1991).
Relevant routes in case of soil contamination: oral and inhalation.

5.4.2. TOXICOLOGY

Toxicokinetics

Tetrachloroethene is readily absorbed following inhalation and oral exposure as well as direct exposure to the skin. Pulmonary absorption is dependent on the ventilation rate, on the duration of exposurew, and at lower concentrations on the proportion of tetrachloroethene in the inspired air. Compared to pulmonary exposure, uptake of tetrachloroethene vapour by the skin is minimal. Once tetrachloroethene is absorped, its relative high lipophilicity results in distribution to fatty tissue. Tetrachloroethene is found in human milk and has also been shown to cross the placental barrier and to distribute to the fetus (ATSDR 1997).
Regardless of the route of exposure, humans metabolise only 1-3% of the absorbed tetrachloroethene, the metabolite being trichloroacetic acid; this metabolic pathway is saturable. Compared to humans, rodents (especially mice) metabolise more tetrachloroethene to trichloroacetic acid: geometric mean V_{max} values for this metabolism of 13, 144 and 710 nmol/min.kg have been reported for humans, rats and mice, respectively. Trichloroacetic acid produced from tetrachloroethene is excreted in the urine, and in humans the excretion of trichloroacetic acid is linearly related to the concentration of tetrachloroethene in air at levels up to about 350 mg/m^3. Unmetabolised tetrachloroethene is exhaled. The half-lifes of tetrachloroethene in vessel-rich tissue, muscle, and adipose tissue of humans have been estimated to be 12-16 h, 30-40 h, and 55 h, respectively (ATSDR 1997).

Toxicity

Since the 1991 evaluation several reviews of the toxicology of tetrachloroethene have appeared. The compound was evaluated by the US-ATSDR in 1997 (ATSDR 1997), by Health Canada (CEPA 1994) and the WHO/IARC (IARC 1995). The WHO Air Quality Guideline for tetrachloroethene was updated in 1995 (WHO 1995) [58]). In addition, the compound is under review in the EU Existing Chemicals Programme, in which scope a draft Risk Assessment Report (RAR) has been prepared [59]). As yet, the latter document has not been finalised, this risk assessment still being in progress. An *ad hoc*

[57]) Conversion factors: 1 ppm = 6.78 mg/m^3; 1 mg/m^3 = 0.1474 ppm.
[58]) The RIVM contributed to this evaluation through preparation of the tetrachloroethene working document and by participating in the Working Group in which this document was reviewed and used for developing an updated WHO Air Quality Guideline for the compound.
[59]) In this EU programme draft RARs are prepared by contact points in the individual member states. The RAR for tetrachloroethene was prepared by experts from the UK. In the Netherlands the RIVM participates in this risk assessment programme.

evaluation aimed at deriving health-based advisory values for acute and short-term exposures via the inhalation route was carried out by the RIVM in 1996 (RIVM 1996).
The available toxicological data base for tetrachloroethene comprises both animal studies and studies in humans. Despite this large data base the number of studies that qualifies for being used as a basis in the derivation of toxicological limit values is very limited.

Genotoxicity and carcinogenicity

Regarding the possible carcinogenicity of tetrachloroethene a number of animal studies are available. Within the US National Toxicology Program (NTP) both oral and inhalation studies have been carried out (NTP 1986). The main findings of these studies were increased incidences of liver tumours (hepatocellular carcinomas) in mice (oral and inhalation), and a slightly increased incidence of kidney tumours (tubular cell adenomas and adenocarcinomas) in the rat inhalation study. In the latter study also the incidence of mononuclear cell leukemias was increased. The significance for humans of these tumours has been evaluated by CEPA (1994) and WHO (1995). The liver tumours most likely are due to the species-specific high trichloroacetic acid levels that are produced in mice because of the higher level of biotransfomation in this species. In the formation of the liver tumours peroxisome proliferation is thought to play a role; probably humans are less sensitive to this effect than mice. The renal tumours seen in male rats (increase not statistically significant) were considered to constitute suggestive evidence only for a carcinogenic effect. Data on the mechanism indicate that these tumours are due to α-2u-globuline nephropathy and/or to the formation of genotoxic metabolites in the kidneys. For both of these possible mechanisms there is evidence indicating that humans are less sensitive than rats [60]). The significance of the mononuclear cell leukemias is unclear due to the lack of understanding of the mechanism underlying the formation of this cancer type, which has a high background incidence in this particular strain of rats (WHO 1995).
A number of epidemiological studies on the occurrence of cancer in tetrachloroethene exposed populations are available. IARC has reviewed this evidence in 1995. Positive associations between exposure to tetrachloroethene and the risk of oesophagal and cervical cancer and non-Hodgkin's lymphomas were found. Confounding factors, however, cannot be ruled out and the statistical power of the studies is limited (IARC 1995, WHO 1995).
Based on its evaluation of the available data IARC conluded that there is *sufficient evidence* that tetrachloroethene is carcinogenic in experimental animals and *limited evidence* for carcinogenicity in humans. The compound was placed in IARC Group 2A, the category in which chemicals are placed that are *probably carcinogenic to humans* (IARC 1995).
Tetrachloroethene genotoxicity has been studied in a large number of test systems. The weight of evidence indicates that the compound is not genotoxic (CEPA 1994, WHO 1995).

Chronic and subchronic toxicity

The primary target organs for tetrachlorothylene non-cancer toxicity are the liver, the kidneys, and the nervous system. The effect on the nervous system in humans was studied extensively, whereas information on liver effects is primarily derived from animal studies (only few human data available). Renal effects have been detected in animal studies and in several studies among workers in the dry-cleaning sector.
For the oral route relatively few human data are available. Chronic animal studies that could be used for limit value derivation are lacking. Full-quality 90-day oral toxicity studies are also lacking. In the 1991 evaluation within the present scope, a 4-week oral study in rats by de Vries et al. (1982) in which liver toxicity was seen, was used for deriving a TDI. The NOAEL in this study was 16 mg/kg bw/day with increased liver weights and increased aniline-hydroxylase activity being present at the higher dose levels of 81 and 405 mg/kg bw/day.
A second study that has been used as the pivotal study in limit value derivation is the 6-week study in mice by Buben & O'Flaherty (1985) in which liver effects were seen at ≥70 mg/kg bw/day, with a NOAEL of 14 mg/kg bw/day.

[60]) For the α-2u-globuline nephropathy this lower human susceptibility is a widely accepted hypothesis (see for instance US-EPA 1991). The evidence for the lower levels of genotoxic metabolites being formed in the human kidney compared to the rat kidney is much more limited (see for instance Volkel et al. 1998).

Another oral study is a 90-day study in rats carried out by Hayes et al. (1986). In this study the NOAEL was 14 mg/kg bw/day, with increased liver weight being observed at 400 and 1400 mg/kg bw/day. The latter study, however, did not include histopathology.
Also for the inhalation route an adequate long-term toxicity study which could be used for limit value derivation is not available. An adequate semichronic inhalation toxicity study is lacking too.
In many studies in humans, tetrachloroethene produced neurological effects after inhalation. These data are pivotal in the derivation of health-based advisory values by the ATSDR (on which the 1996 RIVM advice on short-term limit values was based).
In a volunteer study carried out by Altmann et al. (1992) with inhalatory exposure for 4 h/day on 4 subsequent days, increased visual-evoked reponse latencies and decreased performance in tests for eye-hand coordination, vigilance and reaction time were observed at 340 mg/m^3; these effects were absent at 68 mg/m^3.
In a study for neurobehavioural effects among 60 women working in dry-cleaning shops (Ferroni et al. 1992), exposure to tetrachloroethene was estimated to have lasted about 10 years on average. The median exposure concentration was 100 mg/m^3, with a range of trace to 450 mg/m^3. Exposed women had significantly prolonged reaction times in all tests (simple reaction times, and shape comparison to test vigilance and to test stress) compared to unexposed controls (n = 30). In the exposed women no significant association between measures of exposure and neurobehavioural tests was noted. From this study the ATSDR derived a LOAEL of 100 mg/m^3 (ATSDR 1997).
Renal toxicity was seen in the chronic inhalation carcinogenicity study in mice carried out by the NTP (1986). At both dose levels (680 and 1360 mg/m^3) renal tubular cell karyomegaly was seen (liver cell degeneration and necrosis were also seen at both dose levels). The LOAEL from this study was 680 mg/m^3.
In a cross-sectional study in 50 workers chronically (10 years on average) exposed to tetrachloroethene in dry-cleaning facilities, 23 urinary and serum markers of early nephrotoxic effects were measured. The median exposure concentration was 100 mg/m^3 (range: trace to 580 mg/m^3), the median blood level was 143 µg/L (range: 9-900 µg/L). Compared to the control population (n = 50), the exposed group had significantly higher frequencies of abnormal values for a great number of the markers including albumin, transferrin, tissue non-specific alkaline phosphatase, fibronectin, brush-border antigens, anti-glomerular basement membrane antibodies, and laminin fragments. The study-authors concluded these findings to be diffuse abnormalities which may well represent an early stage of clinically silent but potentially progressive renal disease, indicating a risk for chronic renal failure (Mutti et al. 1992). From this study a LOAEL of 100 mg/m^3 can be derived.
In its 1995 update of the Air Quality Guideline for tetrachloroethene WHO used the latter LOAEL for deriving a new limit value. After conversion of working-week exposure to continuous exposure (back-calculation from 40 h/wk to 168 h/wk), an uncertainty factor (UF) of 100 (10 for the use of a LOAEL and 10 for intraspecies variation) was applied to the LOAEL, giving an Air Quality Guideline value of 0.25 mg/m^3. Because of the uncertainty in the LOAEL due to the rather large range of exposure concentrations, an alternative calculation based on the LOAEL of 680 mg/m^3 from the mouse carcinogenity study (NTP 1986) was made, using a UF of 1000. Because this calculation would result in a limit value in the same order of magnitude as the value of 0.25 mg/m^3, the latter value was chosen as the Air Quality Guideline (WHO 1995). This limit value is proposed to be adopted here as the TCA for tetrachloroethene.

5.4.3. EVALUATION

Based on the data presented in paragraph 5.4.2 with respect to carcinogenicity and genotoxicity, it is concluded that tetrachloroethene is not a genotoxic carcinogen. Consequently, a threshold approach can be chosen in the limit value derivation for this compound.
From the data presented in paragraph 5.4.2 on the (sub)chronic oral toxicity of tetrachloroethene it is concluded that new data (which would warrant a TDI derivation different from that presented in 1991) are not available. Thus, the earlier value of 16 µg/kg bw/day (Vermeire et al. 1991) is to be retained as the TDI.

As outlined in paragraph 5.4.2 regarding the (sub)chronic inhalatory toxicity of tetrachloroethene, the Air Quality Guideline of 0.25 mg/m^3 as derived by the WHO in 1995 is judged to be the most well-considered limit value for inhalatory exposure, and is thus adopted as the TCA for this compound.

5.4.4. EVALUATIONS BY OTHER ORGANISATIONS

The US-EPA derivation of the RfD (≈ TDI) for tetrachloroethene dates back to 1988. A value of 0.1 mg/kg bw/day was calculated from a NOAEL of 14 mg/kg bw/day. This NOAEL was derived from the 6-week mouse gavage study carried out by Buben & O'Flaherty (1985). The derivation is supported by the NOAEL from the rat drinking-water study carried out by Hayes et al. (1986), this NOAEL also being 14 mg/kg bw/day (US-EPA 1988). The US-EPA has not derived a RfC (≈ TCA) for tetrachloroethene.
The ATSDR has published oral and inhalatory Minimal Risk Levels (MRLs) [61]) for tetrachloroethene in 1997. The acute oral MRL is 0.05 mg/kg bw/day, based on an LOAEL of 5 mg/kg bw/day from a 7-day gavage study in young mice with behavioural changes as the critical effect [62]). For the oral route no MRLs for longer durations were derived due to the lack of appropriate studies. The acute inhalatory MRL is 1.36 mg/m^3, based on a NOAEL of 67.8 mg/m^3 from the 4-day inhalatory volunteer study by Altmann et al. (1992). No intermediate inhalatory MRL was derived due to lack of data. The LOAEL of 100 mg/m^3 from the study of Ferroni et al. (1992) was the basis for the chronic inhalatory MRL. In this study increased reaction times (indicating a neurotoxic effect) were found in dry-cleaning workers. The chronic inhalatory MRL is 0.27 mg/m^3, derived from the LOAEL by extrapolating to continuous exposure (8/24 h, 5/7 days) and applying a UF of 100 (10 fore using a LOAEL, 10 for human variability) (ATSDR, 1997).
In an ad hoc assessment carried out in 1996 the RIVM proposed that the acute inhalatory MRL of 1.36 mg/m^3, as derived by the ATSDR, should be used for deriving short-term limit values for inhalation of tetrachloroethene. Thus, a level of 6.8 mg/m^3 was proposed as a maximum for 4-hour exposures and a level of 1.36 mg/m^3 as the maximum for 14 days (RIVM 1996).
In its derivation of Drinking-Water Guidelines in 1991 the WHO used the same oral NOAELs as the US-EPA in its RfD derivation. The WHO derived a TDI of 0.014 mg/kg bw/day (WHO 1991/1996).
Health Canada derived a TDI of 0.034 mg/kg bw/day, based on the LOAEL of 678 mg/m^3 from the mouse carcinogenicity study carried out by the NTP; this inhalatory LOAEL was converted to an oral dose and then divided by a UF of 5000 (CEPA 1994).
The Dutch Expert Committee on Occupational Standards (DECOS) drafted a toxicological evaluation for tetrachloroethene in 1996. A Health-Based Recommended Exposue Limit (HBROEL) of 138 mg/m^3 was proposed, based on a LOAEL of 678 mg/m^3; at this level eye irritation and neurotoxicological effects were seen in humans after short-term exposure (DECOS 1996).
The German Forschungs- und Beratungsinstitut für Gefahrstoffe (FoBiG) derived limit values to be incorporated in the German method for dealing with soil contamination. A short-term inhalatory limit value (for exposure periods up to 30 days) of 3 mg/m^3 was derived from a short-term toxicity study in mice [63]) with hepatotoxicity as the critical effect. The long-term inhalatory limit value is 0.3 mg/m^3, based on a study in humans in which neurological effects were seen [64]). For the oral route the short-term limit value (for exposure periods up to 30 days) is 0.1 mg/kg bw/day based on a 11-day mouse study [65]) with hepatotoxicity as the critical effect. The long-term oral limit value is 0.01 mg/kg bw/day, based on the mouse study by Buben & O'Flaherty (1985) with an NOAEL based on hepatoxicity (FoBiG 1992).

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[61]) Minimal Risk Levels are advisories intended to be used by health professionals for screening for the likelihood of health effects. MRLs are derived for both the oral and the inhalatory exposure route and for three exposure periods: acute MRLs are to be applied for exposures up to 14 days, intermediate MRLs for exposures lasting 14-365 days, and chronic MRLs are intended for exposures lasting longer than one year.
[62]) Reference: Frederiksson et al. (1993).
[63]) Reference: Kjellstrand et al. (1984)
[64]) Reference: Hake & Stewart (1977)
[65]) Reference: Schumann et al. (1980)

5.4.5. BACKGROUND EXPOSURE

General population exposure via drinking-water and food is low. In the WHO document of 1995 (WHO 1995) an estimated average total intake via drinking-water of ≤2 µg/day is given. The estimated daily intake via food is ≤45 µg/day. Average concentrations in ambient air in urban areas generally are below 5 µg/m^3; in rural areas these are ≤1 µg/m^3. In indoor air average concentrations of 5 µg/m^3 or less are usually found. Close to dry-cleaning shops, levels may be considerably higher with indoor levels that may be in the mg/m^3-range. Bringing home freshly dry-cleaned clothes will also lead to higher indoor concentrations than usual (WHO 1995). Based on these data general population background exposure is estimated to equal about 2 µg/kg bw/day (rounded value).

5.4.6. CONCLUSION

Compound	TDI	TCA	Background exposure	Odour threshold
Tetrachloroethene	16	250	2	7000

TDI: tolerable daily intake (oral exposure); µg/kg bw/day
TCA: tolerable concentration in air (inhalation exposure); µg/m^3
Background exposure; µg/kg bw/day
Odour threshold; µg/m^3

Relevant routes of exposure in case of soil contamination: oral and inhalation.

5.4.7. REFERENCES

Altmann L, Wiegand H, Bottger A et al. (1992):
Neurobehavioral and neurophysiological outcomes of acute repeated perchloroethylene exposure.
Applied Physiology: An International Review 41, 269-279; *cited in ATSDR (1997).*

ATSDR (1997):
Toxicological Profile for Tetrachloroethylene (Update).
US Department of Health & Human Services, Public Health Service, Agency of Toxic Substances and Disease Registry, Atlanta (GA), USA.

Buben JA & O'Flaherty EJ (1985):
Delineation of the role of metabolism in the hepatotoxicity of trichloroethylene and perchloroethylene - a dose effect study.
Toxicol Appl Pharmacol 125, 228-236; *cited in US-EPA (1988).*

CEPA (1994):
The Assessment of Risk to Human Health for Priority Substances under the Canadian Environmental Protection Act.
Environmental Carcinogenesis & Ecotoxicology Reviews – Part C of the Journal of Environmental Science and Health (special issue) 12 (2), 493-506.

DECOS (1996):
Health-Based Recommended Occupational Exposure Limit Tetrachloroethylene (PER), 4th Draft.
First Draft prepared by TNO Food and Nutrition, Department of Occupational Toxicology. The Hague, The Netherlands, November 1996.

Ferroni C, Selis L, Mutti A et al. (1992):
Neurobehavioral and neuroendocrine effects of occupational exposure to perchloroethylene.
Neurotoxicology 13, 243-247; *cited in ATSDR (1997).*

FoBiG (1992):
Basisdaten Toxikologie für umweltrelevante Stoffe zur Gefahrenbeurteilung bei Altlasten.
Umweltforschungsplan des Bundesministeriums für Umwelt, Naturschutz und Reaktorsicherheit, Forschunsbericht nr. 102 03 443/01 (two volumes: Zusammmenfassung & Zusammenfassung der Einzelberichte).
Prepared by FoBiG Forschungs- und Beratungsinstitut Gefahrstoffe, Freiburg im Breisgau, Germany.

Hayes JR, Condie LW & Borczelleca F (1986):
The subchronic toxicity of tetrachloroethylene (perchloroethylene) administered in drinking-water of rats.
Fund Appl Toxicol 7, 119-125; *cited in US-EPA (1988).*

IARC (1995):
Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol. 63: Dry cleaning, some chlorinated solvents and other industrial chemicals.
International Agency for Research on Cancer, World Health Organization, Lyon, France.

Mutti A, Alinovi R, Bergamaschi E, Biagini C, Cavazzini S, Franchini I, Lauwerys RR, Bernard AM, Roels H, Gelpi E, Rosello J, Ramis I, Price RG, Taylor SA, DeBroe M, Nuyts GD, Stolte H, Fels LM, Herbort C (1992):
Nephropathies and exposure to perchloroethylene in dry-cleaners.
Lancet 340, 189-193.

NTP (1986):
Toxicology and carcinogenesis studies of tetrachloroethylene (perchloroethylene) (CAS no. 127-18-4) in F344/N rats and B6C3F1 mice (inhalation studies).
National Toxicology Program - technical report series no. 311, NIH publication no. 86-2567.
US Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park (NC), USA.

RIVM (1996):
Perchloorethyleen: afleiding toxicologische richtwaarden voor kortdurende exposities.
RIVM ad hoc assessment dated 10 September 1996; RIVM/CSR-notitie, prepared by Janssen PJCM, Engelen JGM van & Speijers GJA.
National Institute of Public Health and the Environment, Bilthoven, The Netherlands.

US-EPA (1988):
Integrated Rsk Information System: Tetrachloroethylene (oral RfD assessment dated January 3, 1988)
US Environmental Protection Agency, Washington DC, USA.

US-EPA (1991):
Alpha-2u-globulin: association with chemically-induced renal toxicity and neoplasia in the male rat.
EPA Risk Assessment Forum 1991, report no. EPA/625/3-91/019F.
US Environmental Protection Agency, Washington DC, USA.

Vermeire TG, Apeldoorn ME van, Fouw JC de & Janssen PJCM (1991):
Voorstel voor de humaan-toxicologische onderbouwing van C-toetsingswaarden.
National Institute of Public Health and the Environment, RIVM-report no. 725201005, February 1991; Bilthoven, The Netherlands.

Volkel W, Friedewald M, Lederer E et al. (1998):
Biotransformation of perchloroethylene: Dose-dependent excretion of trichloroacetic acid, dichloroacetic acid, and N-acetyl-S-(trichlorovinyl)-L-cysteine in rats and humans after inhalation.
Toxicol Appl Pharmacol 153, 20-27.

Vries Th de, Tonkelaar EM den, Leeuwen FXR van & Danse CHJC (1982):
Onderzoek naar de subacute toxiciteit van perchloorethyleen.
National Institute of Public Health, RIV-report no. 618105 001, June 1982; Bilthoven, The Netherlands.

WHO (1991/1996):
Guidelines for drinking-water quality, 2nd. Ed., vol. 2: Health criteria and other supporting information.
World Health Organization, Geneva, Switzerland.

WHO (1995):
WHO Updating and Revision of the Air Quality Guidlines for Europe: Meeting of the Working Group on Volatile Organic Compounds, Brussels, Belgium, 2-6 October, 1995.
Draft Summary Report and Background Document.

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5.5. DICHLOROMETHANE

5.5.1. INTRODUCTION

Dichloromethane (methylene chloride) was evaluated within the scope of this project by Vermeire et al in 1991. For oral intake a TDI of 60 µg/kg bw/day was derived on the basis of a NOAEL of 6 mg/kg bw/day for effects on the liver and the central nervous system in rats. An uncertainty factor (UF) of 100 was used. In addition a TCA of 1700 µg/m^3 was derived from a NOAEL of 175 mg/m^3 (50 ppm) in rats with a UF of 100.
For the update the recent literature was reviewed. This included a review of BUA (1986), CEPA (1993), Brooke and Howe (1994), WHO (1987, 1996a, 1996b), IARC (1987, 1999), IPCS (1996), and ATSDR (1998).
There are no natural sources of dichloromethane. Consequently its natural occurrence in soil will be negligible. It is manufactured by the chemical industry in substantial quantities on a global scale.
Dichloromethane is used in the industry as a solvent for greases, plastics, and paint binding agents. It can be found in aerosols, foods and pharmaceuticals, in plastics and paints, and in textiles. It will enter the environment by its direct use as a cleaning product, or by aerial emissions and in effluents, by spills and waste disposal (Brooke and Howe 1994). This will lead to soil contaminated sites. Dichloromethane is volatile [66]) and soluble in water, and will not adsorb to the soil. Consequently, it will predominantly be found in groundwater. From this it will evaporate into the air (CEPA 1993). It can therefore be expected that exposure can occur to vapours of dichloromethane from soil and groundwater.

5.5.2. TOXICOLOGY

Toxicokinetics

Absorption
The gastrointestinal absorption of dichloromethane is rapid and almost complete. In mice the maximal blood concentration was found within 10 minutes. Data from humans are not available.
The absorption after inhalation in humans appears to be not linear. According to BUA (1986), the inhalation absorption can be described as a three part exponential function with a rapid uptake of about 50% of the initial dose, and a slower uptake of the rest. After a few hours at least a total of 70% is absorbed.
Experimental studies with humans showed that dermal absorption from direct contact with the liquid substance is very slow. However, in studies with mice up to 70% of the dose was absorbed after a dermal application.
Distribution
After inhalation exposure dichloromethane was found in the liver, lungs and brains, and perirenal fat of experimental animals. It was shown, that it accumulates predominantly in the perirenal fat (BUA 1986). After oral exposure the liver is the primary target organ (WHO 1996a, IPCS 1996, ATSDR 1998).
Metabolism
Dichloromethane is transformed into carbon monoxide and carbon dioxide. One pathway involves microsomal cytochrome P450 in the liver, kidney and lung. This leads to carbon monoxide, carbon dioxide, and carboxy-hemoglobin (COHb) in blood. Another pathway, catalysed by glutathione-S-transferase, leads to formaldehyde and carbondioxide. This pathway is located in the cytosol (BUA 1986, CEPA 1993, IPCS 1996, ATSDR 1998).
Excretion
Unchanged dichloromethane and metabolites are both predominantly excreted by the lungs. Only small amounts of dichloromethane are detected in the urine. The half-lives differ for the various compartments; dichloromethane is eliminated from blood within 10 minutes, whereas the half-life in most organs is about one hour. From adipose tissues the half-life appears to be in the order of 7 hours.

[66]) Conversion factors: 1 mg/m^3 = 0.28 ppm; 1 ppm = 3.53 mg/m^3.

Toxicity

Acute poisoning
In laboratory animals the acute toxicity is low. It has been shown that inhalation of vapours lead to a depressant effect on the central nervous system. This causes loss of reflexes, shallow breathing, narcosis and coma, and eventually death. From accidental poisonings of humans it is known that the effects on the nervous system predominate, finally leading to narcosis. In the blood of these people high carboxy-haemoglobin (COHb) concentrations have been measured (BUA 1986).
Genotoxicity and carcinogenicity
There are no data regarding genetic and related effects of dichloromethane in humans. In experimental animals *in vivo* it did not induce chromosomal aberrations. *In vitro* it induced chromosomal aberrations, but not mutations or DNA damage in rodent cells. It is, however, mutagenic in plants, yeast, and bacteria.
In laboratory animals benign and malignant tumours of the lung and the liver have been found, both after oral and inhalation exposure. In a two years study with rats with dichloromethane in drinking water a small increase of hepatocellular tumours was reported at a dose level of 50 and 250 mg/kg bw/day. In rats and mice the tumour incidence was significantly increased following chronic inhalation exposure to 6940 and 13880 mg/m^3. Alveolar and bronchiolar neoplasms, and hepatocellular neoplasms were observed. The incidence of hepatocellular cytoplasmatic vacuolisation and multinucleated hepatocytes was significantly increased in rats exposed to 1735 mg/m^3 for two years (CEPA 1993, IPCS 1996, ATSDR 1998, IARC 1999). In human cohort studies and a mortality study no excess risk of death from cancer could be found. By PB-PK modelling which included mechanistic information it was shown that the increased tumour incidence observed in rat and mice is highly species specific (IPCS 1996, ATSDR 1998).
On the basis of these results the IARC (1999) concluded to inadequate evidence for carcinogenicity of dichloromethane to humans but sufficient evidence for carcinogenicity to animals, and classified dichloromethane in group 2B: *possibly carcinogenic to humans*.
Subchronic and chronic toxicity
There are no data on the toxicity of dichloromethane after oral exposure of humans. Chronic oral studies are only reported for mice and rats. In rats a NOAEL of 6 mg/kg bw/day was found, the NOAEL in mice is considerably higher. In these studies the hepatic effects are most prominent (WHO 1996a, IPCS 1996, ATSDR 1998).
In experimental animals the lowest LOAELs for non-neoplastic effects following chronic inhalation exposure were reported to be around 1750 mg/m^3 (CEPA 1993, IPCS 1996, ATSDR 1998); the lowest NOAEL is 700 mg/m^3 for an increased incidence of hepatocellular vacuolisation and multinucleated hepatocytes in rats exposed for 6 h/day, 5 days/week during 2 years (Nitschke et al. 1988); after correction for continuous exposure this is equivalent to an adjusted NOAEL of 126 mg/m^3.
Dichloromethane toxicity was examined in humans in several studies in workers and some volunteer studies; WHO evaluated these data in 1987 and 1995 (WHO 1987, WHO 1996b). The critical effects in humans are neurotoxicity and increased COHb levels in the blood, probably there is a causal connection between these two effects in that the CNS-effects are due to the increased COHb levels. The available evidence indicates a linear relationship between exposure concentration and CoHb levels in blood, and it was calculated that a 1% increase in COHb would be associated with a 7.5 hour exposure to about 90 mg/m^3 (DiVincenzo & Kaplan 1981, WHO 1987, WHO 1996b). In one of the studies in workers chronically exposed to concentrations of 260 - 347 mg/m^3 for 10 years or longer, no neurological disorders were found (Cherry et al. 1981).

5.5.3. EVALUATION

Dichloromethane did demonstrate some genotoxic properties in *in vitro* systems. In mammalian test systems the genotoxicity is negative. Therefore it is considered not genotoxic to humans, and a TDI value can be derived on the basis of a NOAEL with extrapolation factors.

Since the previous evaluation of Vermeire et al (1991), no relevant new data on chronic oral exposure to dichloromethane have become available. Consequently the previously derived TDI of 60 µg/kg bw/day is to be maintained.
For the inhalation route the previous MPR of 1.7 mg/m^3 was based on the NOAEL of 175 mg/m^3 selected from the 2-year inhalation study by Nitschke et al. (1988), applying a UF of 100. A critical re-evaluation of this study, however, leads to the conclusion that its NOAEL is 700 mg/m^3. Using this latter NOAEL, and now using the standard dose adjustments that are part of the current method of MPR derivation (i.e. correction of the experimental dosing regimen of 6 h/day, 5 days/week to 24 h/day, 7 days/week) would result in an adjusted NOAEL of 126 mg/m^3, leading to a limit value in air of 1.3 mg/m^3; in calculating this value a UF of 100 (for inter- and intraspecies differences) was applied. An alternative derivation of a limit value for air is the WHO Air Quality Guideline, which is based on human data. Since human data, if their quality is sufficient, are preferable in MPR derivation (their use obviates the extrapolation from animal data to humans), the WHO limit value is adopted here as the new TCA for dichloromethane. Based on an accepted increase in blood COHb of 0.1% the WHO (1987, 1996b) calculated this guideline value to be 3 mg/m^3; it was obtained by linear extrapolation from the data of DiVincenzo & Kaplan (1981) who found a 1% COHB increase following 7.5 h exposure of human volunteers to 90 mg dichloromethane per m^3 [TCA = 0.1/1 × 7.5/24 × 90 = 3 mg/m^3].

5.5.4. EVALUATION OF OTHER ORGANISATIONS

The carcinogenic action of dichloromethane was classified by the IARC (1999) in group 2B: *possibly carcinogenic to humans*. It was concluded that there is inadequate evidence for the carcinogenicity in humans.
US-EPA derived an oral RfD of 60 µg/kg bw/day. This value is based on a NOAEL for liver toxicity in rats of 6 mg/kg bw/day with a UF of 100 for interspecies extrapolation and intrahuman variability (IRIS 1998). Besides an oral slope factor was given of 7.5 x 10^{-3} [mg/kg bw/day]$^{-1}$. For inhalation an inhalation unit risk was presented of 4.7 x 10^{-7} [µg/m^3]$^{-1}$. The latter value equals to a lifetime cancer risk level of 10^{-4} at a concentration of 200 µg/m^3 (IRIS 1998).
WHO calculated a TDI of 6 µg/kg bw/day. The value is based on a NOAEL of 6 mg/kg bw/day for hepatotoxic effects in rats with a UF of 100 for interspecies extrapolation and intrahuman variability, and an additional factor of 10 for the carcinogenic potential of dichloromethane. From this a Drinking Water Quality Guideline of 20 µg/L was derived (WHO 1996a).
The WHO derived an Air Quality Guideline for the general population of 3 mg/m^3. This value was based on a maximal allowable increase in COHb in humans of 0.1% (WHO 1987, WHO 1996b).
Hassauer et al. (1993) advised the UBA (Umwelt Bundes Amt, Germany) an oral "Orientierungswert" of 60 µg/kg bw/day for long term oral exposure to dichloromethane. This value was based on a NOAEL of 6 mg/kg bw/day for hepatotoxic effects in rats with a UF of 100 and 100% absorption. An inhalation "Orientierungswert" of 900 µg/m^3 was included for chronic inhalation on the basis of a LOAEL of 700 mg/m^3 for systemic toxicity in rats [67]), with a UF of 300 and 60% absorption.
ATSDR (1998) derived a MRL for chronic oral exposure of 200 µg/kg bw/day based on a 2-year drinking water study in rats and mice with a NOAEL of 6 mg/kg bw/day for less serious hepatic effects, applying a UF of 30 (3 for extrapolation from animals to humans, 10 for human variability).
ATSDR (1998) derived a MRL for chronic inhalation exposure of 0.3 ppm (which equals 1 mg/m^3) based on a 2-year inhalation study with rats with a NOAEL (corrected for continuous exposure) of 8.9 ppm (31 mg/m^3) for less serious hepatic effects (see footnote 2), applying a UF of 30 (3 for extrapolation from animals to humans, 10 for human variability).
According to WHO (1996a), the odour threshold of perception for dichloromethane in air is in the range of 530 to 2120 mg/m^3.

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[67]) Hassauer (1993) and ATSDR (1998) used a lower NOAEL (50 ppm = 175 mg/m^3) than derived by the authors (Nitschke et al. 1988) and IPCS (1996), who both concluded to a NOAEL of 200 ppm (= 700 mg/m^3). The reason for this difference in judgement is not argued but finds it origin probably in the effects at 200 ppm: at this dose the study results only show a very slight and statistically unsignificant increase of the incidence of multinucleated hepatocytes, which is considered to be of doubtful biological importance.

5.5.5. BACKGROUND EXPOSURE

Vermeire et al (1991) estimated a total daily intake of dichloromethane of 18 µg/kg bw/day, but it was stated that this was based on inadequate data. CEPA (1993) presented values for an estimated background exposure for the Canadian population. Here a total exposure of 5 µg/kg bw/day was reported for adult humans, mainly from the inhalation of (indoor) air. The contribution of drinking water and foods was demonstrated to be negligible. As the major sources of dichloromethane emissions can be expected to be similar for Canada and The Netherlands, it is recommended to use estimate of the CEPA of 5 µg/kg bw/day for the background exposure in The Netherlands.

5.5.6. CONCLUSION

Compound	TDI	TCA	Background exposure	Odour threshold
Dichloromethane	60	3000	5	5×10^5 - 21×10^5

TDI: tolerable daily intake (oral exposure); µg/kg bw/day
TCA: tolerable concentration in air (inhalation exposure); µg/m^3
Background exposure; µg/kg bw/day
Odour threshold; µg/m^3

5.5.7. REFERENCES

ATSDR (1998):
Toxicological profile for methylene chloride (update); draft for public comment.
US Dept. of Health & Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta (GA), USA.

Brooke D & Howe P (1994):
Environmental hazard assessment: dichloromethane.
Toxic Substances Division, Dir Air Climate, Tox Subst, Dept Environm, TSD/18. Garston, Watford, UK.

BUA (1986):
Beratergremium für umweltrelevante Altstoffe, report no. 6: Dichloromethane
Gesellschaft Deutscher Chemiker, VCH, Weinheim, Germany.

CEPA (1993):
Dichloromethane.
Canadian Environmental Protection Act, Priority Substances List Assessment Report, Ottawa, Canada.

Cherry N, Venables H, Waldron HA & Wells GG (1981):
Some observations on workers exposed to methylene chloride.
Brit J Ind Med 38, 351-355 *(cited in WHO 1987 and IPCS 1996).*

DiVincenzo GD & Kaplan CJ (1981):
Effect of exercise or smoking on the uptake, metabolism and excretion of methylene chloride vapor by humans.
Toxicol Appl Pharmacol 59, 141-148 *(cited in WHO 1987 and IPCS 1996).*

Hassauer M, Kalberlah F, Oltmans J & Schneider K (1993):
Basisdate Toxikologie für umweltrelevante Stoffe zur Gefahrenbeurteilung bei Altlasten.
Umwelt Bundes Amt, Berichte 4/93, Erich Schmidt Verlag, Berlin, Germany.

IARC (1987):
Overall Evaluations of Carcinogenicity: an updating of IARC monographs volumes 1 to 42.
IARC Monographs, Supplement 7, International Agency for Research on Cancer, Lyon, France.

IARC (1999):
Re-evaluation of some organic chemicals, hydrazine and hydrogen peroxide. IARC monographs on the evaluation of carcinogenic risks to humans, vol 71 part 1.
International Agency for Research on Cancer, Lyon, France.

IPCS (1996):
Environmental Health Criteria 164 - Methylene chloride (second edition).
International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland.

IRIS (Integrated Risk Information System) (1998):
Summary for dichloromethane.
Oral RfD assessment dated March 1988, carcinogenicity assessment dated February 1995.
US Environmental Protection Agency, Washington DC, USA.

Nitschke KD, Burek JD, Bell TJ, Kociba RJ, Rampy LW & McKenna MJ (1988):
Methylene chloride - a 2-year inhalation toxicity and oncogenicity study in rats.
Fund Appl Toxicol 11, 48-59.

Vermeire TG, Apeldoorn ME van, Fouw JC de & Janssen PJCM (1991):
Voorstel voor de humaan-toxicologische onderbouwing van C-toetsingswaarden.
National Institute of Public Health and the Environment, RIVM-report no. 725201005, February 1991; Bilthoven, The Netherlands.

WHO (1987):
Air quality guidelines for Europe.
World Health Organization, Regional Office for Europe, WHO Regional Publications, European Series No. 23; Copenhagen, Denmark.

WHO (1996a):
Guidelines for drinking-water quality, 2nd ed. Volume 2, Health criteria and other supporting information.
World Health Organization, Geneva, Switzerland.

WHO (1996b):
Updating and revision of the air quality guidelines for Europe
Report of a World Health Organization Working Group on Volatile Organic Compounds, Brussels, Belgium; 2-6 October 1995, EUR/HFA target 21.

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5.6. TRICHLOROMETHANE (CHLOROFORM)

5.6.1. INTRODUCTION

Chloroform (trichloromethane) was evaluated within the scope of the present project in 1991. For the inhalatory route the limit value as originally proposed in the RIVM Criteria Document from 1986 was adopted as the TCA. The 1986 limit value was 0.1 mg/m^3 based on an NOAEL of 110 mg/m^3 from a 6-month inhalation study in rats [68]). In calculating this limit value an uncertainty factor (UF) of 1000 was used (10 for extrapolation from rats to humans, 10 for sensitive subgroups in the human population and 10 to adjust from the experimental exposure regimen (4 hours/day, 5 days/week) to continuous exposure). For the oral route no limit value was derived in 1986, no appropriate NOAEL being available. In 1991 30 mg/kg bw/day was selected as the overall-LOAEL [69]) for the oral route. A UF of 1000 (10 for extrapolation from rats to humans, 10 for sensitive subgroups in the human population and 10 for the use of an LOAEL instead of an NOAEL) was applied to this LOAEL leading to a TDI of 30 µg/kg bw/day (Vermeire et al. 1991, Gerlofsma et al. 1986).
Since the 1991 evaluation several reviews of the toxicology of chloroform have been published, the most important of which are those by IPCS (1994), ATSDR (1997) and WHO (1998). The latter evaluation was carried out within the scope of the drinking-water guidelines programme of the WHO. A review of the carcinogenicity data on chloroform was published recently by the IARC (IARC 1999). ATSDR (1997) summarizes the available data on release of chloroform into the environment [70]). The compound is released as a result of its manufacture and use, its formation in the chlorination of drinking-water, via municipal and industrial waste water, via swimming-pool and spa water and from other water treatment processes involving chlorination. Because of its low soil adsorption and slight but significant water solubility chloroform will leach from soil into groundwater. In groundwater, it is expected to persist for a long time (ATSDR 1997).

5.6.2. TOXICOLOGY

Toxicokinetics

Chloroform is well absorbed after oral administration. An important factor for the uptake rate in the GI-tract is the vehicle of delivery. Absorption after inhalation in humans was 60-80% of the dose. Chloroform is also readily absorbed through the skin (significant dermal absorption from water during showering has been demonstrated). After absorption the compound is distributed throughout the body with the extrahepatic dose being higher after inhalation and dermal uptake than after ingestion. The oxidative biotransformation of chloroform is catalysed by cytochrome P-450 enzymes to form trichloromethanol. From this, phosgene is formed as a reactive intermediate, part of which reacts with water to produce carbon dioxide, and another part forms adducts with thiols. The reaction of phosgene with tissue proteins is associated with cell damage and cell death (this is important for the mechanism of tumour formation – see below). Little binding of chloroform metabolites to DNA is observed. Carbon dioxide and unchanged chloroform are eliminated via expired air; the extent to which this occurs varies with dose and animal species (WHO 1998).

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[68]) Study carried out by Torkelson et al. (1976).
[69]) This LOAEL derives from the drinking-water study in mice carried out by Jorgenson et al. (1982).
[70]) Conversion factors: 1 mg/m^3 = 0.205 ppm, 1 ppm = 4.88 mg/m^3.

Toxicity

The data on chloroform carcinogenicity and related endpoints were recently reviewed by IARC (1999). The compound was classified in Group 2B (*possibly carcinogenic to humans*) based on *inadequate evidence* in humans and *sufficient evidence* in experimental animals [71]).
Chloroform carcinogenicity was examined in several oral bioassays. These studies were carried out in the 1970s and 1980s and were already included in the 1986 RIVM Criteria Document. The main findings in these studies were increased incidences of liver tumours in mice (strain B6C3F1), and kidney tumours in male rats (Osborne-Mendel) and male mice (ICI, but no response in several other strains of mice). In the 1990s a number of experiments have been performed to elucidate the mechanism through which these tumours arise. The liver and kidney tumours in mice appear to be linked to sustained cell toxicity followed by cell replication (threshold mechanism). For male rats the data indicate a similar mechanism of action in the kidney, but the weight of evidence for this is less strong primarily because a different strain of rats (i.e. F-344, known to be highly sensitive for chloroform nephrotoxicity) was used in the mechanistic studies. WHO, in its evaluation of 1998, concluded that both for the liver tumours and kidney tumours the weight of evidence indicates a threshold mechanism of induction. This, incidentally, is in essence the same conclusion as already drawn in the 1986 RIVM Criteria Document. The information presented in the recent evaluation by the IARC is also in line with this (i.e., mechanistic data indicate that the tumours arise as a result of target organ cytotoxicity followed by regenerative cell proliferation) (IARC 1999).
A large number of genotoxicity tests was carried out with chloroform. As in previous evaluations by other groups of experts, WHO (1998) concluded that the weight of evidence indicates that the compound is not genotoxic.
Based on the above information on carcinogenicity and genotoxicity a threshold approach is chosen in the limit value derivation for chloroform.
The most sensitive toxic effect produced by chloroform is damage to the centrilobular region of the liver. Renal toxicity was also seen in many studies. The large toxicity data base is reviewed in IPCS (1994) and WHO (1998).

5.6.3. EVALUATION

Since the 1991 evaluation within the present scope no new oral chronic toxicity studies have become available. The new TDI derived by WHO in its 1998 evaluation was based on the toothpaste study in Beagle dogs by Heywood et al. (1979), the result of which already was taken into account in the previous evaluation by the RIVM. This dog study gave a chronic LOAEL of 15 mg/kg bw/day with slight hepatotoxicity being present at this dose level (test period 7.5 years). The RIVM gave precedence to a chronic LOAEL of 30 mg/kg bw/day (slight heptatoxicity at this dose level) from the drinking-water study in mice by Jorgenson et al. (1982). In the absence of any decisive new data, the approach as taken in 1991 is maintained. Thus, the TDI for chloroform remains at 30 µg/kg bw.
For the inhalation route the previous limit value was based on a NOAEL of 110 mg/m^3 from a 6-month inhalation study in rats by Torkelson et al. (1976). ATSDR (1997) derived an inhalatory limit value from an occupational epidemiology study published by Bomski et al. (1967) (study also evaluated in the 1986 RIVM Criteria Document). In this study 68 workers in a pharmaceutical showed liver effects (increased incidences of liver enlargement, hepatitis, fatty changes) after exposure to chloroform. Inhaled chloroform concentrations ranged from 10 to 1020 mg/m^3 over the 1 to 4 years exposure period. ATSDR identified 10 mg/m^3 as the LOAEL from this study and derived a chronic limit value of 0.1 mg/m^3 by using a UF of 100 (10 for the use of a NOAEL and 10 protection of sensitive groups in the human population). Thus, ATSDR derived a limit value numerically identical to the value previously proposed by RIVM. Because the exposure concentrations in the worker study showed such large fluctuations in time (from 10 to 1000 mg/m^3) the NOAEL from the rat study represents a more

[71]) It should be noted that the IARC classification system is of a purely qualitative nature (i.e. focussing on hazard identification rather than risk assessment). IARC does not provide quantitative estimates of cancer risks nor is any information that may be available on the mechanism of tumour formation taken into account when classifying a compound.

reliable point of departure for limit value derivation and consequently the approach chosen in 1986 (i.e., using the rat NOAEL of 110 mg/m^3) is maintained. In conclusion, for chloroform the TCA remains at 0.1 mg/m^3.

5.6.4. EVALUATIONS BY OTHER ORGANISATION

US-EPA derived an RfD of 10 µg/kg bw/day for chloroform in 1985 (US-EPA 1992). This was based on the LOAEL of 15 mg/kg bw/day from the toothpaste study in Beagle dogs by Heywood et al. (1979). In the derivation of the RfD the LOAEL was first converted to 12.9 mg/kg bw (adjustment from 6 days/week of dosing to continuous dosing, 7 days/week). A UF of 1000 was applied (10 for intraspecies variation, 10 for interspecies variation, and 10 for the use of a LOAEL instead of an NOAEL) (US-EPA 1992). No US-EPA RfC is available for chloroform.
The ATSDR oral chronic duration MRL for chloroform is the same as the US-EPA RfD (derivation identical). The chronic inhalation MRL is 0.1 mg/m^3 based on the LOAEL of 10 mg/m^3 from the epidemiology study by Bomsky et al. (1967). As already noted in the previous paragraph, in this derivation a UF of 100 was applied (10 for the use of a NOAEL and 10 for protection of sensitive groups in the human population) (ATSDR 1997).
WHO (1998) derived a TDI based on the toothpaste study in Beagle dogs by Heywood et al. (1979) (see previous paragraph). The LOAEL from this study, 15 mg/kg bw/day, was corrected for 6 days/week dosing and divided by a UF of 1000 (10 for intraspecies variation, 10 for interspecies variation, and 10 for the use of an LOAEL instead of a NOAEL and for semichronic duration of the pivotal study). This led to a TDI of 13 µg/kg bw/day (WHO 1998).
IPCS (1994) developed two appraches to assess the risk of chloroform exposure: one based on non-neoplastic effects and one on neoplastic effects. Based on the LOAEL from the toothpaste study in dogs with liver toxicity as the critical effect a TDI of 15 µg/kg bw/day was derived. The UF used was 1000 (10 for intraspecies variation, 10 for interspecies variation, and 10 for the use of a LOAEL instead of a NOAEL). The approach based on neoplastic effects comprised calculations based on liver tumours in mice and kidney tumours in rats. For the mouse liver tumours mechanistic evidence was used in the calculation by basing the TDI calculation on the NOAEL for cytolethality and cell proliferation in mice. This NOAEL was 10 mg/kg bw/day, and it was divided by a UF of 1000 (10 for intraspecies variation, 10 for interspecies variation, and 10 for severity of endpoint and less-than chronic study). For the kidney tumours in male mice similar mechanistic evidence was lacking and thus linear extrapolation using the linearized multistage model (the default approach of the US-EPA) was considered appropriate. This led to an estimated additional cancer risk of 1:10^5 at a dose of 8.2 µg/kg bw/day, ingested daily over an entire lifetime (IPCS 1994).

5.6.5. BACKGROUND EXPOSURE

Total background exposure was previously estimated at 25 µg/person/day (0.4 µg/kg bw/day) (Vermeire et al. 1991). In the review published by the WHO in 1998 exposure to chloroform via the various media (food, drinking-water, indoor air) is reviewed. The conclusion in this review is that the total estimated mean intake is approximately 2-3 µg/kg bw/day. It is pointed out that for individuals who use drinking-water containing relatively high concentrations of chloroform total exposure may be up to 10 µg/kg bw/day (exposure through ingestion, inhalation and dermal contact). People visiting indoor swimming-pools may be exposed to even much higher levels. It was estimated that a 1-hour swim would give a daily dose of 65 µg/kg bw/day (WHO 1998).
The estimate of 2-3 µg/kg bw/day is used. The apparant increase in exposure since in the 1980s probably is due to underestimation of exposure via drinking-water and indoor air in the 1991 exposure estimate [72]).

[72]) For drinking-water and food combined for instance the previous estimate was 5.5 µg/day. In WHO (1998) for the Netherlands a maximum concentration in drinking-water of 8.9 µg/litre is given (reported in 1994) indicating that higher background exposures will occur.

5.6.6. CONCLUSION

Compound	TDI	TCA	Background exposure	Odour threshold
Trichloromethane (chloroform)	30	100	2- 3	480×10^{3} [73])

TDI: tolerable daily intake (oral exposure); µg/kg bw/day
TCA: tolerable concentration in air (inhalation exposure); $\mu g/m^3$
Background exposure; µg/kg bw/day
Odour threshold; $\mu g/m^3$

5.6.7. REFERENCES

ATSDR (1997):
Toxicological Profile for Chloroform (update).
Agency of Toxic Substances and Disease Registry, U.S. Department of Health & Human Services, Public Health Service; Atlanta (GA), USA.

Bomski HA, Sobdewska A & Strakowski A (1967):
Toxic damage of the liver by chloroform in chemical industry workers (in German).
Int Arch Gewerbepathol Gewerbehyg 24, 127-134. *Cited in Gerlofsma et al. (1986) and ATSDR (1997).*

Gerlofsma A, Van Der Heijden CA, E. Heijna-Merkus E et al. (1986):
Criteria Document on Chloroform.
VROM Publikatiereeks Lucht no. 54 (in Dutch); Leidschendam, The Netherlands.

Heywood R, Sortwell RJ, Noel PRB et al. (1979):
Safety evaluation of toothpaste containing chloroform. III. Long-term study in Beagle dogs.
J Environm Pathol Toxicol, 2, 835-851. *Cited in Gerlofsma et al. (1986) and WHO (1998).*

IARC (1999):
IARC Monographs on the evaluation of carcinogenic risks to humans – volume 73: Some chemicals that cause tumours in the kidney or urinary bladder in rodents and some other substances.
International Agency for Research on Cancer, World Health Organization, Lyon, France.

IPCS (1994):
Environmental Health Criteria no. 163 – Chloroform.
International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland.

Jorgenson TA. Rushbrook CJ & Jones DCL (1982):
Dose-response study of chloroform carcinogenesis in the mouse and rat: status report.
Environm Health Perspect, 46, 141-149. *Cited in Gerlofsma et al. ,1986.*

Torkelson TR. Oyen F & Rowe VK (1976):
The toxicity of chloroform as determined by single and repeated exposure of laboratory animals.
Am Ind Hyg Ass J, 37, 697-705. *Cited in Gerlofsma et al., 1986.*

US-EPA (1992):
IRIS file on chloroform: oral RfD assessment, Agency Work Group Review 02-12-1985 and 15-05-1986, last revision 01-09-1992.
US Environmental Protection Agency, Washington DC, USA.

Vermeire TG, Apeldoorn ME van, Fouw JC de & Janssen PJCM (1991):
Voorstel voor de humaan-toxicologische onderbouwing van C-toetsingswaarden.
National Institute of Public Health and the Environment, RIVM-report no. 725201005, February 1991; Bilthoven, The Netherlands.

[73]) Reference: Northeastern University, Office of Health & Safety, Boston (MA), USA, at www.dac.neu.edu/oehs/tlv.htm (August 2000).

WHO (1996):
Guidelines for drinking-water quality – Second Edition Volume 2: Health criteria and other supporting information.
World Health Organization, Geneva, Switzerland.

WHO (1998):
Guidelines for drinking-water quality – Second Edition Addendum to Volume 2: Health criteria and other supporting information.
World Health Organization, Geneva, Switzerland.

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5.7. TETRACHLOROMETHANE (CARBON TETRACHLORIDE)

5.7.1. INTRODUCTION

Tetrachloromethane was evaluated within the scope of this project by Vermeire et al in 1991. They derived a TDI of 4 µg/kg bw/day for oral intake on the basis of a NOAEL of 1 mg/kg bw/day, for effects on the liver in rats after a semichronic exposure, with an uncertainty factor (UF) of 250. A TCA of 60 µg/m^3 was derived from a NOAEC of 6.1 mg/m^3 for semichronic exposure of rats.
For the update additional literature, published since 1991, was evaluated. This included reviews of ATSDR (1994) and WHO (1996), and reports of IARC (1999) and IPCS (1999).
Tetrachloromethane is known by many synonyms. Most often it is however referred to as carbon tetrachloride. Besides many trade names are used for tetrachloromethane such as freon, halon, and tetrasol.
It has been suggested that tetrachloromethane can be formed by natural processes; until now it has only been detected in volcanic emissions (IPCS 1999). It can therefore be expected that the natural occurrence in soil is negligible, and that any tetrachloromethane in soil is of anthropogenic origin.
The major use of tetrachloromethane in former days was the production of chlorofluorocarbons propellants and refrigerants. This production is decreasing, as it is agreed internationally to phase-out the production and use of these propellants since 1990. Tetrachloromethane was also used as fumigant, pesticide, solvent for oil and metal degreaser, and in the production of paint, ink, plastic, and as a fuel additive.
The majority of tetrachloromethane emissions into the environment have occurred to air by production, disposal, and use. Only small amounts were released into water. Soil contamination is most likely due to waste disposal, spills, and the use as propellant, solvent and degreaser. Consequently, tetrachloromethane will be found both in industrial and household waste. As it is soluble in water, tetrachloromethane can be found in groundwater also, but it is expected to evaporate rapidly due to its high vapour pressure (ATSRD 1994, IPCS 1999) [74]). It can be expected that vapours of tetrachloromethane from soil and superficial groundwater lead to human exposure to tetrachloromethane from inhalation intake.

5.7.2. TOXICOLOGY

Toxicokinetics

Absorption
There are no data about the gastrointestinal absorption of tetrachloromethane in humans after oral intake. In animal studies it is rapidly and extensively absorbed: 85% of the dose is absorbed from the gastrointestinal tract within a few minutes.
There are some data about the absorption in humans after inhalation. Based on differences of tetrachloromethane in inhaled and exhaled air concentrations in occupationally exposed humans, the absorption in the lungs was estimated to be 60%. Data in monkeys showed an average of 30% absorption at a concentration of 315 mg/m^3.
Percutaneous absorption is demonstrated to exist in human volunteers using liquid tetrachloromethane. In rats an aqueous solution of tetrachloromethane was absorbed totally within 24 hours. Vapours are not absorbed through the skin.
Distribution
Tetrachloromethane is found in fatty tissues after both oral and inhalation exposure. A high uptake is noticed into the white matter of the brain and the central nervous system. After an oral intake, also the liver contains high concentrations of tetrachloromethane.
Metabolism
The metabolic pathways of tetrachloromethane are known in detail from studies with experimental animals. Tetrachloromethane is transformed into a trichloromethyl radical by a cytochrome P450 dependent reductive dehalogenation, which involves the CYP2E1 and CYP2B isoenzymes. The radicals may undergo several reactions that lead to the formation of chloroform, and finally HCl and CO_2.

[74]) Conversion factors: 1 mg/m^3 = 0.159 ppm, 1 ppm = 6.29 mg/m^3.

Studies with ^{14}C have demonstrated that CO_2 is the major metabolite. Besides it was shown in these studies that metabolism only takes place in the liver (ATSDR 1994, IPCS 1999).

Excretion

Following oral, inhalation or dermal exposure of humans and experimental animals, the parent compound and the metabolites are excreted in expired air, and in urine and faeces. The available data suggests that the elimination is biphasic of nature, with a rapid clearance from the blood with a half-life of a few hours and a slower phase for fatty tissues with a half-life of a few days.

At higher doses the liver will be affected. This leads to cytochrome P450 destruction, and will cause a reduced metabolic rate of tetrachloromethane, and accordingly a slower elimination.

Biomarkers

A measurement of tetrachloromethane and its metabolites in expired air is the most convenient way to determine potential exposure. Also tetrachloromethane in blood can be used as an indicator.

Effects in humans from high doses are most pronounced for the liver, kidneys, and the central nervous system. This can be noticed by the elevation of serum levels of various enzymes, oliguria and proteinuria, and symptoms like narcosis. It should be noted, however, that these effects are not specific for tetrachloromethane only. The toxic potency of tetrachloromethane is increased by simultaneous exposure to alcohols, ketones, phenobarbital, halo-alkanes and dietary status. Especially ethanol ingestion has been associated with potentiation of tetrachloromethane-induced hepatic and renal injury in humans (ATSDR 1994).

Toxicity

Acute poisoning

Cases of death of humans by intoxication with tetrachloromethane are known both from inhalation and oral exposure. At ambient temperature the concentrations of vapours in the air can reach up to 800 g/m^3. This can easily lead to accidental poisoning by inhalation. Quantitative data and useful information of effects after inhalation, however, are rare. Clinical signs after oral intake indicate death within hours or days, with severe gastrointestinal irritation, central nervous system depression, and death from severe injury of the liver or kidneys.

Genotoxicity and carcinogenicity

In its review of the genotoxicity of tetrachloromethane IARC (1999) concludes that tetrachloromethane is not mutagenic to bacteria. It did not produce mutations in Drosophila *in vivo*. In humans cells *in vitro* neither chromatid exchange nor chromosomal aberrations were induced. In *in vivo* studies with rats DNA was not affected. Tetrachloromethane does, however, bind covalently to DNA *in vitro*.

Both IARC (1999) and IPCS (1999) have presented a series of human epidemiological studies with respect to the carcinogenicity of tetrachloromethane. They refer to occupational exposed humans and community based studies. In most studies no increased cancer mortality risk was found. On the basis of the outcome IARC (1999) concluded that there is *inadequate evidence in humans* for the carcinogenicity of tetrachloromethane.

In carcinogenicity studies with rats, hamsters and mice, hepatomas and hepatocellular carcinomas have been found after oral exposure to tetrachloromethane. The LOAEL of hepatocellular carcinomas in rats is reported to be 47 mg/kg bw/day for oral exposure. There are no studies regarding carcinogenicity after chronic inhalation exposure. IARC (1999) concluded that there is *sufficient evidence in experimental animals* for the carcinogenicity of tetrachloromethane.

Subchronic and chronic toxicity

Ingestion of tetrachloromethane leads to hepatotoxicity. Because of this, the compound is used as a model chemical for studying the basic mechanism of hepatotoxic chemicals in animal studies. A variety of effects can be noticed on a macroscopic and (ultra)-microscopic scale. Dose levels of 10 mg/kg bw/day can be considered the LOAEL for hepatic effects, with a NOAEL of 1 mg/kg bw/day. Renal effects are also prominent but only at higher dose levels than the hepatic LOAELs.

Liver and renal effects are also found after chronic inhalation exposure of experimental animals to tetrachloromethane. Pulmonary oedema is a respiratory effect in humans exposed to high concentrations in air; in laboratory animals this effect is not prominent. The LOAEC for hepatic effects in rats is 63 mg/m^3, with a NOAEC of 31 mg/m^3 for a chronic inhalation exposure of 200 days.

Dermal exposure of laboratory animals to tetrachloromethane demonstrate that irritation is the most sensitive effect, which is seen in rabbits and guinea pigs within 24 hours at a single dose of 124 mg/cm^2 (ATSDR 1994).

Toxic mechanism of action

The liver is the primary target organ of tetrachloromethane. Most of the data indicate that the effects are caused by the reactive free radicals that are formed by the metabolism of tetrachloromethane via the liver cytochrome P-450 system. It is suggested that the radicals bind to cellular macromolecules in the centrilobular hepatocytes, leading to cell death.

Another mechanism of action that might be of importance for the hepatotoxicity is an interaction of tetrachloromethane with the normal cell calcium homeostasis. Tetrachloromethane might promote the release of calcium to the cytosol. By this it may activate phospholipases, which in turn will cause irreversible membrane damage.

Finally it can be expected that the reactive metabolites bind to nuclear protein, lipids, and DNA, which might be the starting point of tetrachloromethane carcinogenicity. Tracer studies have shown that the reactive compounds react with lipids and proteins only in close proximity to the formation. Only at higher doses the metabolites can reach the nucleus and the DNA (ATSDR 1994, IPCS 1999).

5.7.3. EVALUATION

The available data show that tetrachloromethane has no mutagenic properties. The data also indicate that the carcinogenic potency of tetrachloromethane can only be noticed at dose levels with an apparent hepatotoxicity. This observation can be explained by the suggested mechanism of action. Therefore a MPR can be derived based on the NOAEL of hepatotoxic effects with extrapolation factors.

The NOAEL of hepatotoxic effects for semichronic oral exposure in rats is 1 mg/kg bw/day. For the extrapolation for chronic exposure a UF of 3 is considered sufficient, as tetrachloromethane is rapidly absorbed and eliminated. Using a UF of 100 for inter- and intraspecies extrapolation a TDI of 3.3 µg/kg bw/day can be derived. As this value differs only slightly from the estimation of Vermeire et al (1991), the previous TDI of 4 µg/kg bw/day is to be maintained.

The NOAEC of hepatic effects is 31 mg/m^3 for inhalation exposure of 200 days in rats, 5 days per week, 7 hours per day. This study was also used by Vermeire et al (1991), who corrected this NOEC for continuous exposure (resulting in an adjusted NOAEC of 6.4 mg/m^3), and arrived at a TCA of 60 µg/m^3 by applying a UF of 100 for inter- and intraspecies variation. This previous TCA is to be maintained.

5.7.4. EVALUATION OF OTHER ORGANISATIONS

The carcinogenic potency of tetrachloromethane was classified by the IARC (1999) in group 2B: *possibly carcinogenic to humans*. It was concluded that there is *inadequate evidence for the carcinogenicity in humans* and *sufficient evidence in experimental animals*.

US-EPA derived an oral RfD for tetrachloromethane of 0.7 µg/kg bw/day. This value was based on the NOAEL of 1 mg/kg bw/day for liver lesions in a subchronic gavage study with rats. A UF of 1000 was applied for interspecies and intrahuman variability, and extrapolation from a subchronic study, and a conversion factor of 5/7 for the rate of exposure (IRIS, revised 1991). For the carcinogenic risk US-EPA presented an oral slope factor of 0.13 [mg/kg bw/day.]$^{-1}$ based on hepatocellular carcinomas in rats. A RfC was not derived, but the inhalation unit risk for carcinogenicity was estimated at 1.5×10^{-5} [µg/m^3]$^{-1}$, which by linear extrapolation leads to a lifetime additional cancer risk level of 1:10^4 at a concentration of 7 µg tetrachloromethane per m^3. (IRIS, revised 1991).

ATDSR presented a MRL of 20 µg/kg bw/day for acute oral exposure. This value was based on a LOAEL of 5 mg/kg bw/day for hepatic effects in rats exposed for 10 consecutive days. For intermediate oral exposure a MRL of 7 µg/kg bw/day was estimated using a NOAEL of 1 mg/kg bw/day for hepatic effects in rats, with an adjustment for continuous exposure. For acute inhalation exposure ATSDR proposed a MRL of 1.3 mg/m^3, based on a LOEAL for hepatic effects in rats of 315 mg/m^3). For intermediate inhalation exposure an MRL of 315 µg/m^3 was derived, using a NOAEL of 31.5 mg/m^3 for liver effects in rats. Chronic oral and inhalation MRLs weres not derived (ATDSR 1994).

WHO derived a TDI of 0.71 μg/kg bw/day, based on a NOAEL of 1 mg/kg bw/day in a 12-week gavage study. Following dose conversion, a UF of 100 for inter- and intraspecies extrapolation was used, and an additional factor of 10 for possible non-genotoxic carcinogenicity. Based on the TDI a Drinking Water Quality Guideline of 2 μg/L was presented (WHO 1996)
IPCS (1999) presented an oral TDI of 1.42 resp. 1.72 μg/kg bw/day. The first value was derived from a NOAEL of 1 mg/kg bw/day in rats exposed for 12 weeks, with a correction of 5/7 for continuous exposure and a UF of 100 for intra- and interspecies variation, and an additional factor of 5 for the administration (it was a bolus study). The second value was derived from a NOAEL of 1.2 mg/kg bw/day in mice, with the same UFs and additional correction factor. For inhalation a tolerable concentration (TC) was estimated of 6.1 to 11.4 μg/m^3. The first value was derived from a NOAEC of 6.1 mg/m^3 in a semichronic inhalation study with rats with a UF of 100 for intra- and interspecies variation, and an additional UF of 10 for extrapolation to chronic exposure. The last TC was derived from a LOAEC of 32 mg/m^3 in a chronic inhalation study with rats, which was corrected for continuous exposure, followed by applying UFs of 5 for the extrapolation to a NOAEL and 100 for intra- and interspecies variation.
Hassauer et al. (1993) advised the UBA (Germany) an oral "Orientierungswert" of 0.7 μg/kg bw/day for long-term exposure to tetrachloromethane. This value was derived from a NOAEL of 0.7 mg/kg bw/day on hepatic effects in rats, with a UF of 1000 and 100% absorption. They derived an inhalation "Orientierungswert" of 14 μg/m^3 for chronic inhalation, using a LOAEL of 6.1 mg/m^3 for hepatic effects in rat with a UF of 1000 and 40% absorption.

5.7.5. BACKGROUND EXPOSURE

Vermeire et al (1991) suggested an average daily intake of 0.3 μg/kg/day. IPCS (1999) presented various estimates of total daily background exposure. The intake from drinking water was considered negligible, inhalation from air was estimated to result in a daily intake of 0.1 μg/kg bw/day, and intake from food was suggested to be about twice the intake via air. This resulted in an estimated total daily intake of 0.27 μg/kg bw/day. This estimate is based on a period when tetrachloromethane was still in use in food processing. As this is not longer the case, it can be expected that the intake at present is less than the IPCS estimated. For the present evaluation the total daily intake is estimated at 0.2 μg/kg bw/day, assuming that inhalation still leads to an intake of 0.1 μg/kg bw/day, and that the contribution of food is decreased to 0.1 μg/kg bw/day .

Odour threshold
Tetrachloromethane has a sweetish ether-like odour (Hazardous Substances Database 1999/10). According to IPCS (1999) the odour threshold of tetrachloromethane in air is ≥ 63 mg/m^3, while ATSDR (1994) reported lowest odour threshold values of 10 to 60 mg/m^3. These concentrations are the thresholds of perception.

5.7.6. CONCLUSION

Compound	TDI	TCA	Background exposure	Odour threshold
Tetrachloromethane	4	60	0.2	60×10^3

TDI: tolerable daily intake (oral exposure); μg/kg bw/day
TCA: tolerable concentration in air (inhalation exposure); μg/m^3
Background exposure; μg/kg bw/day
Odour threshold; μg/m^3

5.7.7. REFERENCES

ATSDR (1994):
Toxicological Profile for Carbon Tetrachloride (Update).
TP-93/02, Agency of Toxic Substances and Disease Registry, U.S. Department of Health & Human Services, Public Health Service; Atlanta (GA), USA.

Hassauer M, Kalberlah F, Oltmans J & Schneider K (1993):
Basisdate Toxikologie für umweltrelevante Stoffe zur Gefahrenbeurteilung bei Altlasten.
Umwelt Bundes Amt, Berichte 4/93, Erich Schmidt Verlag, Berlin, Germany.

IARC (1999):
Re-evaluation of some organic chemicals, hydrazine and hydrogen peroxide.
IARC Monographs on the evaluation of carcinogenic risks to humans, Volume 71, Part 2.
International Agency for Research on Cancer, Lyon, France.

IPCS (1999):
Carbon tetrachloride, Environmental Health Criteria 208.
World Health Organization, Geneva, Switzerland.

Vermeire TG, Apeldoorn ME van, Fouw JC de & Janssen PJCM (1991):
Voorstel voor de humaan-toxicologische onderbouwing van C-toetsingswaarden.
National Institute of Public Health and the Environment, RIVM-report no. 725201005, February 1991; Bilthoven, The Netherlands.

WHO (1996):
Guidelines for drinking-water quality, 2nd ed. volume 2, Health criteria and other supporting information.
World Health Organization, Geneva, Switzerland.

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5.8. CHLOROBENZENES MONOCHLOROBENZENE, DICHLOROBENZENES, TRICHLORO-BENZENES, HEXACHLOROBENZENE

5.8.1. INTRODUCTION

Previous evaluation

In 1991 the group of chlorobenzenes was evaluated, and separate TDIs (tolerable daily intake) and TCAs (tolerable concentration in air) were derived for monochlorobenzene (MCB), dichlorobenzenes (1,2-DCB and 1,4-DCB, no values for 1,3-DCB) and hexachlorobenzene (HCB). For the other chlorobenzenes (trichlorobenzenes (TCBs), tetrachlorobenzenes (TeCBs) and pentachlorobenzene (PeCB)) no values were derived due to the lack of sufficient toxicological data (Vermeire et al. 1991). For estimating the risk of oral exposure to a mixture of chlorobenzenes the TDI of the most toxic representative, i.e., HCB, was applied; for estimating the risk of inhalation exposure to a mixture of chlorobenzenes the TCA of one of the more volatile compounds, i.e., 1,2-DCB was applied.
The RIVM criteria document on chlorobenzenes (RIVM 1991) estimated the general population background exposure to the total group of chlorobenzenes to be approximately 0.012 µg/kg bw/day.

Overview of the MPRs of chlorobenzenes as derived by Vermeire et al. (1991)

Compound	MPR oral µg/kg bw/day	MPR inhalation µg/m^3	Background exposure µg/kg bw/day
Monochlorobenzene	300 [A])	not available	< 0.07
Dichlorobenzenes			
- 1,2-DCB	600 [A])	600 [B])	< 0.07
- 1,3-DCB	not available	not available	-
- 1,4-DCB	190 [A])	1200 [B])	< 0.07 [C])
Trichlorobenzenes (all isomers)	not available	not available	< 0.07
Tetrachlorobenzenes (all isomers)	not available	not available	-
Pentachlorobenzene	not available	not available	-
Hexachlorobenzene	0.5 [A])	not available	0.004 - 0.014
Chlorobenzenes (total)	0.5 [A])	600 [B])	0.09 (max.)

[A]) TDI: tolerable daily intake
[B]) TCA: tolerable concentration in air
[C]) Considerably more if chlorobenzene-containing air refresheners are used (1-40 µg/kg bw/day).

Present evaluation

The present evaluation is based on new relevant data that appeared since the evaluation of 1991. Such data were identified for MCB, DCBs, TCBs and HCB. For TeCBs and PeCB no new data could be located, and consequently for these chlorobenzenes no limit values are derived.

5.8.2. MONOCHLOROBENZENE

5.8.2.1. INTRODUCTION

In the previous evaluation of monochlorobenzene (MCB) a TDI (tolerable daily intake) of 0.3 mg per kg bw (body weight) per day (rounded value) was derived (Vermeire et al. 1991), based on the NOAEL of 27.3 mg/kg bw/day in a 13-weeks study with dogs for histopathological changes in the liver as the critical effect (Knapp et al. 1971), as originally derived by RIVM in 1991 (RIVM 1991). Data regarding effects after inhalation were considered to be insufficient for limit value derivation. General

population background exposure of the total group of chlorobenzenes was estimated to be less than 90 ng/kg bw/day.
MCB is a monocyclic aromatic compound with a high vapour pressure (1180 Pa), moderate octanol-water partition coefficient, and moderate to low water solubility. The substance is used mainly as a solvent in pesticide formulations, as a degreasing agent, and as an intermediate in the synthesis of other halogenated compounds Soil contamination may result from the first two applications. In soil, MCB is relatively mobile and degrades slowly, it may therefore leach into groundwater (IPCS 1991, WHO 1996). Exposure can occur via the oral as well as (due to MCP's volatility) the inhalation route.

5.8.2.2. TOXICOLOGY

Toxicokinetics

MCB is readily absorbed by humans via the oral and the inhalation routes of exposure, and given its lipophilic nature it is likely to be absorbed through the skin too; however, quantitative data on uptake are not available for any of these routes of exposure. Once absorbed, MCB is rapidly distributed to many tissues with concentrations being highest in adipose tissue. It is metabolised via oxidation and conjugation with glutathione, glucuronic acid and sulphate, resulting in chlorocatechol, chlorophenols, chlorophenol mercapturic acid, and glucuronide and sulphate conjugates, which are excreted with the urine. Reactive metabolites of MCB, possibly arene oxides and chlorophenols, can bind to cellular proteins; binding of these metabolites appears to be correlated with necrotic pathological damage in the kidneys and liver of rodents. Data on the biological half-life of MCB are not available, but elimination from the human body is almost complete (>95%) after 5 days (IPCS 1991, WHO 1996).

Toxicity

Data on the effects of MCB in humans are very limited (some case reports and three limited epidemiological studies of occupationally exposed populations). Effects on the central nervous system, neonatal development and skin have been reported in occupationally exposed people, but the available studies are inadequate to serve as a basis for risk assessment (IPCS 1991, CEPA 1992).
Prolonged administration of MCB via ingestion or inhalation to experimental animals (rats, mice, rabbits and dogs, dosages of 12.5-750 mg/kg bw/day, and 341-4550 mg/m^3 for 7 h/day, 5 days/wk, respectively) resulted at high doses in reductions in body weight gain and survival, and hepatic and renal toxicity, as indicated by increases in serum enzymes, liver and kidney weights, histopathological changes and necrosis. In addition, depression of bone marrow activity in mice and myeloid depletion of the thymus, spleen, or bone marrow in rats and mice have been observed, also at high doses. NOAELs (not corrected for continuous exposure) of 27.3-125 mg/kg bw/day, and 341 and 910 mg/m^3 were reported (RIVM 1991, IPCS 1991, WHO 1996).
MCB did not impair fertility in experimental animals and was neither embryotoxic nor teratogenic (RIVM 1991, IPCS 1991, WHO 1996).

Genotoxicity and carcinogenicity

MCB was not mutagenic in a number of bacterial test systems, with or without metabolic activation. It has induced chromosomal aberrations in bacteria and plants (in one test only, with questionable positive response, while all the other tests were negative), but not in mammalian systems. In one micronucleus test in mouse bone marrow positive results were observed.
On the basis of the available information it was provisionally concluded that the data are too limited for considering MCB to be genotoxic (RIVM 1991, IPCS 1991, CEPA 1992, WHO 1996). New information that should warrant a change of this provisional conclusion is lacking, and thus MCB is provisionally considered not genotoxic.
In two-year oral NTP carcinogenicity studies in mice and rats, applying dosages of 60 and 120 mg/kg bw/day (gavage) during 103 weeks (NTP 1985), no increased tumour incidences were found, except for a weak dose-related increase in benign liver nodules in male rats in the highest dose group. These changes were not considered to provide evidence of carcinogenicity in male rats (NTP 1985, IPCS

1991, FoBiG 1992). On the basis of this study, RIVM concluded that there is no evidence for carcinogenicity of MCB (RIVM 1991), and the Dutch Health Council arrived at the same conclusion (Gezondheidsraad 1993). This conclusion is maintained.
MCB has not been evaluated by IARC.

5.8.2.3. EVALUATION

Since the weight of the available evidence does not allow to consider MCB a genotoxic compound, in deriving a MPR the threshold approach applying uncertainty factors (UFs) is adopted.
Oral exposure
As can be concluded from the information summarised in the next paragraph, the different expert groups that evaluated MCB present several possible approaches in deriving a limit value. This lack of consensus reflects the limitations of the toxicological data base for MCB. The difference between the individual oral limit values is due to differences in choice of the pivotal study. The NOAELs used are either the chronic NOAEL of 60 mg/kg bw/day (2-year NTP study with rats and mice, 1985) or the subchronic NOAEL of 27.3 mg/kg bw/day (dog study of Knapp et al. 1971, supported by similar short-term results in rats and mice).
Vermeire et al. (1991) adopted the latter NOAEL, with the higher chronic NOAEL as background information. This approach is maintained in the present evaluation. This NOAEL of 27.3 mg/kg bw/day was derived from a study with compound application for 5 days/week. After correction for continuous exposure [75]) a NOAEL of 19.5 mg/kg bw/day results. Using a UF (uncertainty factor) of 100 (as was done in 1991) gives a TDI of 0.2 mg/kg bw; a higher UF is not considered necessary because a chronic NOAEL is available which is higher than the pivotal NOAEL.
In conclusion, 0.2 mg/kg bw/day is selected as the new TDI for MCB.
Inhalation exposure
Since the previous evaluation (Vermeire et al. 1991) no new inhalation studies have become available. In 1991 the data were judged as insufficient, and thus no tolerable concentration in air (TCA) was derived. However, the guideline value as derived by the IPCS (1991) provides a useful indication of what the TCA for MCB might be (cf. next paragraph); this value was based on a "marginally toxic concentration" of 341 mg/m^3. Hence this inhalatory limit value of 0.5 mg/m^3 is accepted as the provisional TCA (pTCA).

5.8.2.4. EVALUATIONS BY OTHER ORGANISATIONS

Oral exposure
Oral limit values were derived by WHO (1996), US-EPA (1993), CEPA (1992) and IPCS (1991).
Based on the 2-year NTP study with rats and mice in which a NOAEL of 60 mg/kg bw was identified (NTP 1985), the WHO derived a TDI of 85.7 µg/kg bw/day by applying a UF of 500 (100 for inter- and intraspecies variation and 5 for the "limited evidence of carcinogenicity") and adjusting for dosing 5 days a week (WHO 1996).
The evaluations carried out before 1996 led to chronic oral limit values of 20 µg/kg bw/day (US-EPA 1993), 8.1 and 86 µg/kg bw/day (CEPA 1992), and 100 µg/kg bw/day (IPCS 1991). The low value of 8.1 µg/kg bw/day as derived by CEPA was based on results of inhalation studies and incorporated a UF of 5000. Owing to limitations of these studies, CEPA also derived a TDI based on the more extensive oral long-term NTP study (NTP 1985), leading to a TDI of 86 µg/kg bw/day (CEPA 1992).
The value of 20 µg/kg bw/day as derived by the US-EPA (US-EPA 1993) was based on the subchronic dog study of Knapp et al. (1971).
Inhalation exposure
Inhalatory limit values were derived by FoBiG (1992) and IPCS (1991).

[75]) Such a duration adjustment was not applied in 1991, but has since been part of the standard procedure within the present project, and is used accordingly in the present updated evaluation.

FoBiG derived a long-term inhalatory value of 0.13 mg/m^3, based on a two-generation study in rats with hepatic and renal toxicity [76]) as the critical effect (Nair et al. 1987), applying a UF of 1000 (FoBiG 1992).
IPCS arrived at an inhalatory value of 0.5 mg/m^3, based on a subchronic study in rats and rabbits in which a concentration of 341 mg/m^3 was identified as the "marginally toxic concentration" (Dilley 1977), using a UF of 1000 (IPCS 1991).
CEPA (1992) did not derive a separate limit value for inhalation exposure but applies its chronic oral limit value (which is based on inhalation studies) also to the inhalation route of exposure.
The Dutch Expert Committee on Occupational Standards derived a MAC value (maximum acceptable concentration for occupational exposure) of 46 mg/m^3 (10 ppm) (DECOS 2000).

5.8.2.5. BACKGROUND EXPOSURE

Background exposure occurs predominantly via air (indoor and ambient). Vermeire et al. (1991) estimated the general population background exposure for the total group of chlorobenzenes to be less than 0.09 µg/kg bw/day. According to the RIVM criteria document on chlorobenzenes the exposure of the average adult to MCB in the Netherlands is 0.2 ng/day (RIVM 1991).
In the same time period, Health Canada and IPCS arrived at clearly higher exposure estimates. The estimated daily intakes of MCB for various age groups in the Canadian population was estimated to range from 0.047 to 0.142 µg/kg bw/day (CEPA 1992). IPCS reported possible daily intakes of 0.166 and 0.882 µg/kg bw/day via ambient air (data from Canada and the USA, respectively) and <0.029 µg/kg bw/day via drinking-water (data from Canada); data on intake via food were not available (IPCS 1991). More recent exposure estimates are not available.
Since the background exposure as estimated in the previous evaluation was based on very limited data Vermeire et al. 1991, RIVM 1991), the data of the IPCS are assumed to be valid for The Netherlands too, and thus the background exposure to MCB is estimated at 0.9 µg/kg bw/day at most (upper level of the range reported by IPCS, 1991).

5.8.2.6. CONCLUSION

TDI: 200 µg per kg body weight per day.
pTCA: 500 µg per m^3.
Background exposure: ≤ 0.9 µg per kg body weight per day.
Relevant routes of exposure in case of soil contamination: oral and inhalation.

5.8.2.7. REFERENCES

CEPA (1992):
Priority Substances List Assessment Report - Monochlorobenzene. Canadian Environmental Protection Act, Health Canada.

DECOS (2000):
Chemiekaarten 15e editie, kaartnummer C-0030

Dilley JV (1977):
Toxic evaluation of inhaled chlorobenzene (monochlorobenzene).
Natl. Technical Information Service, Dept. of Commerce, Springfield, Virginia, USA *(cited in IPCS 1991).*

FoBiG (1992):
Basisdaten Toxikologie für umweltrelevante Stoffe zur Gefahrenbeurteilung bei Altlasten.
Umweltforschungsplan des Bundesministeriums für Umwelt, Naturschutz und Reaktorsicherheit, Forschunsbericht nr. 102 03 443/01 (two volumes: Zusammmenfassung & Zusammenfassung der Einzelberichte).
Prepared by FoBiG Forschungs- und Beratungsinstitut Gefahrstoffe, Freiburg im Breisgau, Germany.

[76]) FoBiG reported (probably by mistake) fetotoxicity as the critical effect. Other reviews consistently report a lack of fetotoxicity in this study.

Gezondheidsraad (1993):
Commissie risico-evaluatie van stoffen: Chloorbenzenen - Toetsing van een basisdocument. Den Haag: Gezondheidsraad, 1993; publicatie nr 1993/07.

IPCS (1991):
Chlorobenzenes other than hexachlorobenzene. Environmental Health Criteria 128.
World Health Organization, Geneva, Switzerland.

Knapp WK Jr, Busey WM & Kundzins W (1971):
Subacute oral toxicity of monochlorobenzene in dogs and rats.
Toxicol Appl Pharmacol 19, 393 (abstract, *cited in RIVM 1991).*

Nair RS, Barter JA & Schroeder RE (1987):
A two-generation reproduction study with monochlorobenzene vapor in rats.
Fundam Appl Toxicol 9, 678-686 *(cited in RIVM 1991).*

NTP (1985):
Toxicology and carcinogenesis studies of chlorobenzene (CAS no. 108-90-7) in F344/N rats and B6C3F1 mice (gavage studies).
National Toxicology Program, Techn. Report Series no. 261, NHI Publ. No. 86-2517.
Dept. of Health and Human Services, Washington DC, USA *(cited in RIVM 1991).*

RIVM (1991):
Slooff W, Bremmer HJ, Hesse JM & Matthijsen AJCM (eds.): Integrated criteria document chlorobenzenes.
National Institute of Public Health and the Environment, RIVM report no. 710401015, October 1991; Bilthoven, The Netherlands.

US-EPA (1993):
Integrated Risk Information System (IRIS) - summary for monochlorobenzene, dated January 1993.
US Environmental Protection Agency, Washington DC, USA.

Vermeire TG, Apeldoorn ME van, Fouw JC de & Janssen PJCM (1991):
Voorstel voor de humaan-toxicologische onderbouwing van C-toetsingswaarden.
National Institute of Public Health and the Environment, RIVM-report no. 725201005, February 1991; Bilthoven, The Netherlands.

WHO (1996):
Guidelines for drinking-water quality, 2nd. ed., vol. 2: Health criteria and other supporting information.
World Health Organization, Geneva, Switzerland.

5.8.3. DICHLOROBENZENES

5.8.3.1. INTRODUCTION

Dichlorobenzene (DCB) exists in three isomeric forms: 1,2-DCB, 1,3-DCB and 1,4-DCB. The MPRs (maximum permissible risk levels) for DCBs were evaluated in 1991 (Vermeire et al. 1991).
For 1,2-DCB a TDI (tolerable daily intake) of 0.6 mg per kg bw (body weight) per day was derived, based on a NOAEL of 60 mg/kg bw/day from the chronic NTP study (1985) in mice and rats (administration 5 days/week) (RIVM 1991). A tolerable concentration in air (TCA) of 0.6 mg/m^3 was derived, based on the NOAEL of 290 mg/m^3 from subchronic studies in various animal species (Hollingworth et al. 1958) which resulted in a NOAEL of 60 mg/m^3 after duration adjustment, a UF of 100 was applied.
For 1,4-DCB a TDI of 0.19 mg/kg bw/day was derived, based on the NOAEL of 19 mg/kg bw/day from a subchronic study in rats (Hollingworth et al. 1956). The TCA was set at 1.2 mg/m^3, based on a NOAEL of 580 mg/m^3 (equaling 121 mg/m^3 after duration adjustment) from subchronic studies in various animal species (Hollingworth et al. 1956).
Due to the lack of data no TDI or TCA could be derived for 1,3-DCB.

General population background exposure of the total group of chlorobenzenes (excluding hexachlorobenzene) was estimated to be less than 5 µg per day (Vermeire et al. 1991).
DCBs are aromatic compounds with moderate to high volatility, moderate octanol-water partition coefficients and low water solubility. The DCBs are widely used in industry and in domestic products such as odour-masking agents, dyestuffs and pesticides; 1,2-DCB and 1,4-DCB are the most widely used isomers (WHO 1996). Thus, both the use of products containing DCBs and waste disposal of such products may cause soil contamination with these compounds. DCBs are not hydrolysed, and biodegrade slowly under aerobic conditions. They are not expected to leach appreciably into groundwater.

5.8.3.2. TOXICOLOGY

Toxicokinetics

The limited data do not note particular differences in the kinetics (including biotransformation) of the DCBs. They are almost completely absorbed from the gastrointestinal tract, while some 20% is absorbed upon inhalation exposure (but this was measured in a rat experiment with 1,4-DCB, using a regimen of 3 h exposure per day for 10 days). Once absorbed, they are readily distributed, primarily to adipose tissue (because of their lipophilicity) and to kidney, liver and lungs (WHO 1996, ATSDR 1998).
Metabolism is mainly by hepatic oxidation to dichlorophenols and their glucuronide and sulphate conjugates. These are eliminated mainly by excretion via the urine. In rats, almost 100% of an oral dose of 1,4-DCB was excreted within 5 days (WHO 1996, ATSDR 1998).

Toxicity

The database for the DCB-isomers is limited, especially for 1,3-DCB for which insufficient data are available for limit value derivation. The data set for the oral route for 1,2-DCB is similar to that for 1,4-DCB. There are no usable human data either but animal data are available. Both isomers have been tested in semichronic rat studies by Hollingworth et al. (1956, 1958) and in carcinogenicity studies in rats and mice by the NTP (NTP 1985, 1987). In general, the effects of (sub)chronic oral and inhalation exposures to 1,2-DCB and 1,4-DCB in experimental animals include decreased survival, reduced body weight (gain), hepatic and renal toxicity, and induction of porphyria. In addition, in one or more animal species effects were observed on the thymus, spleen, heart and muscle tissue (RIVM 1991, CEPA 1993a,b).
For 1,2-DCB the semichronic toxicity study in rats (Hollingworth et al. 1958), with gavage administration on 5 days/week, showed a NOAEL of 19 mg/kg bw/day with increased liver and kidney weights as the critical effect (LOAEL was 188 mg/kg bw/day). Toxic effects seen in the long-term toxicity/carcinogenicity studies of the NTP in rats and mice (dose levels 60 and 120 mg/kg bw/day) were limited to tubular regeneration in mice at 120 mg/kg bw/day (no effects in rats). Thus, the NOAEL from the NTP study for 1,2-DCB is 60 mg/kg bw/day (NTP 1985).
In the subchronic study of 1,4-DCB in rats by Hollingworth et al. (1956) the NOAEL was 19 mg/kg bw/day with increased liver and kidney weights as the critical effect (LOAEL was 188 mg/kg bw/day). In the chronic carcinogenicity study in rats (NTP 1987) with 1,4-DCB (dose levels 150 and 300 mg/kg bw/day) the non-neoplastic effects observed were increased incidences of nephropathy in males, starting with hyaline droplet accumulation in renal cells, ocurring at both dose levels (LOAEL was 150 mg/kg bw/day). This hyaline droplet nephropathy is initiated by reversible binding of 1,4-DCB to α-2-microglobulin, which is specific to the male rat and does not represent a risk to human health. In this study the NOAEL for female rats was 150 mg/kg bw/day. In mice (dose levels 300 and 600 mg/kg bw/day) liver effects (primarily in males), nephropathy and lymphoid hyperplasia were seen; these effects were present at both dose levels (LOAEL 300 mg/kg bw/day) (NTP 1987). A one-year study with dogs dosed 10, 50 and 150 mg/kg bw/day (highest dose adjusted to 100 mg/kg bw/day at week 3 and 75 mg/kg bw/day at week 6, due to lethality after 12 days) resulted in a number of clinical effects, while also haematological effects, hepato- and nephrotoxicity, and increased relative adrenal and thyroid weights were observed; the NOAEL in this study was 10 mg/kg bw/day (Naylor et al. 1996).

Five to seven months inhalation studies (7 h/day, 5 days/week) of both isomers with several animal species were carried out by Hollingworth et al. (1956, 1958).
The NOAEL for 1,2-DCB was 290 mg/m^3 for the absence of adverse effects (at the LOAEL of 560 mg/m^3 decreased spleen weights were seen in male guinea pigs, which is considered a marginal effect).
The NOAEL for 1,4-DCB was 580 mg/m^3 for growth depression, increased liver and kidney weights, and swelling and granular degeneration of the liver as the critical effects (LOAEL was 950 mg/m^3). In a chronic inhalation study with rats exposed to 1,4-DCB (5 h/day, 5 days/week during 76 weeks followed by 36 weeks without exposure) increased liver and kidney weights, and increased urinary protein and coporphyrin (but no hyaline droplet nephropathy) were observed at 3000 mg/m^3, the NOAEL in this study was 450 mg/m^3 (Riley et al. 1980).
All three isomers of DCB were reported to be non-teratogenic (WHO 1996). Some relatively minor embryotoxic and fetotoxic effects have been observed for DCBs, but only at doses that were toxic for the mother (IPCS 1991, CEPA 1993b, WHO 1996).

Genotoxicity and carcinogenicity

All three isomers were non-mutagenic in several *Salmonella typhimurium* strains, both in the presence and in the absence of metabolic activation. Only 1,4-DCB was tested in a number of other *in vitro* and *in vivo* assays. Tests for the potential of 1,4-DCB to induce chromosomal aberrations in Chinese hamster ovary cells and Chinese hamster lung fibroblast cells, forward mutations in mouse lymphoma cells, and unscheduled DNA synthesis in human lymphocytes all gave negative results. In one micronucleus test all three isomers did produce a dose related increase in the formation of micronucleated polychromatic erythrocytes in mice when administered intraperitoneally, but these results could not be confirmed in similar studies by other workers. Orally administered 1,4-DCB did not produce an increase in micronuclei in mouse bone marrow. Taken together the results indicate that 1,2-DCB and 1,4-DCB are not genotoxic (IPCS 1991, CEPA 1993a,b, WHO 1996).
On the basis of the 2-year oral carcinogenicity study in mice and rats (NTP 1985) it was concluded that there is no evidence for carcinogenicity of 1,2-DCB, in accordance with RIVM (1991) and WHO (1996). A carcinogenicity study with 1,2-DCB by inhalation in several species (Hollingworth et al. 1958) was considered inadequate. IARC included 1,2-DCB in Group 3: *not classifiable as to its carcinogenicity to humans* (IARC 1987, 1999).
In the 2-year oral carcinogenicity studies in mice and rats with 1,4-DCB (NTP 1987), a dose-related increase in the incidence of tubular-cell adenocarcinomas of the kidney was observed in male rats. Male rats also showed hyperplasia of the parathyroid. With mice, both sexes showed increased incidences of hepatocellular adenomas and carcinomas in the high dose group (600 mg/kg bw/day). The induction of kidney tumours was considered to be a species- and sex-specific response, probably a result of hyaline droplet formation. Furthermore, the observed liver tumours have a very high spontaneous incidence in the mouse strain used (B6C3F1). The development of liver and kidney tumours was accompanied by toxicity in the target organ. These results provide limited evidence of carcinogenicity by 1,4-DCB, in accordance with the conclusions of RIVM (1991) and WHO (1996).
1,4-DCB was also tested in mice and rats by inhalation (Riley et al. 1980): no increase in the incidence of tumours was noted, but the duration of exposure was limited.
IARC included 1,4-DCB in Group 2B: *possibly carcinogenic to humans* (IARC 1987, 1999).
On the basis of an extensive database it is concluded that 1,4-DCB is not genotoxic (IPCS 1991, CEPA 1993b, WHO 1996).

5.8.3.3. EVALUATION

1,2-DCB

In the absence of evidence for genotoxic and carcinogenic potential of 1,2-DCB, a TDI can be derived on the basis of a NOAEL and uncertainty factors (UFs) (threshold approach).

1,2-DCB, oral exposure
In the evaluation of 1991 a TDI of 0.6 mg/kg bw/day was derived, based on a NOAEL of 60 mg/kg bw/day from the chronic NTP study (1985) in mice and rats (administration 5 days/week), applying a UF of 100 (RIVM 1991). Because since 1991 no new experimental data for 1,2-DCB have become available that warrant the use of a different NOAEL, this NOAEL is kept as the basis for limit value derivation. In the 1991 evaluation no duration adjustment was done, but this has since been part of the standard procedure within the present project, and is thus applied accordingly in the present evaluation. After correction for duration of administration an adjusted NOAEL of 43 mg/kg bw results. Using a UF of 100 (as was done in 1991) a TDI for 1,2-DCB of 0.43 mg/kg bw is derived.
1,2-DCB, inhalation exposure
In the 1991 evaluation, a tolerable concentration in air (TCA) for 1,2-DCB of 0.6 mg/m^3 was derived, based on the NOAEL of 290 mg/m^3 from semichronic studies in various animal species (Hollingworth et al. 1958) which resulted in a NOAEL of 60 mg/m^3 after duration adjustment; a UF of 100 was applied. Since this previous evaluation new experimental data that warrant the use of a different NOAEL have not become available, and thus the approach chosen in 1991 is maintained despite the limited database. After duration adjustment for exposure to the compound (7 h/day, 5 days/week), an adjusted NOAEL of 60 mg/m^3 results. Using a UF of 100 results in a provisional TCA (pTCA) of 0.6 mg/m^3. An additional UF is not necessary: the observed effect is considered to be marginal (cf. paragraph 5.8.3.2), and in addition the kinetic data for 1,2-DCB, although scarce, do not indicate appreciable bioaccumulation. The TCA is provisional due to the limited database from which it is derived.

1,3-DCB

Due to the lack of available data a TDI and a TCA for this isomer cannot be derived.

1,4-DCB

In the absence of evidence for 1,4-DCB being a genotoxic carcinogen, a TDI can be derived applying the threshold approach.
1,4-DCB, oral exposure
In the evaluation of 1991 for 1,4-DCB a TDI of 0.19 mg/kg bw/day was derived, based on the NOAEL of 19 mg/kg bw/day from a semibchronic study in rats (Hollingworth et al. 1956). This was the approach chosen in the RIVM criteria document of 1991. Several other organisations, however, have used the LOAEL of 150 mg/kg from the NTP rat long-term toxicity/carcinogenicity study as the basis in limit value derivation (cf. next paragraph). This study resulted in a LOAEL of 150 mg/kg bw/day, which can be extrapolated to a NOAEL of 15 mg/kg bw/day by applying a UF of 10. After correction for duration of administration an adjusted NOAEL of 11 mg/kg bw results. Using a UF of 100 would result in a limit value for oral intake of 0.11 mg/kg bw/day. The one-year dog study of Naylor et al. (1996) resulted in a NOAEL of 10 mg/kg bw/day; applying a UF of 100 results in a TDI for 1,4-DCB of 0.10 mg/kg bw/day. This value agrees well with the value derived from the NTP study and is taken as the new TDI for 1,4-DCB.
1,4-DCB, inhalation exposure
For 1,4-DCB, the 1991 evaluation derived a TCA of 1.2 mg/m^3, based on a NOAEL of 580 mg/m^3 (equaling 121 mg/m^3 after duration adjustment) from semichronic studies in various animal species (Hollingworth et al. 1956). The ATSDR (1998) provides additional information (compared to what was available in 1991) on the more extensive chronic rat study of Riley et al. (1980), the NOAEL in this study was 450 mg/m^3. This study is now preferred as the pivotal one. Correction for exposure duration (animals were exposed for 5 h/day, 5 days/week) resulted in an adjusted NOAEL of 67 mg/m^3. Using a UF of 100, a TCA for 1,4-DCB of 0.67 mg/m^3 is derived.

5.8.3.4. EVALUATIONS BY OTHER ORGANISATIONS

Since the evaluation of 1991 chronic oral limit values for 1,2-DCB and 1,4-DCB were derived by WHO (1996), CEPA (1993a,b), IPCS (1991), and US-EPA (1991). Inhalation limit values were only derived for 1,4-DCB, by ATSDR (1998), US-EPA (1996) and IPCS (1991).

1,4-DCB is under review in the EU Existing Chemicals Programme, in which scope a draft Risk Assessment Report has been prepared. As yet, this document has not been finalised.

1,2-DCB

The evaluations carried out since 1991 resulted for 1,2-DCB in chronic oral limit values of 430 (rounded figure) (WHO 1996, CEPA 1993a), 600 (IPCS 1991) and 90 µg/kg bw/day (US-EPA 1991). These expert groups derived limit values on the basis of the chronic NTP study in mice and rats (1985), applying different UFs (US-EPA used a UF of 1000 instead of 100). In the evaluations of WHO, CEPA and US-EPA duration adjustment was applied, because the NTP study applied the compound during 5 days/week. US-EPA derived a higher overall NOAEL from this study (120 mg/kg bw), because the decrease in survival and the increase in renal tubular regeneration in male mice at this dose level were considered to be of questionable significance.

Limit values for inhalation exposure are not available.

The Dutch Expert Committee on Occupational Standards (DECOS) derived for 1,2-DCB a MAC value (maximum acceptable concentration) of 190 mg/m^3 (35 ppm); the 15 minutes time-weighted average MAC value is 538 mg/m^3 (100 ppm) (DECOS 1999).

1,4-DCB

For 1,4-DCB the evaluations carried out led to chronic oral limit values of 400 (ATSDR 1998, for intermediate duration [77]), 107 (WHO 1996), 100 (IPCS 1991) and 78 µg/kg bw/day (CEPA 1993b).

The WHO and IPCS expert groups derived their oral limit values using the 2-year LOAEL (150 mg/kg bw) of the chronic NTP study of 1987. CEPA (1993b) derived its TDI from the inhalation study of Riley et al. (1980) as cited in Loeser and Lichfield (1983), applying route-to-route extrapolation (CEPA 1993b).

Since 1991 several inhalatory limit values were derived for 1,4-DCB; the evaluations resulted in chronic inhalatory limit values for 1,4-DCB of 0.6 (ATSDR), 0.8 (US-EPA), and 1 mg/m^3 (IPCS). The ATSDR and IPCS expert groups based their inhalatory limit values on the 2-year rat study of Riley et al. (1980) with a NOAEL of 450 mg/m^3, but applied slightly different UFs and duration adjustment factors (ATSDR 1998, IPCS 1991). US-EPA derived an inhalatory limit value of 0.8 mg/m^3, based on a NOAEL of 300 mg/m^3 from a two-generation reproduction study in rats reported by the Chlorobenzene Producers Association (1986), with increased liver weights of P1 males as the critical effect (US-EPA 1996).

The Dutch Expert Committee on Occupational Standards (DECOS) derived for 1,4-DCB a MAC value (maximum acceptable concentration) of 190 mg/m^3 (35 ppm); the 15 minutes time-weighted average MAC value is 538 mg/m^3 (100 ppm) (DECOS 1999).

5.8.3.5. BACKGROUND EXPOSURE

The limited available data indicate that background exposure is predominantly via ambient and indoor air (via DCB-containing air fresheners and toilet blocks). Vermeire et al. (1991) estimated the general population background exposure of the total group of chlorobenzenes (excluding hexachlorobenzene) to be less than 5 µg per day. According to the RIVM criteria document the total exposure to DCBs is <1 µg per day per isomer (< 0.017 µg/kg bw/day per isomer). The authors noted that the use of 1,4-DCB has declined considerably during 1985 and 1988 (from about 350 tonnes/year to about 100 tonnes/year) and was expected to fall further to 0-80 tonnes per year in the 1990s as a result of autonomous developments (RIVM 1991).

In the same time period, Health Canada and IPCS arrived at somewhat higher exposure estimates. The estimated daily intake of DCBs for various age groups in the Canadian population was estimated to range from 0.03 (adults) to 0.93 (infants) µg/kg bw/day for 1,2-DCB and 0.1-1.7 (adults) to 2.1 (infants) µg/kg bw/day for 1,4-DCB (CEPA 1993a, b). The IPCS reported for total DCBs possible daily intakes of 0.203 (data from Canada) and 0.930 µg/kg bw/day (data from USA) via ambient air, 0.00049 µg/kg bw/day via drinking-water and 0.0013 µg/kg bw/day via food (IPCS 1991). Infants have a higher exposure mainly due to intake via human milk.

Since recent exposure data are not available, the background exposure of the Dutch general population as estimated in the RIVM criteria document (RIVM 1991) are to be maintained:

[77]) ATSDR defines intermediare duration as a period of 15-364 days of continuous exposure.

1,2-DCB: 0.001 µg/kg bw/day
1,3-DCB: 0.001 µg/kg bw/day
1,4-DCB: 0.006 µg/kg bw/day

5.8.3.6. CONCLUSION

1,2-DCB
- TDI: 430 µg per kg body weight per day.
- pTCA: 600 µg per m^3 (provisional TCA).
- Background exposure: 0.001 µg/kg bw/day.

1,3-DCB
- TDI: not available.
- TCA: not available.
- Background exposure: 0.001 µg/kg bw/day.

1,4-DCB
- TDI: 100 µg per kg body weight per day.
- TCA: 670 µg per m^3.
- Background exposure: 0.006 µg/kg bw/day.

Relevant routes of exposure for all DCBs in case of soil contamination: oral and inhalation.

5.8.3.7. REFERENCES

ATSDR (1998):
Toxicological profile for 1,4-dichlorobenzene (update).
US Department of Health & Human Services, Public Health Service, Agency of Toxic Substances and Disease Registry, Atlanta (GA), USA.

CEPA (1993a):
Priority Substances List Assessment Report: 1,2-dichlorobenzene.
Canadian Environmental Protection Act, Health Canada, Ottawa, Canada.

CEPA (1993b):
Priority Substances List Assessment Report: 1,4-dichlorobenzene.
Canadian Environmental Protection Act, Health Canada, Ottawa, Canada.

Chlorobenzene Producers Association (1986):
Para-dichlorobenzene - two-generation reproduction study in Sprague-Dawley rats.
Study 86-81-90605, MRID no. 411088-1. Available from US-EPA, Washington DC, USA *(cited in US-EPA 1996).*

DECOS (1999):
Chemiekaarten 14e editie.

FoBiG (1992):
Basisdaten Toxikologie für umweltrelevante Stoffe zur Gefahrenbeurteilung bei Altlasten.
Umweltforschungsplan des Bundesministeriums für Umwelt, Naturschutz und Reaktorsicherheit, Forschunsbericht nr. 102 03 443/01 (two volumes: Zusammmenfassung & Zusammenfassung der Einzelberichte).
Prepared by FoBiG Forschungs- und Beratungsinstitut Gefahrstoffe, Freiburg im Breisgau, Germany.

Hollingworth RL, Rowe VK, Oyen F, Hoyle HR & Spencer H (1956):
Toxicit of para-dichlorobenzene - determinants on experimental animals and human subjects.
Arch Ind Health 14, 138-147 *(cited in RIVM 1991 and US-EPA 1996).*

Hollingworth RL, Rowe VK, Oyen F, Torkelson TR & Adams EM (1958):
Toxicity of ortho-dichlorobenzene - studies on animals and industrial experience.
Arch Ind Health 17, 180-187 *(cited in RIVM 1991).*

IARC (1987):
Overall evaluations of carcinogenicity: an updating of IARC Monographs volume 1-42.
International Agency for Research on Cancer, World Health Organization, Lyon, France.

IARC (1999):
Some chemicals that cause tumours of the kidney of urinary bladder in rodents and some other substances. IARC Monographs on the Evaluation of carcinogenic risks to humans.
International Agency for Research on Cancer, World Health Organization, Lyon, France.

IPCS (1991):
Chlorobenzenes other than hexachlorobenzene. Environmental Health Criteria 128.
World Health Organization, Geneva, Switzerland.

Loeser E & Litchfield MH (1983):
Review of recent toxicology studies on para-dichlorobenzene.
Food Chem Toxicol 21, 825-832 *(cited in RIVM 1991).*

Naylor MW et al. (1996):
One year study of p-dichlorobenzene. Monsanto Company Environmental Health Laboratory, October 1989.
(cited in US-EPA memorandum dated March 23, 1990; US-EPA 1996).

NTP (1985):
Toxicology and carcinogenesis studies of 1,2-dichlorobenzene (ortho-dichlorobenzene) (CAS no. 59-50-1) in F344/N rats and B6C3F1 mice (gavage studies).
National Toxicology Program, Techn. Report Series no. 255, NHI Publ. No. 86-2511.
Dept. of Health and Human Services, Washington DC, USA *(cited in RIVM 1991).*

NTP (1987):
Toxicology and carcinogenesis studies of 1,4-dichlorobenzene in F344/N rats and B6C3F1 mice (gavage studies).
National Toxicology Program, Techn. Report Series no. 319, NHI Publ. No. 87-2575.
Dept. of Health and Human Services, Washington DC, USA *(cited in RIVM 1991).*

Riley RA, Chart IS, Doss A, Gore CW, Patton D & Weight TM (1980):
Para-dichlorobenzene - long-term inhalation study in the rat.
ICI report no. CTL/P/447, August 1980 *(cited in Loeser & Litchfield 1983 and US-EPA 1996).*

RIVM (1991):
Slooff W, Bremmer HJ, Hesse JM & Matthijsen AJCM (eds.): Integrated criteria document chlorobenzenes.
National Institute of Public Health and the Environment, RIVM report no. 710401015, October 1991; Bilthoven, The Netherlands.

US-EPA (1991):
Integrated Risk Information System (IRIS): summary for 1,2-dichlorobenzene.
US Environmental Protection Agency, Washington DC, USA.

US-EPA (1996):
Integrated Risk Information System (IRIS): summary for 1,4-dichlorobenzene.
US Environmental Protection Agency, Washington DC, USA

Vermeire TG, Apeldoorn ME van, Fouw JC de & Janssen PJCM (1991):
Voorstel voor de humaan-toxicologische onderbouwing van C-toetsingswaarden.
National Institute of Public Health and the Environment, RIVM-report no. 725201005, February 1991; Bilthoven, The Netherlands.

WHO (1996):
Guidelines for drinking-water quality, 2nd. ed., vol. 2: Health criteria and other supporting information.
World Health Organization, Geneva, Switzerland.

5.8.4. TRICHLOROBENZENES

5.8.4.1. INTRODUCTION

In the evaluation of 1991 oral and inhalation maximum permissible risk levels (MPRs) for 1,2,3-trichlorobenzene (1,2,3-TCB), 1,2,4-trichlorobenzene (1,2,4-TCB) or 1,3,5-trichlorobenzene (1,3,5-TCB) could not be derived due to the lack of adequate data. General population background exposure of the total group of chlorobenzenes (excluding hexachlorobenzene) was estimated to be less than 5 µg per day (Vermeire et al. 1991).
The three isomers of TCB are chlorinated cyclic aromatic compounds with moderate volatility, slight to moderate water solubility and moderate to high octanol-water partition coefficients (CEPA 1993). TCBs are likely to bioconcentrate. 1,2,4-TCB is economically the most important isomer. It is used as an intermediate in chemical synthesis, as a solvent, a coolant, a lubricant and a heat-transfer medium; it is also used in polyester dying, in termite-control preparations and as an insecticide (WHO 1996). TCBs are rather stable in the environment: they are not hydrolysed and are unlikely to biodegrade significantly. They do not leach appreciably into groundwater (WHO 1996).

5.8.4.2. TOXICOLOGY

Toxicokinetics

In experimental animals all three TCB isomers are readily absorbed following oral administration. Also after inhalation and dermal exposure the TCBs are taken up in the body, but quantitative data only exist for the oral route, suggesting an absorption of 70-90%. Following oral administration, high concentrations of the parent compound are found in fat, skin, and liver, whereas high levels of metabolites were found in kidney and muscle. The major metabolites are trichlorophenols (though oxidation) and the corresponding glucuronides, sulfates and mercapturic acids; in monkeys the pathway via dihydrodiol to glucuronides prevales, while in rat glutathione conjugation followed by mercapturic acid formation is predominant. In rats the biological half-life of 1,2,4-TCB is approx. 6 h.
Generally, excretion of TCBs is more rapid in rats than in monkeys: after 24 h rats had excreted 84% of the oral dose in the urine and 11% in the faeces, as compared with 40% and <1%, respectively, in monkeys.
TCBs are broad inducers of metabolising enzymes (IPCS 1991, WHO 1996).

Toxicity

Available data on the toxicity of TCBs are very limited. There are no epidemiological studies of exposed populations, and information on chronic toxicity or carcinogenicity in animal studies is only available for 1,2,4-TCB (WHO 1996, CEPA 1993, IPCS 1991).
In a subchronic (13 weeks) dietary study with Sprague Dawley rats all three TCB isomers caused a similar toxicity pattern: significant increases in liver/body weight ratios and mild to moderate histopathological changes in liver, thyroid and kidneys. NOAELs were 7.8, 7.7 and 7.6 mg per kg bw (body weight) per day for 1,2,4-, 1,2,3- and 1,3,5-TCB, respectively (Cote et al. 1988).
A 3-months dietary study with Fischer F344 rats exposed to 1,2,4-TCB resulted in comparable toxic effects in the liver, kidneys and thyroid: increased absolute and relative weights, with treatment-related pathological changes in liver and kidneys; the liver changes were more prominent in males than in females. Based on liver weights and kidney pathology a NOAEL of 13 mg/kg bw/day was derived for females, while for males a LOAEL of 11 mg/kg bw/day was derived (a NOAEL could not be derived) (Bio/dynamics 1989).
A 3-months dietary study with 1,2,4-TCB in B6C3F1/CrlBR mice resulted in lowered body weights and reduced body weight gain, increased absolute and relative liver weights, and decreased absolute brain weights. From this study a NOAEL of 71 mg/kg bw/day was derived for females; for males the LOAEL was 62 mg/kg bw/day (a NOAEL could not be derived) (Hiles 1989).
In a 2-years dietary study with 1,2,4-TCB in Fischer F344 rats the target organs were liver and kidney: increased absolute and relative weights, with increased severity of chronic progressive nephropathy in

males. The NOAELs in this study were 5.5 and 6.7 mg/kg bw/day for males and females, respectively (Moore 1994b).
In a 2-years dietary study with 1,2,4-TCB in B6C3F1 mice the target organ was the liver: increased absolute and relative weights confirmed by histopathology showing enlarged centrilobular hepatocytes. This study resulted in NOAELs of 21 - 26 mg/kg bw/day for males and females, respectively (Moore 1994a).
A 13-weeks inhalation study in rats with 1,3,5-TCB exposure up to 1000 mg/m^3 (6 h/day, 5 days/week) resulted in a NOAEL of 100 mg/m^3, with squamous metaplasia and hyperplasia of the respiratory epithelium of the nasal passages as the critical effects (Sasmore et al. 1983).
Administration of 1,2,4-TCB by inhalation (7 h/day, 5 days/week during 44 days) to rats, rabbits and dogs has caused hepatic and renal toxicity, as indicated by increases in liver and kidney weight and increased urinary excretion of porphyrins. The NOAEL for these effects was 223 mg/m^3 in dogs and 742 mg/m^3 in rabbits, in rats the effects were seen at the lowest dose applied, thus resulting in a LOAEL of 223 mg/m^3 (Kociba et al. 1981). Watanabe et al. (1977) observed a NOAEL of 22.3 mg/m^3 for a slight, reversible increase in urinary porphyrins in an inhalation study with 1,2,4-TCB in rats (6 h/day, 5 days/week during 3 months).
In a multigeneration reproductive study with 1,2,4-TCB in rats (administered in drinking water; study ended at 32 days of age of the F2 generation) fertility was not affected. A LOAEL was derived from a significant increse in adrenal gland weights in the groups dosed 53.6 mg/kg bw/day of the F0 and F1 generations; the NOAEL was 14.8 mg/kg bw/day (Robinson et al. 1981).
No evidence of teratogenic effects was reported when rats were given oral doses up to 600 mg/kg bw/day of either 1,2,3-, 1,2,4- or 1,3,5-TCB on days 6-15 of gestation (Ruddick et al. 1983).

Genotoxicity and carcinogenicity

None of the TCB-isomers was mutagenic in several *Salmonella typhimurium* strains, with or without metabolic activation. Treatment of Chinese lung fibroblast cells (with and without metabolic activation) with either isomer did not cause chromosomal aberrations. In two micronucleus studies the TCBs caused dose-related increases in the formation of micronucleated polychromatic erythrocytes in mice injected with doses up to 70% of the LD_{50}; it was considered that the effects were due to clastogenic activity of the TCBs. These tests, however, were inadequately performed, and the results have not been confirmed in similar (and well-performed) studies by others.
1,2,4-TCB was further tested in the *umu*-test for DNA repair: positive results were seen without metabolic activation, while negative results were obtained in the presence of S9 mix. The substance was negative in two DNA repair tests with rat hepatocytes *in vitro*. A cell transformation assay with adult rat liver epithelial cells was positive only at doses that caused severe cytotoxicity (IPCS 1991, WHO 1996).
Microsomal metabolism of 1,2,4-TCB was studied with emphasis on binding to protein and DNA. The substance was metabolised to a number of trichlorophenols and to a lesser extent to trichlorohydroquinone. About 10% of all metabolites became covalently bound to proteins, which was completely inhibited by ascorbic acid, indicating that the quinone species are the sole reactive species involved. Only 0.5% of the metabolites alkylated DNA, and the possibility of labelled proteins having contaminated the isolated DNA cannot be excluded.
The database for genotoxicity of the TCBs (with 1,2,4-TCB as the most extensively tested isomer) is complicated and does not lead to a clear conclusion. There is some evidence of DNA damage, and there are weakly positive results from two inadequately performed *in vivo* micronucleus assays. The negative Ames test results do not provide strong evidence of a lack of genotoxicity, and the negative clastogenicity studies suffer from a lack of metabolic activation. However, there are no effects on DNA repair in primary hepatocytes, and a well-conducted in vivo micronucleus test was negative. On balance, the TCBs are not considered to express systemic genotoxic effects in vivo, in line with the conclusions of IPCS (1991) and WHO (1996).
Only 1,2,4-TCB has been tested for carcinogenic effects. The two-years dietary study of Moore (1994a) with B6C3F1 mice (doses of 0, 21, 100 and 522, and 0, 26, 127 and 575 mg/kg bw/day for males and females, respectively) showed a significant increase of hepatocellular carcinoma in the mid and high dose groups, but the mortality rate at the high dose group was high and the use of this strain

of mouse is complicated because it produces a high incidence of hepatocellular carcinoma with compounds that have a toxic effect on the liver. The relevance for humans of this tumour formation in B6C3F1 mice is debatable. The finding that the low dose did not induce liver tumours supports the view that that these tumours are the result of a general toxic effect, which is also indicated by the absence of tumour formation in other organs.
The two-years dietary study of Moore (1994b) with Fischer F344 rats (doses of 0, 5, 19 and 67, and 0, 7, 23 and 79 mg/kg bw/day for males and females, respectively) resulted in neoplasia as the major cause of death in all groups, including mononuclear cell leukemia and tumours in the pituitary and Zymbal's glands. Mononuclear leukemia and pituitary gland tumours, however, are common findings in old F344 rats, and no difference between control and high-dose animals was seen. Regarding the Zymbal's gland tumours, a slight and non-significant increase was seen in high dosed animals. These tumours have been induced by various chemical carcinogens and thus it cannot be excluded that the observed increase in frequency is due to the administration of 1,2,4-TCB.
On balance 1,2,4-TCB is not considered to be genotoxic in vivo, and binding studies indicated no or only marginal adduct formation with DNA. The compound-induced liver tumours in mice are considered not to be relevant for humans. The Zymbal's gland tumours in rats are of concern, but the incidence reported is not sufficiently high to lead to the firm conclusion that this study showed a positive carcinogenic effect.
It must be concluded that the available data do not provide evidence for the mutagenicity or carcinogenicity of the TCBs, in line with IPCS (1991) and WHO (1996).
1,2,4-TCB is under review in the EU Existing Chemicals Programme, in which scope a draft Risk Assessment Report has been prepared. As yet, this document has not been finalised.

5.8.4.3. EVALUATION

Oral exposure
Based on the limited data available the study of Cote et al (1988) is chosen as the pivotal one. In this study all three isomers were orally administered to rats via the diet during 13 weeks, which resulted in NOAELs of 7.6-7.8 mg/kg bw/day (these NOAELs are consistent with the NOAEL of 6 mg/kg bw/day resulting from the long term toxicity/carcinogenicity study of Moore (1994b)). Applying an uncertainty factor (UF) of 1000 (which includes a factor of 10 for lack of chronic data - only for 1,2,4-TCB chronic studies are available) results in a TDI (tolerable daily intake) of 8 µg/kg bw/day for all TCB isomers, in accordance with the oral limit value derived by WHO (1996).
Inhalation exposure
The available dataset is quite limited, and data for 1,2,3-TCB are lacking entirely. Inhalation limit values were only derived by IPCS (1991). Based on the above mentioned NOAELs of 100 mg/m^3 for 1,3,5-TCB and 22.3 mg/m^3 for 1,2,4-TCB (no duration adjustments) the IPCS derived limit values of 0.2 mg/m^3 for 1,3,5-TCB and 0.05 mg/m^3 for 1,2,4-TCB by applying a UF of 500 (IPCS 1991). The database used for these limit values was the same as that in the evaluation of Vermeire et al. (1991). In conclusion, for the inhalation route no new toxicity data have become available since the previous evaluation within the present scope. The data were already judged as insufficient, therefore no TCA value can be derived. Nevertheless, the guideline derivation as developed by the IPCS provides a useful indication of what the TCA for TCBs might be. Thus, the inhalation limit value of 0.05 mg/m^3 is adopted as the provisional TCA (PTCA) for TCBs. This is the lowest guideline value derived by the IPCS for TCBs, and it is to be applied to all isomers of TCB.

5.8.4.4. EVALUATIONS BY OTHER ORGANISATIONS

Oral exposure
Oral limit values were derived by WHO (1996), US-EPA (1996), CEPA (1993) and IPCS (1991).
The WHO derived its TDI of 7.7 µg/kg bw for total TCBs by applying a UF of 1000 (100 for inter- en intraspecies variation and 10 for the short duration of the study) to the NOAELs of 7.6 - 7.8 mg/kg bw for liver toxicity identified in the 13-week rat study of Cote et al. (1988) (WHO, 1996).
IPCS based its oral limit value (a rounded value of 20 µg/kg bw/day) for all three isomers also on the study of Cote et al. (1988), but applied a UF of 500 (IPCS 1991).

CEPA based its TDIs for 1,2,4-TCB of 2.3 µg/kg bw/day and 1,3,5-TCB of 1.0 µg/kg bw/day on the results of inhalation studies (considered to be the most relevant exposure route) applying route-to-route extrapolation, and incorporated a UF of 10000 (100 for inter- and intraspecies variation, 10 for less than chronic study and 10 for lack of data on carcinogenicity and chronic toxicity). In deriving its TDI for 1,2,3-TCB of 0.77 µg/kg bw/day, CEPA used the same NOAEL as did WHO, but applied a UF of 10000 (CEPA, 1993).
US-EPA based its oral limit value for 1,2,4-TCB of 10 µg/kg bw/day on the NOAEL of 14.8 mg/kg bw/day of a multi-generation study of this isomer in rats (Robinson et al. 1981) with increased adrenal weights and vacuolisation of the (adrenal) zona fasciculata as the critical effect, applying a UF of 1000 (which included a factor of 10 to account for lack of chronic studies) (US-EPA 1996).
Inhalation exposure
Limit values for inhalation exposure were only derived by IPCS (1991). Based on the NOAELs of 100 mg/m^3 for 1,3,5-TCB (Sasmore et al. 1983) and 22.3 mg/m^3 for 1,2,4-TCB (Watanabe et al. 1978) IPCS estimated limit values of 0.2 mg/m^3 for 1,3,5-TCB and 0.05 mg/m^3 for 1,2,4-TCB by applying a UF of 500 (IPCS, 1991); correction for duration of exposure was not applied.
The Dutch Expert Committee on Occupational Standards (DECOS) derived a MAC value (maximum acceptable concentration) for TCBs of 15.1 mg/m^3 (2 ppm); the 15 minutes time-weighted average MAC value is 37.8 mg/m^3 (5 ppm) (DECOS 2000).

5.8.4.5. BACKGROUND EXPOSURE

Background exposure is predominantly via ambient and indoor air. Vermeire et al. (1991) estimated the general population background exposure of the total group of chlorobenzenes (excluding hexachlorobenzene) to be less than 5 µg per day (<0.07 µg/kg bw/day). According to the RIVM criteria document on chlorobenzenes the total exposure to TCBs is < 0.0024 µg/kg bw/day (RIVM 1991).
In the same time period, Health Canada and IPCS arrived at somewhat higher exposure estimates. The estimated daily intake of TCBs for various age groups in the Canadian population was estimated to range from 0.1 to 1.2 µg/kg bw/day for 1,2,4-TCB, ≤ 0.24 to ≤ 0.33 µg/kg bw/day for 1,3,5-TCB, and ≤ 0.25 to ≤ 0.35 for 1,3,5-TCB (CEPA 1993). For all TCBs together IPCS reported possible daily intakes of 0.039 µg/kg bw/day via ambient air, 0.00006 µg/kg bw/day via drinking-water and 0.0010 µg/kg bw/day via food (IPCS 1991). The latter values, i.e., a rounded value of 0.04 µg/kg bw/day for total TCBs, is taken as the best estimate for background exposure to the TCBs.

5.8.4.6. CONCLUSION

1,2,4-TCB
TDI: 8 µg per kg body weight per day.
pTCA: 50 µg per m^3
Background exposure: < 0.04 µg per kg body weight per day.
1,3,5-TCB
TDI: 8 µg per kg body weight per day.
pTCA: 50 µg per m^3
Background exposure: < 0.04 µg per kg body weight per day.
1,2,3-TCB
TDI: 8 µg per kg body weight per day.
pTCA: 50 µg per m^3
Background exposure: < 0.04 µg per kg body weight per day.
All TCBs
Relevant routes of exposure in case of soil contamination: oral and inhalation.

5.8.4.7. REFERENCES

Bio/dynamics (1989):
A three months dietary range-finding study of 1,2,4-trichlorobenzene in rats.
Project no. 86-3122, January 1989 *(cited in US-EPA 1996).*

CEPA (1993):
Priority Substances List Assessment Report. Trichlorobenzenes.
Canadian Environmental Protection Act, Health Canada, Ottawa, Canada.

Cote M, Chu I, Villeneuve DC, Secours VE & Valli VE (1988):
Trichlorobenzenes - results of a thirteen-week feeding study in the rat.
Drug Chem Toxicol 11, 11-28 *(cited in IPCS 1991 and WHO 1996).*

DECOS (2000)
Chemiekaarten 15e editie, kaartnummer 0394.

FoBiG (1992):
Basisdaten Toxikologie für umweltrelevante Stoffe zur Gefahrenbeurteilung bei Altlasten.
Umweltforschungsplan des Bundesministeriums für Umwelt, Naturschutz und Reaktorsicherheit, Forschunsbericht nr. 102 03 443/01 (two volumes: Zusammmenfassung & Zusammenfassung der Einzelberichte).
Prepared by FoBiG Forschungs- und Beratungsinstitut Gefahrstoffe, Freiburg im Breisgau, Germany.

Hiles AH (1989):
Thirteen week toxicity study with 1,2,4-trichlorobenzene in mice.
Hazleton Laboratories America, project no. HLA 6221-104; April 1989 *(cited in US-EPA 1996).*

IPCS (1991)
Chlorobenzenes other than hexachlorobenzene. Environmental Health Criteria 128.
World Health Organization, Geneva, Switzerland.

Kociba RJ, Leong BJK & Hefner RE Jr (1981):
Subchronic toxicity study of 1,2,4-trichlorobenzene in the rat, rabbit and beagle dog.
Drug Chem Toxicol 4, 229-249 *(cited in IPCS 1991).*

Moore MR (1994a):
104-week dietary carcinogenicit study with 1,2,4-trichlorobenzene in mice.
Study no. HWA 2603-102, Hazleton Washington, Rockville (MD), USA *(cited in US-EPA 1996).*

Moore MR (1994b):
104-week dietary carcinogenicit study with 1,2,4-trichlorobenzene in rats.
Study no. HWA 2603-103, Hazleton Washington, Rockville (MD), USA *(cited in US-EPA 1996).*

Robinson KS, Kavlock RJ, Chernoff N & Gray E (1981):
Multigeneration study of 1,2,4-trichlorobenzene in rats.
J Toxicol Environm Health 8, 489-500 *(cited in US-EPA 1996).*

Ruddick JA, Black WD, Villeneuve CD & Valli VE (1983):
A teratological evaluation following oral administration of trichloro- and dichlorobenzene isomers to the rat.
Teratology 27, 73A *(cited in IPCS 1991).*

Sasmore DP, Motoma C, Tyson CA & Johnson JS (1983):
Subchronic inhalation study of 1,2,4-trichlorobenzene.
Drug Chem Toxicol 6, 241-258 *(cited in IPCS 1991).*

US-EPA (1996):
Integrated Risk Information System (IRIS): summary for 1,2,4-trichlorobenzene (toxicity assessment dated January 1996, carcinogenicity assessment dated March 1991).
US Environmental Protection Agency, Washington DC, USA.

Vermeire TG, Apeldoorn ME van, Fouw JC de & Janssen PJCM (1991):
Voorstel voor de humaan-toxicologische onderbouwing van C-toetsingswaarden.
National Institute of Public Health and the Environment, RIVM-report no. 725201005, February 1991; Bilthoven, The Netherlands.

Watanabe PG, Yankel HO & Kociba RJ (1977):
Subchronic toxicity study of inhaled 1,2,4-trichlorobenzene in rats.
Internal report, Toxicology Research Laboratory, Dow Chemical Co., Midland, Mossouri, USA *(cited in US-EPA 1996).*

WHO (1996):
Guidelines for drinking-water quality, 2nd. ed., vol. 2: Health criteria and other supporting information.
World Health Organization, Geneva, Switzerland.

5.8.5. HEXACHLOROBENZENE

5.8.5.1. INTRODUCTION

The maximum permissible risk level (MPR) for hexachlorobenzene (HCB) was evaluated in 1991 and set at a TDI (tolerable daily intake) of 0.5 µg per kg bw (body weight) per day, based on the NOAEL of 0.05 mg/kg bw/day from the subchronic studies in rats of Mollenhauer et al. (1975, 1976), for ultrastructural hepatic changes observed by electron microscopy as the critical effect, which was the approach developed in the RIVM criteria document on chlorobenzenes (RIVM 1991). Inhalation studies were lacking, and hence no tolerable concentration in air (TCA) was derived. General population background exposure at that time was estimated to be 0.004 (mean value) to 0.014 (maximum) µg/kg bw/day (Vermeire et al. 1991).
HCB is a chlorinated aromatic compound with slight volatility and very low water solubility. It is highly lipid-soluble and bioaccumulative. HCB is persistent in soil and surface waters. It has been used extensively as a selective fungicide since 1940, but in many countries its production and use as a fungicide have ceased. At present, its main importance appears to be as a by-product of several chemical processes and as an impurity in some pesticides (WHO 1996, IPCS 1997). Soil contamination can be the result of its use as a pesticide in the past, or as the result of waste disposal.

5.8.5.2. TOXICOLOGY

Toxicokinetics

Absorption following oral administration of HCB is greatly influenced by the vehiculum used: in rats approximately 80% is absorbed if administered in olive oil, as compared with < 20% if administered in aqueous suspension or as the solid crystalline form. Highest concentrations were detected in adipose tissue, bone marrow, the Harderian gland, nasal mucosa, and the preputial gland. Data on absorption following inhalation exposure are not available; ATSDR (1996) suggested a rather low absorption.
HCB is metabolised slowly to give lower chlorinated benzenes, chlorinated phenols, and other lower chlorinated metabolites; glucuronide and glutathione conjugates have also been found. Most is excreted as the parent compound in the faeces, about 5% is excreted in the urine as polar metabolites. Elimination half-lives for HCB range from approximately one month in rats and rabbits to 2 or 3 years in monkeys (WHO 1996, ATSDR 1996).

Toxicity

The critical effects induced by HCB comprise both non-neoplastic (this paragraph) and neoplastic effects (see below). Some human data are available, but these are inadequate to serve as a basis for risk assessment (IPCS 1997).
HCB is a mixed-type cytochrome P450 inducing compound; it is known to bind to the Ah receptor.
Prolonged oral exposure to HCB has been found to cause a wide range of non-neoplastic effects in several species of animals; the haem biosynthesis appears to be a major target of HCB toxicity. Elevated levels of porphyrins and/or porphyrin precursors have been found in the liver and other tissues and excreta of several species of laboratory mammals. Repeated exposure has also been shown to affect a wide range of organ systems, including the liver, lungs, kidneys, thyroid, skin, and nervous and immune systems. In addition, effects on calcium metabolism in rats, on ovarian histopathology in

monkeys, on neurotransmitter levels in the hypothalamus of mink, on postnatal survival in mink, and on neurobehavioral development in rats have been reported. The dose range over which the various effects have been observed is quite narrow; the lowest LOAELs range from 0.1 to 0.8 mg/kg bw per day, and the lowest NOAELs range from 0.05 to 0.08 mg/kg bw per day (CEPA 1993, IPCS 1997).
Den Tonkelaar et al. (1978) reported a NOAEL of 0.05 mg/kg bw/day in a 3 months diet study with pigs, with increased urinary coproporphyrin and microsomal enzyme activity as the critical effects.
Increased cell-mediated and humoral immune function, intraalveolar macrophage accumulation and induction of microsomal mixed-function oxidase activity were observed in rats exposed to HCB *in utero*, via nursing and in the diet up to five weeks of age, the LOAEL for these effects was 0.2 mg/kg bw/day (Vos et al. 1983). In mice exposed *in utero* and via nursing up to 45 days of age, severely depressed delayed-type hypersensitivity response to the contact allergen oxazolone was reported with a LOAEL of 0.5 mg/kg bw/day Barnett et al. 1987). Mice subchronically exposed via the diet (3 - 18 weeks) showed increased susceptibility to *Leishmania* infection, and reductions in the resistance to a challenge with tumour cells and in the cytotoxic macrophage activity of the spleen; the LOAEL for these effects was 0.6 mg/kg bw/day (Loose et al. 1981, Loose 1982).
A chronic two-generation feeding study with rats, reported by Arnold et al. (1985) and Arnold & Krewski (1988), resulted in a NOAEL of 0.08 mg/kg bw/day with altered Ca metabolism and increased liver weights as the critical effects. From this latter study the ATSDR derived an even lower LOAEL of 0.016 mg/kg bw, based on dose-related effects seen at the lowest dose: peribiliary lymphocytosis, peliosis (multiple small blood-filled cystic lesions throughout the liver) and fibrosis of the liver (ATSDR 1996; cf. paragraph 5.8.5.4).
In dietary studies with rats exposed for 3, 6 or 12 months Mollenhauer et al. (1975, 1976) also found a NOAEL of 0.05 mg/kg bw/day for ultrastructural changes in the liver observed by electron microscopy.
Studies on prolonged exposure to HCB by inhalation are not available.

Genotoxicity and carcinogenicity

HCB did not cause either frameshift or base pair substitution mutations in 5 strains of *Salmonella typhimurium*, with or without metabolic activation.
A weak positive response was reported in *S. typhimurium* TA98, but the authors reported also mutagenicity for lindane, in contrast to the results of others.
HCB did not induce tryptophan reversion or DNA damage in *Escherichia coli* WP2 and WP2uvrA, with or without metabolic activation.
A positive finding for methionine reversion in *Saccharomyces cerevisiae* was reported, but upon re-evaluation the observed increase was considered not to meet current standards of a positive response.
The compound did not induce OUA^r mutation in Chinese hamster lung cells (V79), but did induce $8AG^r$ mutations in these cells. However, both the magnitude of the (small) increase and the uncertain dose-response indicate that the result is debatable.
It did not induce chromosomal aberrations *in vitro* in cultured Chinese hamster fibroblast cells (at concentrations up to 12 mg/ml), with or without metabolic activation, or in human peripheral blood lymphocytes exposed to up to 30 µg/ml.
Rat and human hepatocytes *in vitro* exposed to HCB (30-160 µg/ml) both showed a significant increase in the frequency of micronucleated cells (the increase being only modest in human hepatocytes), while with human hepatocytes also a modest but significant increase of DNA breaks was observed (Canonero et al. 1997); the authors interpreted their results by stating that *"HCB should be considered a weak genotoxic carcinogen"*.
HCB up to 221 mg/kg bw/day (5 or 10 days) was negative in two dominant lethal mutation studies with rats.
The compound did not increase the frequency of sister chromatid exchanges in the bone marrow of male mice given 400 mg/kg bw (route not specified), but the lack of details in this report limits the interpretation.
Treatment of rats with 1000 mg HCB per kg diet for 15 days was hepatotoxic but did not induce early diploidisation in hepatocytes.

(Data summarised from CEPA 1993, ATSDR 1996 and IPCS 1997, except the cited study of Canonero et al., 1997).

Taken together the available information does not allow a firm conclusion regarding the genotoxicity of HCB.

Long-term bioassays in several strains of mice, rats and hamsters demonstrated the carcinogenic potential of HCB as evidenced by increased incidences of hepatomas, hemangioendotheliomas, or thyroid tumours as the most frequently seen effects.

In a 104-week dietary study with Sprague-Dawley rats (with doses of 0, 4 and 8, and 0, 5 and 9 mg/kg bw/day for males and females, respectively), significant increases in the incidence of hepatomas/haemangiomas and of renal cell adenomas were found in both sexes at both doses. In females the incidences of hepatocellular carcinomas, bile duct adenomas/carcinomas and phaeochromocytomas were elevated at both doses; at the low dose also the incidence of adrenal cortical adenomas was increased (Ertürk et al. 1986).

The combined *in utero*, lactational and oral exposure of rats was studied by Arnold et al. (1985) and Arnold & Krewski (1988) by feeding HCB in the diet at doses of 0, 0.01, 0.06, 0.29 and 1.5, and 0, 0.01, 0.07, 0.38 and 1.9 mg/kg bw/day for males and females, respectively. After 3 months the F0 rats were bred and F1 pups were reared on the same diet for up to 130 weeks. In exposed F1 females increased incidences of neoplastic liver nodules and adrenal phaeochromocytomas were noted at the highest dose. In males at the highest dose a significantly increased incidence of parathyroid adenomas was noted.

In a dietary study with mice HCB was administered at doses of 0, 6, 12 and 24 mg/kg bw/day during 120 weeks (Cabral et al. 1979). In females at the highest dose a significant increase in the incidence of liver cell tumours was found; the number of tumour-bearing animals, the latent period and the multiplicity and size of tumours increased with dose.

Cabral et al. (1977) reported a significant dose-related increase in the incidence of hepatomas and liver haemangioendotheliomas in Syrian golden hamsters exposed for life to HCB in the diet at doses 0, 4, 8 and 16 mg/kg bw/day. The incidence of hepatomas was statistically significantly increased in each treated group, while liver haemangioendothelioma incidence was statistically significantly elevated in the high-dose groups of both sexes and in middle-dosed males. Thyroid alveolar adenomas were observed in all treated groups except low-dosed males, but a significantly increased incidence was found only in high-dosed males. In males the increased incidence of these adenomas was significantly dose-related.

Results from a number of studies have indicated that HCB is a cocarcinogen or promoter of cancer. Concomitant exposure to HCB in the diet enhanced the induction of liver tumours by polychlorinated terphenyl in mice. Dietary exposure of rats to HCB promoted the development of liver tumours from prior exposure to iron, and of hepatocellular carcinomas and/or hepatic γ-glutamyltranspeptidase-positive foci initiated by diethylnitrosamine. Short-term exposures (< 1 day) of Sprague-Dawley rats to sublethal doses of HCB produced a 1.3-fold increase in ornithine decarboxylase activity, a marker for promotion (CEPA 1993, IPCS 1997).

The IPCS Task Group on HCB noted that tumours, some of which were malignant, have been induced in multiple species, at multiple sites, in some cases at doses that were not overtly toxic in other respects and that are within an order of magnitude of those that produce more subtle toxicological effects, or following subchronic exposure. Although there is some evidence to suggest that HCB may cause cancer by indirect mechanisms, the evidence is not definitive at this time and does not address all tumour sites (IPCS 1997). Based on the induction of a variety of tumours in hamsters, rats and mice exposed to HCB by ingestion, IPCS concluded to sufficient evidence for HCB being carcinogenic in animals (IPCS 1997). The IARC has evaluated the evidence for carcinogenicity of HCB in animals and humans, and assigned it to Group 2B (*possibly carcinogenic to humans*), based on *sufficient evidence* for carcinogenicity in experimental animals and *inadequate evidence* for carcinogenicity in humans (IARC 1987).

5.8.5.3. EVALUATION

Oral exposure
In the evaluation of 1991 a TDI of 0.5 µg/kg bw/day was derived, based on the NOAEL of 0.05 mg/kg bw/day from the subchronic studies in rats of Mollenhauer et al. (1975, 1976). This was the approach developed in the RIVM criteria document of 1991. No tolerable concentration in air (TCA) was derived, due to lack of data (Vermeire et al. 1991).
Given the low dose levels at which tumours have been observed, in multiple species and at multiple sites, HCB is evaluated on the basis of its carcinogenic risk being the most sensitive and most severe endpoint.
Of the reported animal carcinogenicity studies, two studies are considered adequate in terms of number of animals, study design, etc. (in accordance with IPCS 1997 and US-EPA 1996): Ertürk et al. (1986), and Arnold et al. (1985) and Arnold & Krewski (1988). Ertürk et al. reported hepatocellular carcinomas in 36 out of 56 female rats exposed to a dose of 5 mg/kg bw/day during two years (lowest dose administered) and 0 out of 52 for controls. Arnold and coworkers observed neoplastic liver nodules in 2 out of 50 female rats exposed for 130 weeks to 0.08 mg/kg bw/day (exposure started *in utero* and included lactation), and 0 out of 49 both at a dose level of 0.016 mg/kg bw/day as well as for controls. The latter study is chosen as the pivotal one. Application of the linear extrapolation model results in a $1{:}10^4$ lifetime excess cancer risk of 0.16 µg/kg bw/day; this limit value is adopted as the new MPR for HCB.
For comparison a tolerable daily intake for non-neoplastic toxic effects can be derived by applying the threshold approach. A number of subchronic and chronic animal studies (Arnold et al. 1985; Arnold & Krewski 1988; Mollenhauer et al. 1975, 1976; den Tonkelaar et al. 1978) resulted in NOAELs of 0.05 mg/kg bw/day. Applying an uncertainty factor (UF) of 100 (as was also done in the previous evaluation by Vermeire et al. (1991)) would result in a tolerable daily intake of 0.5 µg/kg bw/day. This value is approximately 3 times higher than the $1{:}10^4$ lifetime excess cancer risk estimated above.
Inhalation exposure
Data that allow the estimation of a TCA or an excess cancer risk due to inhalation exposure to HCB are lacking. Hence such a limit value can only be derived by route-to-route extrapolation. Taking the oral cancer risk as the basis, this extrapolation [78]) results in a value of 0.75 µg/m^3 as the provisional $1{:}10^4$ excess lifetime cancer risk for inhalation exposure. This limit value is provisional because it was derived via route-to-route extrapolation, a procedure involving considerable uncertainty.

5.8.5.4. EVALUATIONS BY OTHER ORGANISATIONS

Non-neoplastic effects

The approach of IPCS (1997) for non-neoplastic effects resulted in a TDI of 0.17 µg/kg bw/day on the basis of the lowest reported NOAELs of approximately 0.05 mg/kg bw/day primarily for hepatic effects observed in a subchronic study in pigs (den Tonkelaar et al. 1978) and in (sub)chronic studies in rats (Mollenhauer et al. 1975, 1976, Arnold et al. 1985, Arnold & Krewski 1988), incorporating a UF of 300 (100 for intra- and interspecies variation, and 3 for the severity of effects).
CEPA (1993) arrived at a chronic oral limit value of 0.05 µg/kg bw/day based on the same studies as IPCS, but applying a UF of 1000 (100 for intra- and interspecies variation and 10 for evidence of carcinogenicity).
US-EPA (IRIS 2000) derived a RfD (oral reference dose ≈ TDI) of 0.8 µg/kg bw/day based on the NOAEL of 0.08 mg/kg bw/day for liver effects in the study of Arnold et al. (1985), applying a UF of 100.
ATSDR (1996) derived a chronic oral MRL (minimal risk level ≈ TDI) of 0.02 µg/kg bw/day based on the LOAEL of 0.016 mg/kg bw/day for dose-related effects seen at this dose (lowest dose administered) in the study of Arnold et al. (1985): peribiliary lymphocytosis, peliosis and fibrosis of the liver

[78]) 0.16 × 70 (mean adult body weight in kg) ÷ 20 (mean adult breathing volume in m^3) × 100/75 (correction for 75% absorption upon inhalation exposure, assuming 100% absorption upon oral exposure).

(this LOAEL is concluded by ATSDR, not by the study authors); ATSDR applied a UF of 1000 (which includes a factor of 10 for extrapolating from LOAEL to NOAEL)
Inhalation values for the general population were not derived due to lack of inhalation data, but a preliminary value was derived by FoBiG (1992) using route-to route extrapolation based on the US-EPA RfD of 0.8 μg/kg bw/day. This resulted in a long-term inhalation limit value of 3 μg/m^3 (FoBiG 1992).
The Dutch Expert Committee on Occupational Standards (DECOS) derived a MAC value (maximum acceptable concentration) of 30 μg/m^3 (DECOS 2000).

Neoplastic effects

IPCS (1997) estimated a tumorigenic dose TD_5 i.e. the intake associated with a 5% excess incidence of tumours in experimental studies in animals. Based on the results of the two-generation carcinogenicity bioassay in rats (Arnold et al. 1985, Arnold & Krewski 1988) and using a multistage model, the TD_5 is 0.81 mg/kg bw/day for neoplastic liver nodules in females. Considering the insufficient mechanistic data, a UF of 5000 was used to develop a health-based guidance value of 0.16 μg/kg bw/day (IPCS 1997).
On the basis of the same study and the same endpoint, Health Canada (CEPA 1993), using a multistage model and applying a surface, estimated the carcinogenic potency (expressed as $TD_{0.05}$, which is identical to TD_5 as used by IPCS) to be 0.06 mg/kg bw/day [79]).
US-EPA (IRIS 2000) applied its linearised multistage model and arrived at a oral slope factor of 1.6 per [mg/kg bw/day] [80]), this estimation was based on hepatocellular carcinomas in female rats as reported by Ertürk et al. (1986).
For the inhalation route of exposure no separate cancer risk estimate has been developed due to lack of inhalation data. US-EPA (IRIS 2000) extrapolated across routes based on its oral cancer risk estimate, which resulted in a 1:10^4 excess lifetime cancer risk level at 0.2 μg/m^3.

5.8.5.5. BACKGROUND EXPOSURE

Background exposure results predominantly (> 90%) from intake via the diet. Vermeire et al. (1991) estimated the general population background exposure to HCB in the Netherlands to be 0.004 (mean) to 0.014 (maximum) μg/kg bw/day.
According to IPCS (1997), the results of most studies on the levels of HCB in foods and human tissues over time indicate that exposure of the general population to HCB declined from the 1970s to mid-1990s in many locations. The total intake via food, air and water of HCB by adults in the general population in various countries is estimated to be between 0.0004 and 0.003 μg/kg bw/day. Owing to the presence of HCB in breast milk, mean intakes by nursing infants have been estimated to range from < 0.018 to 5.1 μg/kg bw/day in various countries (IPCS 1997). The background exposure as estimated by IPCS (1997) (0.0004 - 0.003 μg/kg bw/day) is adopted for the present evaluation, this estimate being the most recent and most extensively reviewed one.

5.8.5.6. CONCLUSION

1:10^4 lifetime excess cancer risk from oral exposure: 0.16 μg per kg body weight per day.
Provisional 1:10^4 lifetime excess cancer risk from inhalation exposure: 0.75 μg per m^3.
Background exposure: 0.0004 - 0.003 μg per kg body weight per day.
Relevant routes of exposure in case of soil contamination: oral and inhalation.

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[79]) The origin of the more than ten-fold difference between the results of the estimations of IPCS and CEPA is not clear.

[80]) Linear extrapolation of this slope factor to the 1:10^4 lifetime excess cancer risk results in a value of 0.06 μg/kg bw/day.

5.8.5.7. REFERENCES

Arnold DL & Krewski D (1988):
Long-term toxicity of hexachlorobenzene.
Food Chem Toxicol 26, 169-174 *(cited in CEPA 1993, ATSDR 1996, IPCS 1997 and IRIS 2000).*

Arnold DL, Moodie CA, Charbonneau SM, Grice HC, McGuire PF, Bryce FR, Collins BT, Zwadizka ZZ, Krewski D, Nera EA & Munro IC (1985):
Long-term toxicity of hexachlorobenzene in the rat and the effect of dietary vitamin A.
Food Chem Toxicol 23, 779-793 *(cited in CEPA 1993, ATSDR 1996, IPCS 1997 and IRIS 2000).*

ATSDR (1996):
Toxicological profile for hexachlorobenzene (update).
US Department of Health & Human Services, Public Health Service, Agency of Toxic Substances and Disease Registry, Atlanta (GA), USA.

Barnett JB, Barfield L, Walls R, Joyner R, Owens R & Soderberg LSF (1987):
The effect of *in utero* exposure to hexachlorobenzene on the developing immune response of BALB/c mice.
Toxicol Letters 39, 263-274 *(cited in CEPA 1993, ATSDR 1996 and IPCS 1997).*

Cabral JRP, Mollner T, Raitano F & Shubik P (1979):
Carcinogenesis of hexachlorobenzene in mice.
Int J Cancer 23, 47-51 *(cited in CEPA 1993, ATSDR 1996, IPCS 1997 and IRIS 2000).*

Cabral JRP, Shubik P, Mollner T & Raitano F (1977):
Carcinogenic activity of hexachlorobenzene in hamsters.
Nature 269, 510-511 *(cited in CEPA 1993, ATSDR 1996, IPCS 1997 and IRIS 2000).*

Canonero R, Campart GB, Mattioli F, Robbiano L & Martelli A (1997):
Testing of p-dichlorobenzene and hexadichlorobenzene for their ability to induce DNA damage and micronucleus formation in primary cultures of rat and human hepatocytes.
Mutagenesis 12, 35-39.

CEPA (1993):
Priority Substances List Assessment Report. Hexachlorobenzene.
Canadian Environmental Protection Act, Health Canada, Ottawa, Canada.

DECOS (2000)
Chemiekaarten 15e editie, kaart no. C-0328

Den Tonkelaar EM, Verschueren HG, Bankovska J, Vries T de, Kroes R & Esch GJ van (1978):
Hexachlorobenzene toxicity in pigs.
Toxicol Appl Pharmacol 43, 137-145 *(cited in CEPA 1993, ATSDR 1996 and IPCS 1997).*

Ertürk E, Lambrecht RW, Peters HA, Cripps DJ, Gocmen A, Morris CR & Bryan GT (1986):
Oncogenicity of hexachlorobenzene.
In: Hexachlorobenzene - proceedings of an international symposium (Morris CR & Cabral JRP, eds), IARC Scientific Publ. No. 77, 399-401.
International Agency for Research on Cancer, Lyon, France *(cited in CEPA 1993, WHO 1996, IPCS 1997 and IRIS 2000).*

FoBiG (1992):
Basisdaten Toxikologie für umweltrelevante Stoffe zur Gefahrenbeurteilung bei Altlasten.
Umweltforschungsplan des Bundesministeriums für Umwelt, Naturschutz und Reaktorsicherheit, Forschunsbericht nr. 102 03 443/01 (two volumes: Zusammmenfassung & Zusammenfassung der Einzelberichte).
Prepared by FoBiG Forschungs- und Beratungsinstitut Gefahrstoffe, Freiburg im Breisgau, Germany.

IARC (1987):
Overall evaluations of carcinogenicity: an updating of IARC Monographs volumes 1-42.
International Agency for Research on Cancer, World Health Organization, Lyon, France.

IPCS (1997)
Hexachlorobenzene. Environmental Health Criteria 195.
World Health Organization, Geneva, Switzerland.

IRIS (2000):
US-EPA Integrated Risk Information System: summary for hexachlorobenzene (toxicity assessment dated January 1991, carcinogenicity assessment dated January 1996).
US Environmental Protection Agency, Washington DC, USA.

Loose LD (1982):
Macrophage induction of T-suppressor cells in pesticide-exposed and protozoan-infected mice.
Environm Health Perspect 43, 89-97 *(cited in CEPA 1993 and IPCS 1997).*

Loose LD, Silkworth JB, Charbonneau T & Blumenstock F (1981):
Environmental chemical-induced macrophage dysfunction.
Environm Health Perspect 39, 79-92 *(cited in CEPA 1993 and IPCS 1997).*

Mollenhauer HH, Johnson JH, Younger RL & Clark DE (1975):
Ultrastructural changes in the liver of the rat fed hexachlorobenzene.
Am J Vet Res 36, 1777-1781 *(cited in RIVM 1991 and IPCS 1997).*

Mollenhauer HH, Johnson JH, Younger RL & Clark DE (1976):
A unique intracellular aberration related to hexachlorobenzene ingestion.
Am J Vet Res 37, 847-850 *(cited in RIVM 1991 and IPCS 1997).*

RIVM (1991):
Slooff W, Bremmer HJ, Hesse JM & Matthijsen AJCM (eds.): Integrated criteria document chlorobenzenes.
National Institute of Public Health and the Environment, RIVM report no. 710401015, October 1991; Bilthoven, The Netherlands.

Vermeire TG, Apeldoorn ME van, Fouw JC de & Janssen PJCM (1991):
Voorstel voor de humaan-toxicologische onderbouwing van C-toetsingswaarden.
National Institute of Public Health and the Environment, RIVM-report no. 725201005, February 1991; Bilthoven, The Netherlands.

Vos JG, Brouwer GMJ, Van Leeuwen FXR & Wagenaar Sj (1983):
Toxicity of hexachlorobenzene in the rat following combined pre- and popstnatal exposure - comparison of the effects on the immune system, liver and lung.
In: Parke DV, Gibson GG & Hubbard R (eds.): Immunotoxicology. Academic Press, London, UK; p 219-235
(cited in CEPA 1993, ATSDR 1996 and IPCS 1997).

WHO (1996):
Guidelines for drinking-water quality, 2nd. ed., vol. 2: Health criteria and other supporting information.
World Health Organization, Geneva, Switzerland.

5.8.6. SUMMARY

Overview of the MPRs of chlorobenzenes as derived in 2000

Compound	MPR oral µg/kg bw/day	MPR inhalation µg/m^3	Background exposure µg/kg bw/day
Monochlorobenzene	200 [A])	500 [B])	≤ 0.9
Dichlorobenzenes			
- 1,2-DCB	430 [A])	600 [B])	0.001
- 1,3-DCB	not available	not available	0.001
- 1,4-DCB	100 [A])	670 [C])	0.006
Trichlorobenzenes (all isomers)	8 [A])	50 [B])	< 0.04
Tetrachlorobenzenes (all isomers)	not available	not available	
Pentachlorobenzene	not available	not available	
Hexachlorobenzene	0.16 [D])	0.75 [E])	0.0004 - 0.003

[A]) TDI: tolerable daily intake
[B]) pTCA: provisional tolerable concentration in air
[C]) TCA: tolerable concentration in air
[D]) 1:10^4 lifetime excess cancer risk from oral exposure
[E]) provisional 1:10^4 lifetime excess cancer risk from inhalation exposure (derived via route-to-route extrapolation)

Relevant routes of exposure in cases of soil contamination: oral and inhalation.

5.8.7. REFERENCES

RIVM (1991):
Slooff W, Bremmer HJ, Hesse JM & Matthijsen AJCM (eds.): Integrated criteria document chlorobenzenes. National Institute of Public Health and the Environment, RIVM report no. 710401015, October 1991; Bilthoven, The Netherlands.

Vermeire TG, Apeldoorn ME van, Fouw JC de & Janssen PJCM (1991):
Voorstel voor de humaan-toxicologische onderbouwing van C-toetsingswaarden.
National Institute of Public Health and the Environment, RIVM-report no. 725201005, February 1991; Bilthoven, The Netherlands.

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Date: *24-10-2000*

5.9. CHLOROPHENOLS MONOCHLOROPHENOL, DI-, TRI- AND TETRACHLOROPHENOLS, PENTACHLOROPHENOL

5.9.1. MONOCHLOROPHENOL, DI-, TRI- AND TETRACHLOROPHENOLS

5.9.1.1. EVALUATION

The mono-, di-, tri- and tetrachlorophenols were evaluated in the scope of this project by Vermeire et al. (1991). Only for 2,4-dichlorophenol the database permitted the estimation of a TDI, which was set at 3 µg/kg bw/day on the basis of the NOAEL of 0.3 mg/kg bw/day in an oral reproduction study with rats, for effects on the immune system; a UF (uncertainty factor) of 100 for inter- and intraspecies variation was applied. Subsequently this TDI was taken as the TDI valid for all mono-, di-, tri- and tetrachlorophenols. TCAs were not derived since inhalation exposure in cases of soil contamination was considered not relevant.
For the re-evaluation of the mono-, di-, tri- and tetrachlorophenols, the following national and international reviews were consulted:

- Toxicological profiles of the US Agency for Toxic Substances and Disease Registry;
- IRIS files of the US Environmental Protection Agency;
- Environmental Health Criteria of the WHO's International Programme on Chemical Safety;
- Evaluations of carcinogenicity of the WHO's International Agency for Research on Cancer;
- Criteria documents of the RIVM;
- Other relevant information available in the compounds database of the library of the RIVM's Centre for Substances & Risk Assessment.

Regarding the mono- and dichlorophenols new relevant information was not available. Consequently the MPRs as derived by Vermeire et al. in 1991 are to be maintained.
Regarding the tri- and tetrachlorophenols only limited new and relevant information was available. However, due to time constraints this information could not be evaluated in time to be included in the present report. Consequently, and for the time being, the MPRs as derived by Vermeire et al. in 1991 are to be maintained.

5.9.1.2. CONCLUSION

Compound	TDI	Background exposure
Monochlorophenols	3.0	negligible
Dichlorophenols	3.0	negligible
Trichlorophenols	3.0	negligible
Tetrachlorophenols	3.0	negligible

TDI: tolerable daily intake (oral exposure); µg/kg bw/day
Background exposure; µg/kg bw/day

5.9.2. PENTACHLOROPHENOL

5.9.2.1. INTRODUCTION

Pentachlorophenol was evaluated within the scope of this project by Vermeire et al in 1991. A TDI of 30 µg/kg bw/day was derived. The value was based on a NOAEL of 3 mg/kg bw/day for foetotoxic effects in an oral reproduction study, with a UF of 100. A TCA was not derived since inhalation exposure in cases of soil contamination was considered not relevant.
For the update additional literature was evaluated. This included a review of IPCS (1987), ATSDR (1999), and the environmental hazard assessment of Hobbs et al. (1993).

It has been suggested that pentachlorophenol can be formed by fungi under natural circumstances, however, this has not been actually demonstrated. Hence it is assumed that pentachlorophenol in soil is exclusively related to human activities, and background levels of pentachlorophenol of natural origin in soil are negligible (IPCS 1987).
Pentachlorophenol is mainly used as a pesticide. It is used in timber, in textiles and leather and paper, in paint and cables, as a biocide, insecticide, and fumigant. In various countries including The Netherlands the use of pentachlorophenol is restricted or to be banned (Hobbs et al. 1993).
Soil contamination can be caused both by the use of pentachlorophenol, and by disposal of industrial and household waste. It can thus be expected that diffuse and local soil contaminated sites can be found.

5.9.2.2. TOXICOLOGY

Toxicokinetics

Absorption
It is shown in laboratory animals that the gastrointestinal absorption of pentachlorophenol is rapid and complete: tracer studies indicate that more than 90% is absorbed after oral intake. Studies with human volunteers have shown that pentachlorophenol is also well absorbed in humans, with maximum blood levels within 4 hours.
Studies on the absorption after inhalation are limited; in a tracer study with rats 75% was absorbed in the lungs. From a study with two humans it was suggested that absorption after inhalation is in the order of 80% for humans.
Dermal studies have shown that dermal absorption in humans can be as much as 50% when administered in oily formulations. In aqueous solutions the dermal absorption is about 10%. Dermal absorption of pentachlorophenol from soil was investigated in monkeys. In this study about 25% was percutaneously absorbed from soil at an initial concentration of 0.7 $\mu g/cm^2$ for 24 hours.
Distribution
In rats the highest levels of pentachlorophenol are detected in liver and kidneys 9 days after a single oral dose. Lower concentrations are found in brain and fat tissue. In monkeys pentachlorophenol enters the enterohepatic circulation, leading to a whole body half-life of many days.
After inhalation only small concentrations accumulate in laboratory animals, and pentachlorophenol is rapidly cleared within 24 hours.
The binding of pentachlorophenol to plasma proteins plays a major role in the distribution. About 95% is bound to proteins, the rest to lipids and lipoproteins. The concentration in plasma varies linearly with the dose, both for oral and inhalation exposure.
Metabolism
Studies with rats and mice have demonstrated that pentachlorophenol is biotransformed into a urinary metabolite via conjugation with glucuronic acid to pentachlorophenol glucuronide. It can also be dechlorinated by the P450-3A enzyme complex, ultimately leading to tetrachloro- and trichlorophenol-glucuronides, and tetrachloro- and trichloro-(hydro)-quinones. In studies with monkeys, however, the hydroquinone and glucuronide conjugates could not be detected in urine. These data suggest that pentachlorophenol is not metabolised to any degree in monkeys.
In a study with humans that were possibly exposed by inhalation of pentachlorophenol, tetrachloro-p-quinone was identified in the urine. The presence of glucuronide conjugates was not investigated in this study.
Excretion
Results from animal and human studies indicate that pentachlorophenol is not extensively metabolised, as most of the dose is excreted unchanged in all species studied. Both the parent compound and the metabolites are eliminated through urine; only a small amount can be found in the faeces.
Available data on the excretion of pentachlorophenol by humans after oral ingestion are not conclusive. In one study it was slowly eliminated with a half-life of 14 days, whereas in another study the half-life was about one day. It was concluded in that study that the diet and the vehicle of administration might be responsible for the differences.

Excretion following inhalation exposure is known from occupational studies. These studies indicated that pentachlorophenol elimination is biphasic with an initial rapid step followed by a slow second step. It is suggested that the kinetics differ for a high level single dose and low level chronic exposure.

Biomarkers

Unmetabolized pentachlorophenol in urine is well suited as a biomarker for exposure. It can easily be detected at concentrations as low as 1 μg/L. It is not advised to measure pentachlorophenol in body fluids or tissues because other compounds such as hexachlorobenzene and lindane can be transformed into pentachlorophenol within the body. A major metabolite in humans is tetrachloro-p-hydroquinone, which is also well suited as an indicator of exposure to pentachlorophenol.

Biomarkers to characterise effects caused by pentachlorophenol do not exist; clinical manifestations of renal and hepatic toxicity as indicated by increased serum enzyme levels are also associated with exposure to many other chemical compounds (IPCS 1987, ATSDR 1999).

Toxicity

Acute poisoning

There are very little data about the effects by poisonings of humans with pentachlorophenol. From one study it can be concluded that the lethal oral dose for humans is in the order of 1 gram.

Death from inhalation exposure (probably in combination with dermal exposure) is known from herbicide sprayers and sawmill workers. In these cases various other effects were reported like bronchitis, tachycardia, abdominal pain and vomiting, and haemolytic anaemia. In addition various neurological effects are reported, such as lethargy and focal swelling of the myelin sheath. It should be noted that these people were exposed to technical pentachlorophenol mixtures that are known to contain impurities, so it can be questioned whether pentachlorophenol or its impurities have caused these effects.

Genotoxicity and carcinogenicity

Pentachlorophenol does not cause gene mutations in *in vitro* test systems with prokaryotic organisms and mammalian cells. However, some metabolites, such as tetrachlorohydroquinone and tetrachloroquinone, showed DNA damage and DNA adduct formation in mammalian cells (IPCS 1987, ATSDR 1999).

In *in vivo* systems, such as gene mutations in the mouse host-mediated assay, the sex linked recessive lethal mutation in Drosophila, and gene mutations and micronuclei tests in mice and rats, pentachlorophenol did not demonstrate genotoxic effects. In studies with occupational exposed humans no chromosomal aberrations or sister chromatid exchange were found (ATSDR 1999).

One study demonstrated significantly elevated risk ratios for non-Hodgkin's lymphoma and soft tissue sarcoma in people who consumed fish contaminated with tri-, tetra- and pentachlorophenols. An association with he same type of tumours is reported after occupational exposure to technical pentachlorophenol. These studies are limited by confounding factors such as concurrent exposure to other potentially carcinogenic chemicals. In other epidemiological studies no association was found between inhalation and any form of cancer even though the urinary pentachlorophenol excretion levels were increased.

The carcinogenic potency of pentachlorophenol has been tested in animal studies for both technical mixtures of pentachlorophenol and the pure compound (purity >99%) after oral exposure. In the studies with purified pentachlorophenol mesotheliomas and nasal squamous carcinomas in mice have been observed. Technical mixtures caused hepatocellular adenomas and carcinomas in mice and rats. Hemangiosarcomas of liver and spleen and hepatocellular sarcomas in mice showed a LOAEL of 17.5 mg/kg bw/day (IPCS 1987, ATSDR 1999).

Based on the available data IARC classified pentachlorophenol in group 2B: *possible carcinogenic to humans.*

Subchronic and chronic toxicity

There are no data concerning chronic oral intake of pentachlorophenol by humans. In oral semichronic studies with experimental animals the liver is the primary target organ. Both increased liver weight and microscopic changes, and changes in liver enzyme activity are noticed. From studies of chronic oral exposure of rats and mink to technical mixtures and pure pentachlorophenol it can be concluded that the LOAEL for small changes in serum thyroxin and thyroid weight is 1 mg/kg bw/day. The NOAEL for reproductive effects is reported to be 1 mg/kg bw/day.

There are no data of semichronic or chronic inhalation exposure of humans or laboratory animals to pentachlorophenol that can be used to derive a NOAEC.
Toxic mechanism of action
It is generally accepted that uncoupling of the mitochondrial oxidative phosphorylation is the basis for the toxic effects of pentachlorophenol. It has been found to bind to mitochondrial protein, and the ultra-structural changes reported in mitochondria of rat liver cells are consistent with uncoupling of oxidative phosphorylation. The compound might induce structural changes in enzymes. According to ATSDR (1999) the known effects, such as tachycardia, do also fit in this model.
The binding of pentachlorophenol with serum proteins might cause competition for serum thyroxin binding sites, which could cause the adverse effects on thyroid homeostasis (ATSDR 1999).

5.9.2.3. EVALUATION

Pentachlorophenol did not demonstrate genotoxicity in *in vitro* and *in vivo* test systems and in occupational exposed humans. Consequently a TDI can be derived from NOAELs with uncertainty factors.
In chronic studies in mink a LOAEL of 1 mg/kg bw/day was reported for minor changes in thyroid homeostasis. No other effects could be noticed at this exposure level. This value is used for the estimation of the TDI, by applying a UF of 3 for the extrapolation of a marginal effect level to a NOAEL, and a UF of 100 for inter- and intraspecies variation. This results in a TDI of 3 µg/kg bw/day.
Due to the lack of appropriate data a TCA can not be derived.

5.9.2.4. EVALUATION OF OTHER ORGANISATIONS

IARC classified pentachlorophenol in group 2B: *possibly carcinogenic to humans* with *inadequate evidence of carcinogenicity in humans* but *sufficient evidence in experimental animals*.
US-EPA derived a RfD of 0.03 mg/kg bw/day. It was based on a NOAEL of 3 mg/kg bw/day for liver and kidney pathology in a rat oral chronic study, with a UF of 100 for intra- and interspecies variability (IRIS, revised 1993). In their assessment of carcinogenicity an oral slope factor of 0.12 [mg/kg bw/day]$^{-1}$ was presented, based on a linearized multistage procedure of data of hepatocellular and hemangiosarcoma tumours in mice (IRIS, revised 1993). According to ATSDR (1999) this is equal to a lifetime excess cancer risk of $1{:}10^4$ at a daily intake of 0.9 µg/kg bw/day.
ATDSR presented an acute oral MRL of 5 µg/kg bw/day. This was based on a LOAEL of 5 mg/kg bw/day for developmental effects in rat pups when dams were exposed to pentachlorophenol in corn oil; a UF of 10 was used for the extrapolation to a NOAEL, and 100 for intra- and interspecies variability. An intermediate oral MRL of 1 µg/kg bw/day was derived using an LOAEL of 1.4 mg/kg bw/day for increased serum enzyme levels in male rats exposed for 12 weeks. A UF of 10 was used for the extrapolation to a NOAEL, and 100 for intra- and interspecies variability. A chronic oral MRL of 1 µg/kg bw/day was derived using an LOAEL of 1 mg/kg bw/day for effects on serum thyroxin and thyroid weight in a multi-generation study with mink. A UF of 10 was used for the extrapolation to a NOAEL, and 100 for intra- and interspecies variability (ATDSR 1999).
Hassauer et al. (1993) advised the UBA (Germany) an oral "Orientierungswert" of 30 µg/kg bw/day for long term exposure to pentachlorophenol. This was based on a NOAEL of 3 mg/kg bw/day for foeto- hepato-, and nephrotoxic effects, with a UF of 100, and 100% resorption. It their advice an inhalation "Orientierungswert" of 40 ng/m^3 was included for chronic inhalation, based on a LOAEC for hepatotoxic effects of 0.8 µg/m^3 in humans, with a UF of 20.

5.9.2.5. BACKGROUND EXPOSURE

Vermeire et al (1991) estimated the daily intake of pentachlorophenol in The Netherlands at 0.33 µg/kg bw/day at most. According to Hattemen-Frey & Travis (cited in ATSDR 1999) food is the most important source for pentachlorophenol exposure of the general population. Available data of concentrations pentachlorophenol in various food items demonstrate a substantial decrease since the 1970s. An estimate of the WHO of 1987 ranged from 0.1 to 6 µg/day (cited in ATSDR 1999). However, in the most recent Total Diet Study the FDA estimated for 1991 a mean daily intake in the US of 1 ng/kg bw/day.

Tuinstra (1995) reported a median concentration of 0.03 µg/kg in cow's milk. With a $logK_{ow}$ of 5 for pentachlorophenol it can be assumed that it accumulates in fat. When it is presumed that all animal fat is equally contaminated with pentachlorophenol, it can be calculated that the average concentration in animal food products will be in the order of 1 µg/kg fat. With an average daily intake of 70 g of fat from animal products the exposure of the general population in The Netherlands can be estimated at 1 ng/kg bw/day.

5.9.2.6. CONCLUSION

Compound	TDI	Background exposure
Pentachlorophenol	3.0	0.001

TDI: tolerable daily intake (oral exposure); µg/kg bw/day
Background exposure; µg/kg bw/day

5.9.3. SUMMARY

Compound	TDI	TCA	Background exposure
Monochlorophenols	3.0	n.d.	negligible
Dichlorophenols	3.0	n.d.	negligible
Trichlorophenols	3.0	n.d.	negligible
Tetrachlorophenols	3.0	n.d.	negligible
Pentachlorophenol	3.0	n.d.	0.001

TDI: tolerable daily intake (oral exposure); µg/kg bw/day
TCA: tolerable concentration in air (inhalation exposure); $\mu g/m^3$
Background exposure; µg/kg bw/day
n.d.: data permitting the estimation of a TCA are not available

5.9.4. REFERENCES

ATSDR (1999):
Toxicological Profile for Pentachlorophenol (Update).
US Department of Health & Human Services, Public Health Service, Agency of Toxic Substances and Disease Registry, Atlanta (GA), USA.

Hassauer M, Kalberlah F, Oltmans J & Schneider K (1993):
Basisdate Toxikologie für umweltrelevante Stoffe zur Gefahrenbeurteilung bei Altlasten.
Umwelt Bundes Amt, Berichte 4/93, Erich Schmidt Verlag, Berlin, Germany.

Hobbs SJ, Howe PD & Dobson S (1993):
Environmental hazard assessment: pentachlorophenol.
Toxic Substances Division, Dir. Air Climate Tox. Subst., Dept. Environm. TSD/10. Garston, Watford, UK.

IARC (1991):
Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol. 53: Occupational exposures in insecticide application, and some pesticides.
International Agency for Research on Cancer, Lyon, France.

IPCS (1987):
Environmental Health Criteria 71 - Pentachlorophenol.
World Health Organization, Geneva, Switzerland.

Tuinstra LGMTh (1995):
Survey of pesticides and veterinary drugs 1994/1995 - toxaphenes, pyrethroids, organophosphorus pesticides, chlorophenols, and olaquindox in animal products.
State Institute for Quality Control of Agricultural Products, RIKILT report no. 95.33, October 1995; Wageningen, The Netherlands.

Vermeire TG, Apeldoorn ME van, Fouw JC de & Janssen PJCM (1991):
Voorstel voor de humaan-toxicologische onderbouwing van C-toetsingswaarden.
National Institute of Public Health and the Environment, RIVM-report no. 725201005, February 1991; Bilthoven, The Netherlands.

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5.10. CHLORONAPHTALENES MONOCHLORONAPHTALENES

5.10.1. INTRODUCTION

Chlorinated PAHs were evaluated within the scope of this project by Vermeire et al. in 1991 and by Vermeire in 1993. A TDI for chlorinated PAHs of 0.5 μg/kg bw/day and a TCA of 600 μg/m^3 were derived. These values were taken from the TDI of hexaclorobenzene and the TCA of 1,2-dichlorobenzene as derived by Vermeire et al. in 1991. For derivation of the Dutch Intervention values for soil contamination these TDI and TCA were assigned to monochloronaphthalene only.
For the update of the evaluation of monochloronaphthalene a review of Grandjean (1989) and the TSD (1993) were used.
There are two forms of monochloronaphthalene: 1-chloronaphthalene and 2-chloronaphthalene, also known as α-chloronaphthalene and β-chloronaphthalene, respectively. These two compounds are congeners of a group of a total of 75 chlorinated naphthalenes with one to eight chlorine atoms at different positions. They are manufactured under various trade names, such as Halowax. These waxes are mixtures of chlorinated naphthalenes with different chlorine content, such as liquid waxes with a high percentage of mono- and dichloronaphthalene, and flakes and powder with various congeners of tetra-, penta-, and hexachloronaphthalenes. The mixtures are used in electronic and automobile applications, as heat exchange fluids, in paper coating, and as additives in oil and other types of lubricants. In former days chlorinated naphthalenes were also used as wood preservatives.
The chlorinated naphthalenes are commercially produced, and it can be expected that the natural occurrence of chloronaphthalenes in soil is negligible.
The major sources of chloronaphthalene in soil are waste dumps of both industrial and household waste. Another source of emissions is waste incineration where chlorinated naphthalenes are emitted into air. The aerial depositions can lead to a more diffuse soil contamination. As a result chlorinated naphthalenes are found in soil and sediment in the US and Europe, including The Netherlands. In soil samples both monochloronaphthalene and higher chlorinated congeners have been detected (TSD 1993).

5.10.2. TOXICOLOGY

Toxicokinetics

HSDB (2000) reported that 1- and 2-chloronaphthalene are absorbed through the skin, in lungs, and in the gastro-intestinal tract. It tends to accumulate in adipose tissue, and brain, kidney and liver. As a metabolite the mono-hydroxy compound (i.e. 3-chloro-2-naphthol) has been identified. The metabolites are excreted in urine and bile.

Toxicity

Acute poisoning
On the basis of a few oral studies 1-chloronaphthalene can be considered moderately to highly toxic. Adverse effects following acute inhalation exposure have not been reported (TSD 1993).
Dermal and oral exposure of humans to chlorinated naphthalenes results in chloracne. According to Grandjean (1989) this effect can only be caused by higher chlorinated naphthalenes: chloracne is not observed after exposure to lower chlorinated naphthalenes.
Genotoxicity and carcinogenicity
Genotoxicity and carcinogenicity studies could not be located.
Subchronic and chronic toxicity
According to an overview in TSD (1993) there are no data of repeated dose toxicity studies with 1- or 2-chloronaphthalene. US-EPA, however, presented a 13 week oral study with 2-chloronaphthalene in mice. A LOAEL of 600 mg/kg bw/day and a NOAEL of 250 mg/kg bw/day was reported for liver and gall bladder weights and centrilobular hepatocellular enlargement in both sexes (HLA study 2399-124 reported in IRIS, revised 1990). The oral studies with higher chlorinated naphthalenes in different ex-

perimental animals demonstrate that the liver is the primary target organ (TSD 1993). Interference with vitamin A biotransformation leading to vitamin A depletion was observed. From the overview in TSD (1993) it can be concluded that upon oral exposure penta-, hexa-, hepta-, and octa-chlorinated naphthalenes appear to be more toxic than di- and trichlorinated naphthalenes.
With respect to inhalation exposure TSD (1993) reported the results of a study of 1938. Very slight liver damage was noticed due to inhalation of tri- and tetrachlorinated naphthalenes at a concentration of 1.3 mg/m^3, and slight to moderate liver damage by inhalation of penta- and hexachlorinated naphthalenes at 1.2 mg/m^3, in rats exposed for a period of 134 days during 16 hours per day.

5.10.3. EVALUATION

Since there are no data about the genotoxic and carcinogenic activity of monochloronaphthalane, a TDI for chloronaphthalene can only be derived from a NOAEL and uncertainty factors (UFs).
US-EPA reported a subchronic NOAEL for 2-chloronaphthalene of 250 mg/kg bw/day for liver effects in mice. A UF of 10 was used for extrapolation to chronic exposure, and 100 for inter- and intraspecies variation; an additional factor of 3 was applied for the restricted database of chloronaphthalene. This resulted in a TDI of 80 µg/kg bw/day was derived. This TDI of the US-EPA is to be adopted, and also to be applied to 1-chloronaphthalene.
Small liver effects were noticed after chronic inhalation exposure to 1.3 mg/m^3 of di- and trichlorinated naphthalenes, for 16 hours per day. This value is used to derive a NOAEC for 1- and 2- chloronaphthalene. The available data suggest that the di- and trichlorinated naphthalenes are more toxic than the monochloronaphthalenes. Consequently a UF of 3 is considered sufficient for the extrapolation of the LOAEC of the di- and trichlorinated naphthalenes to the NOAEC for the monochloronaphthalenes. An additional UF of 100 is to be used for inter- and intraspecies variation, and a further factor or 3 is used to correct for the restricted database. With a correction factor of 0.7 for continuous exposure a TCA of 1 µg/m^3 is derived. Due to the restricted data the TCA is to be considered a provisional TCA (pTCA).
The available data suggest that the higher chlorinated naphthalenes are more toxic than the monochloronaphthalenes after both oral and inhalation exposure. The TDI and TCA can therefore not be used for the higher chlorinated naphthalenes.

5.10.4. EVALUATIONS BY OTHER ORGANISATIONS

US-EPA proposed a RfD of 80 µg/kg bw/day for 2-chloronaphthalene. This value was derived from a NOAEL of 250 mg/kg bw/day for dyspnea, skin effects, and liver enlargement in a subchronic oral mouse study. A UF of 10 was used for extrapolation to chronic exposure, a factor of 100 for inter- and intraspecies variation, and an additional factor of 3 for the lack of reproductive and developmental toxicity data (IRIS, revised 1990).

5.10.5. BACKGROUND EXPOSURE

Vermeire (1993) assumed that the background exposure of the general population to chlorinated PAHs to be negligible.
There are no data of estimates of the daily intake of chloronaphthalene. According to TSD (1993) the lower chlorinated naphthalenes can be found in ambient air in the neighbourhood of different sources. From these data a concentration in the order of 1 ng/m^3 can be estimated for chloronaphthalenes in residential areas. This leads to a daily intake of 20 ng. Chloronaphthalene can also be found in drinking water after chlorination processing, leading to a daily intake in the order of 0.1 ng. Finally chloronaphthalenes have been found in fish, but only the higher chlorinated congeners have been detected. It can therefore be assumed that exposure of the population to 1- and 2-chloronaphthalene from food is negligible. The total background exposure of the general population in The Netherlands to monochloronaphthalene is thus estimated to be in the order of magnitude of 20 ng/day, which equals an intake of less than 0.001 µg/kg bw/day.

5.10.6. CONCLUSION

Compound	TDI	TCA	Background exposure
Monochloronaphtalene (1- and 2- isomers)	80	1.0 *)	< 0.001

TDI: tolerable daily intake (oral exposure); µg/kg bw/day
TCA: tolerable concentration in air (inhalation exposure); µg/m^3
Background exposure; µg/kg bw/day
*) Provisional MPR because of the limited database.

5.10.7. REFERENCES

Grandjean P (1989):
Identification and description of substances absorbed through the skin and to which workers are exposed at the workplace.
Final report to the Commission of the European Communities.

TSD (1993):
Environmental hazard assessment: halogenated naphthalenes.
Toxic Substances Division, Dir. Air, Climate and Toxic Substances, TSD/13,
Building Res. Establishment, Garston, Watford, UK.

Vermeire TG (1993):
Voorstel voor de humaan-toxicologische onderbouwing van C-(toetsings)waarden - Addendum op RIVM rapport nr. 725201005.
National Institute of Public Health and the Environment, RIVM report no. 715801001, May 1993; Bilthoven, The Netherlands.

Vermeire TG, Apeldoorn ME van, Fouw JC de & Janssen PJCM (1991):
Voorstel voor de humaan-toxicologische onderbouwing van C-toetsingswaarden.
National Institute of Public Health and the Environment, RIVM-report no. 725201005, February 1991; Bilthoven, The Netherlands.

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5.11. VINYLCHLORIDE

5.11.1. INTRODUCTION

Vinyl chloride (H_2C=CHCl; synonyms chloroethene, chloroethylene; VC) is a synthetic chemical widely used as a starting material for the synthesis of other chemicals, mainly polyvinylchloride (PVC) resins. At room temperature it is a flammable, colourless gas with a mild, sweet odour; the odour threshold in humans is approximately 7.8 g/m^3 (3000 ppm) [81]).
In the scope of the present project the compound has been evaluated in 1991. Since VC is considered to be a genotoxic carcinogen, a 1:10^4 lifetime excess cancer risk of 3.5 µg per kg body weight per day and 100 µg per m^3 for oral and inhalatory exposure, respectively, was derived (Vermeire et al. 1991). These values were based on experimental animal data for the oral, and on epidemiological data for the inhalation exposure.
General population background was estimated to be 59 ng/kg bw/day.
Relevant routes in case of soil contamination: oral and inhalation.

5.11.2. TOXICOLOGY

Toxicokinetics

VC is readily absorbed following inhalation or oral administration; absorption through the skin is negligible. Once absorbed, VC is widely distributed, but its storage in the body is limited by rapid metabolism and excretion. The highest concentrations of metabolites are found in the liver, kidneys and spleen. VC is metabolised by epoxidation to chloroethene oxide, which can rearrange spontaneously to chloroacetaldehyde; both metabolites are highly reactive and mutagenic, and are generally accepted to be responsible for the carcinogenic properties of VC. Binding studies showed covalent interaction with DNA, RNA and protein. Chloroacetaldehyde can be oxidised further to chloroethanoic acid, and all three metabolites can conjugate with glutathione followed by excretion in the urine. VC metabolism is dose-dependent and saturable. Low doses are metabolised and eliminated primarily in the urine, whereas at higher doses a substantial proportion is excreted unchanged via the lungs. Major urinary metabolites include thiodiacetic acid and N-acetyl-S-(2-hydroxyethyl)cysteine; these metabolites have also been found in the urine of humans following inhalation of VC. VC does not accumulate in the body to any significant extent. In rats, estimated half-lives for urinary elimination were approximately 4.5 h (both for oral and inhalation exposure), pulmonary excretion of unaltered VC (following inhalation exposure) had a half-life of 20-30 min, depending on the exposure level (reviewed in ECETOC 1988, BUA 1989, WHO 1996, and ATSDR 1997). VC passes the placental barrier (Ungvary et al. 1978).

Toxicity

Carcinogenicity
There is sufficient evidence of VC's carcinogenicity to several animal species, and experimental data show VC to be a multisite carcinogen (IARC 1987).
When administered by inhalation, it induced angiosarcomas in the liver in rats, mice and hamsters, Zymbal gland tumours in rats and hamsters, nephroblastomas in rats, pulmonary and mammary gland tumours in mice, and forestomach papilomas in hamsters; generally the effects were dose-related. The minimum concentrations at which compound-related tumours were observed were 65, 130 and 1300 mg/m^3 in rats, mice and hamsters, respectively (reviewed in IARC 1987, ECETOC 1988, ATSDR 1997, and EPA 1999).
Rats orally exposed to VC in food, in drinking water or by gavage, developed dose-related increases of angiosarcomas in the liver and lungs, hepatocellular carcinomas, mammary gland adenomas at dosages of 1.3 mg/kg bw/day and higher. In addition, small numbers of other tumours were found, in-

[81]) Conversion factors: 1 ppm = 2.60 mg/m^3; 1 mg/m^3 = 0.38 ppm.

cluding nephroblastomas, Zymbal gland carcinomas and hepatomas (Feron et al. 1981, Til et al. 1991; these and other studies reviewed in IARC 1987, ECETOC 1988, ATSDR 1997, and EPA 1999).
There is sufficient evidence of the carcinogenicity of VC in humans from studies of industrial populations exposed to high concentrations via the inhalation route; IARC has classified VC in group I: *sufficient evidence of carcinogenicity in humans* (IARC 1987). A causal association between VC exposure and angiosarcoma in the liver is sufficiently proved, and some studies suggest that VC is also associated with hepatocellular carcinoma, brain tumours, lung tumours, and malignancies of the lymphatic and haematopoietic tissues (reviewed in IARC 1987, ECETOC 1988, ATSDR 1997, and EPA 1999).
Genotoxicity
VC is mutagenic and genotoxic in a variety of test systems, both *in vitro* and *in vivo*.
It caused DNA damage and mutations in bacteria and, with metabolic activation, bound covalently to isolated DNA. VC induced gene conversion in yeast, sister chromatid exchange in human lymphocytes *in vitro*, mutations in Chinese hamster cells, unscheduled DNA synthesis in rat hepatocytes, and transformation of BALB/c 3T3 cells.
VC was mutagenic to plants, and caused sex-linked recessive lethal mutations in *Drosophila*. It induced chromosomal aberrations, sister chromatid exchanges and micronuclei in rodents exposed *in vivo*, but did not induce mutations in the mouse spot test or dominant lethal mutations in rats or mice. It alkylated DNA in several tissues of mice and rats exposed *in vivo*.
VC induced chromosomal aberrations in peripheral blood lymphocytes of workers exposed to VC at levels of 13-1300 mg/m^3, but studies looking for sister chromatid exchanges in exposed workers produced conflicting results (reviewed in IARC 1987, WHO 1996, ATSDR 1997, and EPA 1999).
Chronic and subchronic toxicity
Depending on exposure period and concentration, inhalation exposure of experimental animals to VC caused damage to the liver, lung, spleen and kidneys. In rats, exposure to VC at a concentration of 1280 mg/m^3 (7 h/day, 5 days/wk, 4.5 months) resulted in increased liver weights and histopathological alterations of livers and kidneys. Similar exposure to 256 and 510 mg/m^3 caused increased liver weights in rats after 6 months, but did not cause any changes in guinea pigs and dogs. The liver alterations seen in rats at 256 mg/m^3 were reversible. At 510 mg/m^3 histopathological liver alterations were observed in rabbits. In none of these experimental animals histologically detectable organ alterations were found at 130 mg/m^3 (same exposure regimen) (Torkelson et al. 1961). Comparable results were obtained by others (reviewed in ATSDR 1997, and EPA 1999). Rats orally exposed to VC (dosages of 0 to 300 mg/kg bw/day up to 140 weeks) showed increased mortality in groups given ≥5.0 mg/kg bw/day. Liver enlargement, increased relative liver weights, decreased blood clotting time, increased α-fetoprotein in serum, increased haematopoietic activity in the spleen, and much higher incidence of foci of cellular alteration were seen in groups given ≥1.7 mg/kg bw/day (Feron et al. 1981). Since effects were seen at the lowest dose applied, this experiment was repeated with lower dosages. The effects observed were quite comparable and started at a dose of 1.3 mg/kg bw/day. Together, these studies defined a LOAEL of 1.3 and a NOAEL of 0.13 mg/kg bw/day for liver effects (Til et al. 1983, 1991).
In most studies no significant effects on malformations or anomaly rates were seen following inhalation exposure of mice, rats, or rabbits to VC during different periods of pregnancy. However, in some experiments with rats a decrease in male fertility was observed after exposure to VC at a concentration of 650 mg/m^3, which was not seen at 130 mg/m^3 (Short et al. 1977). Two other studies with rats showed adverse effects on the testes after exposure to 260 mg/m^3, 6 hours/day, 6 days/week, for 12 months (Bi et al. 1985); the exposure level of 26 mg/m^3 was considered to be the NOAEL for biologically significant testicular changes (equivalent to 5.6 mg/m^3 for continuous exposure).
Prolonged occupational exposure of humans (by inhalation) caused several characteristic organ diseases described as the so-called VC-disease. The essential symptoms are characteristic liver damage with esophageal varices or stomach fundus varices, spleen enlargement, thrombocytopenia, acroosteolysis, as well as damage to the arterial circulation of the hand and skin damage (reviewed in ECETOC 1988, ATSDR 1997, and EPA 1999).
A number of case reports of occupationally exposed workers suggests that VC might affect sexual performance (impotence, loss of libido; elevated blood pressure and edema during pregnancy), but the value of these studies is limited due to confounding factors and poor statistics (ATSDR 1997, EPA 1999).

NOAELs for non-carcinogenic toxic effects are thus 0.13 mg/kg bw/day and 5.6 mg/m^3 for oral and (continuous) inhalation exposure, respectively.

5.11.3. EVALUATION

Since VC is considered to be a genotoxic carcinogen, the non-threshold linear extrapolation approach, as outlined by Janssen and Speijers (1997), is warranted for risk estimation.
Because there are no data on carcinogenic risk following oral exposure of humans, the risk estimation of cancer in humans after oral exposure has to be based on animal carcinogenicity bioassays involving oral exposure (see table).

Pivotal studies used for the MPR estimations

Species, exposure [1])	**Carcinogenic respons**	
[reference]	**Dose [2])**	**No. of tumour markers [3])**
Rat, oral (140/140 weeks)	0	2/112
[Feron et al. 1981]	1.7	32/116
Rat, oral (149/149 weeks)	0	1/197
[Til et al. 1991]	1.3	22/98
Mouse, inhalation, 4 hrs/day, 5 ds/wk (30/81 weeks)	0	1/127
[Maltoni et al. 1981, 1984]	130	4/47
Rat, inhalation, 4 hrs/day, 5 ds/wk (52/135 weeks)	0	0/249
[Maltoni et al. 1981, 1984]	65	6/81

[1]) between ( ): duration of exposure and duration of experiment
[2]) lowest tumorigenic dose: mg/kg bw/day (oral); mg/m^3 (inhalation)
[3]) sum of cellular carcinomas, angiosarcomas and neoplastic nodules in the livers

In the well-conducted chronic study of Feron et al. (1981), which was repeated by Til et al. (1983, 1991) with lower doses, rats were orally exposed to VC. The design of these studies was fully comparable. Vermeire et al. (1991) based their risk estimation for carcinogenicity on the incidence of hepatocellular carcinomas in the study of Feron and coworkers. Til et al. (1991) also applied the linear non-threshold extrapolation model but concluded to a 1:10^6 excess carcinogenic risk from oral exposure of 0.4 µg per person per day, based on the incidence of hepatocellular carcinomas, angiosarcomas, and neoplastic nodules. This is equivalent with a 1:10^4 excess lifetime carcinogenic risk (oral exposure) of 0.64 µg/kg bw/day. Using the corresponding data of the earlier study of Feron c.s. and applying the same methodology results in a similar risk: 0.63 µg/kg bw/day (see Table 1 and the addendum). The present evaluators accept the basis of the estimations of Til c.s., i.e., taking hepatocellular carcinomas, angiosarcomas and neoplastic nodules as markers for carcinogenic respons, and conclude to a 1:10^4 excess lifetime cancer risk for oral exposure of 0.6 µg/kg bw/day based on both studies mentioned.
Regarding inhalation exposure, epidemiological data are available; these data were used for the 1991 MPR estimation (Vermeire et al. 1991). However, re-evaluation showed that all of these suffer from shortcomings, the most prominent being the lack of reliable information on exact exposure levels and duration (ATSDR 1997, EPA 1999). Consequently, also the risk estimation of cancer in humans after inhalation exposure has to be based on animal carcinogenicity data. The elaborate and well-conducted studies of Maltoni et al. (1981, 1984) in which rats and mice were inhalatory exposed to VC, are considered the pivotal ones. Application of the extrapolation method results in a 1:10^4 excess lifetime cancer risk for inhalation exposure of 3.6 µg/m^3 (see Table 1 and the addendum).
Estimations based on NOAELs for non-carcinogenic toxic effects would result in tolerable daily intakes of 1.3 µg/kg bw/day for oral exposure (based on the NOAEL from the study of Til et al. [1991] of 0.13 mg/kg bw/day with an uncertainty factor of 100), and 56 µg/m^3 for inhalation exposure (based on the NOAEL from the study of Bi et al. [1985] of 5.6 mg/m^3 with an uncertainty factor of 100), respectively (see paragraph 5.11.2). Thus, the MPR values for carcinogenic risks protect also against the non-carcinogenic toxic risks of VC.

5.11.4. EVALUATIONS BY OTHER ORGANISATIONS

Non-carcinogenic risks
ATSDR (1997) derived an intermediate-duration (15-364 days) inhalation MRL of 78 μg/m^3, based on increased liver weight in rats (Bi et al. 1985); a UF of 100 was applied.
US-EPA (EPA 1999) derived a RfD of 5 μg/kg bw/day for non-carcinogenic toxic effects after oral exposure, based on liver cell polymorphism observed in the rat chronic feeding study of Til et al. (1983, 1991). The PBPK model of Clewell et al. (1995a,b) was used to convert the animal dose NOAEL to the human equivalent dose, and a UF of 30 was applied.
US-EPA (EPA 1999) derived a RfC of 100 μg/m^3 for non-carcinogenic toxic effects after inhalation exposure, using the same PBPK model, the same studies and endpoint, and a similar UF of 30.
Carcinogenic risks
ATSDR (1997) derived a chronic-duration (365 days and longer) oral MRL of 0.02 μg/kg bw/day, based on angiosarcomas in the livers of rats (Til et al. 1983, 1991); a UF of 1000 was applied.
US-EPA (EPA 1999) classified VC as a *Group A human carcinogen of medium carcinogenic hazard*. It considered VC a carcinogen of the non-threshold category, and derived a unit risk per [mg/kg bw/day] of 2.6 for continuous lifetime oral exposure from birth, which by linear extrapolation equals a MPR of 0.04 μg/kg bw/day for 1:10^4 excess lifetime cancer risk for oral exposure. This oral exposure unit risk was based on the study of Feron et al. (1981) with liver angiosarcomas, hepatocellular carcinomas and neoplastic nodules in female rats as the endpoints, applying PBPK modelling according to Clewell et al. (1995a) and the linearised multistage model.
Likewise, US-EPA (EPA 1999) derived a unit risk per [μg/m^3] of 8.7×10^{-6} for continuous lifetime inhalation exposure from birth, which by linear extrapolation equals a MPR of 11.5 μg/m^3 for 1:10^4 excess lifetime cancer risk for inhalation exposure (EPA 1999). This inhalation unit risk was based on the rat and mouse studies by Maltoni et al. (1981, 1984), with liver angiosarcomas, angiomas, hepatomas and neoplastic nodules as the endpoints, applying PBPK modelling according to Clewell et al. (1995a) and the linearised multistage model.

5.11.5. BACKGROUND EXPOSURE

Recent data regarding background levels of VC in Western Europe are not available, and thus there is no justification to alter the earlier background exposure estimation of 59 ng/kg bw/day (Vermeire et al. 1991), which was based on the background level of VC in ambient air, ranging from 0.1 to 0.5 (average: 0.2) μg/m^3, and an intake from food and water of (at most) 0.1 μg/day.

5.11.6. CONCLUSION

Compound	CR_{oral}	CR_{inhal}	Background exposure	Odour threshold
Vinylchloride	0.6	3.6	0.06	7.8×10^6

CR_{oral}: 1:10^{-4} excess lifetime cancer risk intake (oral exposure); μg/kg bw/day
CR_{inhal}: 1:10^{-4} excess lifetime cancer risk air (inhalation exposure); μg/m^3
Background exposure; μg/kg bw/day
Odour threshold; μg/m^3

Relevant routes of exposure in case of soil contamination: oral and inhalation.

5.11.7. CLOSING REMARK

After finalising this re-evaluation of vinylchloride, reference IPCS (1999) became available through the Internet. However, since this review did not contain essential new information, it is not further referred to in the current MPR re-evaluation.

5.11.8. REFERENCES

ATSDR (1997):
Toxicological profile for vinyl chloride (update).
US Dept. of Health & Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta (GA), USA.

Bi W, Wang Y, Huang M et al. (1985):
Effect of vinyl chloride on testis in rats.
Ecotoxicol Environm Safety 10: 281-289 *(cited in ATSDR 1997 and EPA 1999).*

BUA (1989):
Vinyl chloride.
Beratergremium für Umweltrelevante Altstoffe der Gesellschaft Deutscher Chemiker, report no. 35.
VCH Publishers, Weinheim, Germany.

Clewell HJ, Gentry PR, Gearhart JM et al. (1995a):
The development and validation of a physiologically based pharmacokinetic model for vinyl chloride and its application in a carcinogenic risk assessment for vinyl chloride.
ICF Kaiser report prepared for EPA/OHEA and OSHA/DHSP *(cited in EPA 1999).*

Clewell HJ, Covington TR, Crump KS et al. (1995b):
The application of a physiologically based pharmacokinetic model for vinyl chloride in a non-cancer risk assessment.
ICF/Clement report prepared for EPA/NCEA under contract number 68-D2-0129 *(cited in EPA 1999).*

ECETOC (1988):
The mutagenicity and carcinogenicity of vinyl chloride, a historical review and assessment.
European Chemical Industry Ecology and Toxicology Centre, Technical report no. 31, Brussels, Belgium.

EPA (1999):
Integrated Risk Information System (IRIS): summary for vinyl chloride (draft), dated May 17, 1999.
US Environmental Protection Agency, Washington DC, USA.

Feron VJ, Hendriksen CFM, Speel AJ, Til HP & Spit BJ (1981):
Lifespan oral toxicity study of vinyl chloride in rats.
Food Cosmet Toxicol 19: 317-333.

IARC (1987):
Monographs on the evaluation of carcinogenic risks to humans.
Supplement 7: Overall evaluations of carcinogenicity - an updating of IARC monographs volumes 1 to 42 - vinyl chloride; pp 373-376.
International Agency for Research on Cancer, World Health Organization, Lyon, France.

IPCS (1999):
Environmental Health Criteria 215: Vinyl chloride (summary).
International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland *(Internet website IPCS, November 11, 1999).*

Janssen PJCM & Speijers GJA (1997):
Guidance on the derivation of maximum permissible risk levels for human intake of soil contaminants.
National Institute of Public Health and the Environment, RIVM report no. 711701006, January 1997; Bilthoven, The Netherlands.

Maltoni C, Lefemine G, Ciliberti A, Cotti G & Carretti D (1981):
Carcinogenicity bioassays of vinyl chloride monomer - a model of risk assessment on an experimental basis.
Environm Health Perspect 41: 3-29 *(cited in IARC 1987, WHO 1996, ATSDR 1997 and EPA 1999).*

Maltoni C, Lefemine G, Ciliberti A, Cotti G & Carretti D (1984):
Experimental research on vinyl chloride carcinogenesis.
In: Archives of Research on Industrial Carcinogenesis, Vol II (Maltoni C & Mehlman MA, eds), Princeton Scientific Publishers, Princeton (NJ), USA *(cited in ECETOC 1988, ATSDR 1997 and EPA 1999).*

Short RD, Minor JL, Winston JM & Lee C-C (1977):
A dominant lethal study in rats after repeated exposures to vinyl chloride or vinylidene chloride.
J Toxicol Environm Health 3: 965-968 *(cited in ATSDR 1997 and EPA 1999).*

Til HP, Immel HR & Feron VJ (1983):
Lifespan oral carcinogenicity study of vinyl chloride in rats.
Netherlands Organisation for Applied Scientific Research, CIVO-TNO report no V 93.285/291099, Zeist, The Netherlands *(cited in ECETOC 1988, WHO 1996, ATSDR 1997 and EPA 1999).*

Til HP, Feron VJ & Immel HP (1991):
Lifetime (149 week) oral carcinogenicity study of vinyl chloride in rats.
Food Chem Toxicol 29: 713-718

Torkelson TR, Oyen F & Rowe VK (1961):
The toxicity of vinyl chloride as determined by repeated exposure of laboratory animals.
Am Ind Hyg Ass J 22: 354-361 *(cited in BUA 1989).*

Ungvary G, Hudak A, Tatrai E, Lörincz M & Folly G (1978):
Effects of vinyl chloride exposure alone and in combination with trypan blue - applied systematically during all thirds of pregnancy on the fetuses of CFY rats.
Toxicol 11: 45-54 *(cited in ATSDR 1997 and BUA 1989).*

Vermeire TG, Apeldoorn ME van, Fouw JC de & Janssen PJCM (1991):
Voorstel voor de humaan-toxicologische onderbouwing van C-(toetsings)waarden.
National Institute of Public Health and the Environment, RIVM report no. 725201005, February 1991; Bilthoven, The Netherlands.

WHO (1996):
Guidelines for drinking-water quality, 2nd. ed., vol. 2: Health criteria and other supporting information - vinyl chloride; pp 424-431.
World Health Organization, Geneva, Switzerland.

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ADDENDUM

Carcinogenic risks (§ 3) were calculated according to the non-threshold linear extrapolation model as outlined by Janssen and Speijers (1997):

$$D = \frac{I_h}{I_{experiment}} \times \frac{t_{experiment}}{t_{life}} \times \frac{t_{exposure}}{t_{life}} \times d_{experiment}$$

D : dose for humans at accepted cancer risk
I_h : accepted human cancer risk (10^{-4} excess, lifetime)
$I_{experiment}$: tumour incidence at lowest tumorigenic dose in animal experiment
$t_{experiment}$: duration of animal experiment (days)
$t_{exposure}$: duration of exposure in animal experiment (days)
t_{life} : duration of lifetime of experimental animals (days; rat 1000, mouse 750)
$d_{experiment}$: lowest tumorigenic dose in animal experiment

Risk evaluation for inhalation carcinogenicity:

1. Studies with mice (Maltoni et al. 1981 and 1984)

$$D = \frac{10^{-4}}{(4/47 - 1/127)} \times \frac{81 \times 7}{750} \times \frac{30 \times 7\ (4/24 \times 5/7)}{750} \times 130\ (mg/m^3) = 3.8\ \mu g/m^3$$

2. Studies with rats (Maltoni et al. 1981 and 1984)

$$D = \frac{10^{-4}}{6/81} \times \frac{135 \times 7}{1000} \times \frac{52 \times 7\ (4/24 \times 5/7)}{1000} \times 65\ (mg/m^3) = 3.6\ \mu g/m^3$$

Risk evaluation for oral carcinogenicity:

1. Study with rats (Feron et al. 1981)

$$D = \frac{10^{-4}}{(32/116 - 2/112)} \times \frac{140 \times 7}{1000} \times \frac{140 \times 7}{1000} \times 1.7\ (mg/kg\ bw/day) = 0.63\ \mu g/kg\ bw/day$$

2. Study with rats (Til et al. 1991)

$$D = \frac{10^{-4}}{(22/98 - 1/197)} \times \frac{149 \times 7}{1000} \times \frac{149 \times 7}{1000} \times 1.3\ (mg/kg\ bw/day) = 0.64\ \mu g/kg\ bw/day$$

5.12. DIOXINS, FURANS AND DIOXIN-LIKE PCBs

5.12.1. INTRODUCTION

A human-toxicological MPR for dioxins was established in 1995 (Janssen et al. 1995). 'Dioxins' were defined as polychlorinated dibenzo-p-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs), being compound classes with comparable chemical structures and similar toxic effects. The most toxic and most studied of these compounds is 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD). The total toxicity of PCDD/PCDF-mixtures is expressed as equivalents of 2,3,7,8-TCDD. This approach involves multiplication of the concentrations of the individual congeners by a toxic equivalence factor (TEF), expressing the toxicity of the individual congener relative to the toxicity of 2,3,7,8-TCDD, yielding (i)TEQs (international toxic equivalents of 2,3,7,8,-TCCD) as the units in which PCDD/PCDF toxicity is expressed (Van den Berg et al. 1998).
Regarding carcinogenicity, the IARC evaluated 2,3,7,8-TCDD in 1987 and concluded that there was *sufficient evidence for carcinogenicity in animals* and *inadequate evidence for carcinogenicity in humans*, consequently the compound was classified in group 2B: *possibly carcinogenic to humans* (IARC 1987). On the basis of the results of genotoxicity studies 2,3,7,8-TCDD was considered non-genotoxic, and thus a threshold approach was deemed justified (Liem et al. 1993).
In the toxicological evaluation of PCDD/PCDF mixtures Janssen et al. (1995) followed earlier extensive evaluations (WHO 1991, Liem et al. 1993) in recommending a TDI of 10 pg TEQ/kg bw/day. The background exposure (children and adults) was estimated to be 6 pg TEQ/kg bw/day (95% percentile), mainly originating from food (Janssen et al. 1995).
In agreement with the 1995 report (Janssen et al. 1995), the oral and the dermal route are considered to be the relevant routes of exposure; the availability of TCDD from soil is estimated to be 2 % and 100 % for dermal and oral exposure, respectively.

5.12.2. TOXICOLOGY

Recently the health risks of dioxins were re-evaluated by consultation of an international panel of experts under the auspices of the WHO (1998).
Purpose of this consultation was to re-evaluate the TDI of dioxins on the basis of new toxicological, epidemiological and mechanistic data, in particular with respect to neurodevelopmental and endocrinological effects. The consultation reviewed working papers on the following subjects: health risks for infants, cancer and non-cancer endpoints in humans and animals, mechanistic aspects on pharmacokinetics and pharmacodynamics, dose-effect modelling, estimation of exposure, the applicability of the TEQ concept and risk assessment approaches for dioxins in various countries. The re-evaluation included PCDDs, PCDFs and dioxin-like (planar) PCBs (polychlorinated biphenyls).
With respect to the applicability of dose-response modelling and (advanced) pharmacokinetic-pharmacodynamic modelling it was noted that there are a number of uncertainties in the interpretation of the results of these models. Therefore, more traditional approaches using simple body burden calculations and empirical observations (LOAELs and NOAELs) have been used as the basis for the calculation of the TDI.

Toxicity

For the most toxic dioxin, i.e. 2,3,7,8-TCDD, body burdens (amount of TCDD per kg body weight) in experimental animals were calculated at the LOAEL for the following endpoints (WHO 1998): decreased sperm count in offspring (rat), immune suppression in offspring (rat), increased genital malformations in offspring (rat), neurobehavioural effects in offspring (monkey) and endometriosis (monkey). These endpoints represent the most sensitive adverse toxic effects of TCDD in animals. The matching calculated maternal body burdens ranged from 28 to 73 ng TCDD/kg bw. These body burdens were translated to humans with the aid of a one compartmental toxicokinetic model (assumptions: "steady state" kinetics of TCDD after chronic exposure in animals and man, absorption fraction of TCDD in humans: 0.5; half-life of TCDD in humans: 7.5 years). In this way the range of the daily human exposure which led to the same body burden of TCDD as observed in animals at the level of

the above mentioned LOAELs was calculated to be 14-37 pg TCDD/kg bw/day. The TDI for dioxins was obtained by correcting this range with an uncertainty factor (UF) of 10. This factor compensates for the use of animal body burdens associated with LOAELs instead of NOAELs, possible differences between humans and experimental animals in susceptibility to dioxins, potential differences in susceptibilities within the human population and differences in half-lives of elimination for the compounds of a complex mixture of dioxins, furans and dioxin-like PCBs. So, for chronic human exposure to mixtures of dioxins, furans and dioxin-like PCBs a TDI ranging from 1 to 4 pg TEQ/kg bw/day was calculated (WHO 1998).
Zeilmaker and Van Eijkeren (1998) used a physiologically based pharmacokinetic (PBPK) modelling approach to extrapolate TCDD toxicity from animals to man. Firstly, NOAELs of TCDD for hepatic and extrahepatic toxicity in the rat and embryotoxicity, endometriosis and disturbed cognitive development of offspring after *in utero* exposure in the monkey were selected. With the aid of a human PBPK model the chronic, daily, human intake which leads to these concentrations in humans was calculated. These intakes are expected to be without TCDD toxicity in humans. Calculated human intake levels were 34 pg TCDD/kg bw/day for hepatic toxicity, 2 pg TCDD/kg bw/day for extrahepatic toxicity (assumption: human organs ten times more sensitive for TCDD than rat organs), 8 pg TCDD/kg bw/day for embryotoxicity and less than 5 and 3 pg TCDD/kg bw/day for endometriosis and disturbed cognitive development of offspring after *in utero* exposure (assumption: human organs and monkey organs equally sensitive for TCDD), respectively.
Using a different approach the Health Council of the Netherlands evaluated PCDDs, PCDFs and dioxin-like PCBs. The Health Council recommended a public health-based exposure limit for humans of 1 pg TEQ/kg bw/day (Health Council of The Netherlands 1996).

Carcinogenicity

The carcinogenicity of PCDDs and PCDFs was recently evaluated by the International Agency for Research on Cancer (IARC 1997). This evaluation resulted in the following conclusions:
- 2,3,7,8-TCDD is carcinogenic to humans (classification: group 1).
- Other PCDDs are not classifiable as to their carcinogenicity to humans (classification: group 3).
- PCDFs are not classifiable as to their carcinogenicity to humans (classification: group 3).

The most extensive chronic cancer study in rat resulted in a NOAEL and LOAEL of 1 ng/kg bw/day and 10 ng/kg bw/day, respectively, with corresponding body burdens 60 and 294 ng TCDD/kg. Applying the same pharmacokinetic-pharmacodynamic modelling as above the calculated human daily intake values which lead to these body burdens were well above those which were calculated for non-cancer endpoints (WHO 1998).

Recommendations of the WHO

The WHO Consultation Group (WHO 1998) emphasised, that the TDI represents a tolerable daily intake for lifetime exposure and that occasional short-term excursions above the TDI would have no health consequences provided that the averaged intake over long periods is not exceeded. Furthermore, the consultation group recommended that every effort should be made to limit environmental releases of dioxin and related compounds to the extent feasible in order to reduce their presence in the food chain, thereby resulting in continued reductions in human body burdens. In addition, immediate efforts should be made to specifically target exposure reductions towards more highly exposed subpopulations (WHO 1998).

5.12.3. BACKGROUND EXPOSURE

An extensive and critical review of various recent Dutch food consumption survey studies resulted in a calculated average daily intake of the Dutch population for PCDDs, PCDFs and dioxin-like PCBs (95 percentile) of 3.6 pg TEQ/kg bw/day; the median intake was 1.2 pg TEQ/kg bw/day (Liem & Theelen 1997).

5.12.4. CONCLUSION

The WHO consultation (1998) established a TDI for PCDDs, PCDFs and dioxin-like PCBs, expresssed as a range, of 1-4 TEQ pg/kg bw. The consultation stressed that the upper range of the TDI of 4 pg TEQ/kg bw should be considered a maximum tolerable intake on a provisional basis and that the ultimate goal is to reduce human intake levels below 1 pg TEQ/kg bw per day. RIVM adopts this TDI as derived by the WHO.

Compound	TDI	Background exposure
PCDDs, PCDFs, coplanar PCBs [a])	1×10^{-6} - 4×10^{-6} [b])	1.2×10^{-6} [c])

TDI: tolerable daily intake (oral exposure); µg/kg bw/day
Background exposure; µg/kg bw/day

[a]) PCDDs: polychlorinated dibenzo-p-dioxins, PCDFs: polychlorinated dibenzofurans; PCBs: polychlorinated biphenyls; amounts expressed in TCDD equivalents (cf. § 1).

[b]) A range of 1-4 pg/kg bw/day, on a provisional basis (see text).

[c]) Median value 1.2 pg/kg bw/day; 95 percentile 3.6 pg/kg bw/day.

5.12.5. CLOSING REMARK

After finalising this re-evaluation of PCDDs, PCDFs and 'dioxin-like' PCBs, the full WHO evaluation of these compounds (reference Leeuwen van & Younes 2000) became available.

5.12.6. REFERENCES

Berg M van den, Birnbaum LS, Bosveld ATC, Brunström B, Cook Ph, Feeley M, Giesy JP, Hanberg A, Hasegawa R, Kennedy SW, Kubiak T, Larsen JC, Leeuwen FXR van, Liem AKD, Nolt C, Peterson RE, Poellinger L, Safe S, Schrenk D, Tillitt D, Tysklind M, Younes M, Wærn F & Zacharewski T (1998):
Toxic Equivalency Factors (TEFs) for PCBs, PCDDs, PCDFs for humans and wildlife.
Env. Health Persp. 106, 775-792.

Health Council of The Netherlands (1996):
Dioxins: polychlorinated dibenzo-p-dioxins, dibenzofurans and dioxin-like polychlorinated biphenyls.
Health Council of The Netherlands (Gezondheidsraad), Report nr. 1996/10E, August 1996; Rijswijk, The Netherlands.

IARC (1987):
IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Supplement 7 - Overall Evaluations of Carcinogenicity: an Updating of IARC Monographs Volumes 1 to 42.
International Agency for Research on Cancer, Lyon, France.

IARC (1997):
IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 69: Polychlorinated Dibenzo-p-dioxins and Polychlorinated Dibenzofurans.
International Agency for Research on Cancer, Lyon, France.

Leeuwen, FXR van & Younes MM (eds) (2000):
Assessment of the health risk of dioxins - re-evaluation of the tolerable daily intake.
Food Add Contam 17, 223-369.

Liem AKD, Berg R vd, Bremmer HJ, Hesse JM & Slooff W (1993):
Integated Criteria Document Dioxins.
National Institute of Public Health and the Environment, RIVM report no. 710401032, December 1993; Bilthoven, The Netherlands.

Liem AKD & Theelen RMC (1997):
Dioxins - Chemical Analysis, Exposure and Risk Assessment.
Thesis, October 1997, University of Utrecht, The Netherlands.

Janssen PJCM, Apeldoorn ME van, Koten-Vermeulen JEM van & Mennes WC (1995):
Human-toxicological criteria for serious soil contamination: compounds evaluated in 1993 and 1994.
National Institute of Public Health and the Environment, RIVM report no. 715810009, August 1995; Bilthoven, The Netherlands.

WHO/EURO (1991):
Summary Report: Consultation on Tolerable Daily Intake from Food of PCDDs and PCDFs, Bilthoven (The Netherlands), December 4-7, 1990.
World Health Organization, Copenhagen, Denmark.

WHO (1998):
Draft Executive Summary, Assessment of the Health Risk of Dioxins: Re-evaluation of the Tolerable Daily Intake (TDI), WHO Consultation, May 25-29, 1998; Version of August 20, 1998.
World Health Organization, Geneva, Switzerland.

Zeilmaker MJ & Eijkeren JCH van (1998):
The calculation of human toxicity thresholds of 2,3,7,8-TCDD: a physiologically based pharmacokinetic modelling approach.
National Institute of Public Health and the Environment, RIVM report no. 601503010, May 1998; Bilthoven, The Netherlands.

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5.13. POLYCHLORINATED BIPHENYLS (PCBs) NON "DIOXIN-LIKE" PCBs

5.13.1. INTRODUCTION

PCBs were evaluated within the scope of this project by Vermeire et al in 1991. They derived a TDI of 0.09 µg/kg bw/day for oral intake of a PCB mixture. The value was derived from a LOAEL of 0.09 mg/kg bw/day for dermal and immunological effects in Rhesus monkeys after oral exposure to a technical PCB mixture of Aroclor 1248. An uncertainty factor (UF) of 1000 was applied; the composition of this UF was not described. A TCA was not derived.
For the update of the MPR of PCBs additional literature was evaluated. This included an update of IARC (1987), a Nordic review (Ahlborg et al. 1992), a report of the CCRX (1993), a review of IPCS (1993), and a (draft) update by ATSDR (1998).
The term "PCB" is used as an acronym for a mixture of congeners of polychlorinated biphenyls. The compounds in the mixture share two phenyl molecules in the chemical structure but they differ mutually in the pattern of chlorine substitution. The IUPAC numbers are used to identify the different congeners. Theoretically a total of 209 congeners exist. The various (commercial) technical mixtures of PCBs differ in their chlorine content. In the legal framework of the Dutch Intervention values the PCBs are to be assessed by the sum of 7 (indicator) PCB congeners. The IUPAC numbers of these indicator PCBs are PCB #28, 52, 101, 118, 138, 153, and 180.
PCBs are man-made chemicals. They are mainly produced as mixtures; individual congeners are hardly synthesised. The natural concentration of PCBs in soil will be negligible.
PCB mixtures were used in the past in a wide scale of applications, such as coatings, inks, flame retardants, paints, in duplicating paper, and in immersion oil in microscopy. Its major use, however, was in electronic appliances, heat transfer systems, and hydraulic fluids. For the different applications many different technical mixtures were being used.
Due to the persistent nature of PCBs in the environment it was decided by many states some decades ago to ban the use of PCBs in open applications. PCBs may, however, be still in use in closed systems such as capacitors and transformers. The use in these applications will decrease in time.
Waste disposal, both of households and industrial waste, is the major source of PCBs emissions into the environment. Due to the historical use of PCB, residues of technical mixtures are found on a global scale. As most PCBs congeners are very lipophilic and persistent, PCBs tend to accumulate in soils. The quantities of PCB congeners in water will be rather limited. Due to the low vapour pressure of PCBs, concentrations in air will also be rather small. As the various congeners differ in their physiochemical properties, they demonstrate different behaviour in the environment. Some congeners are easily being degraded by light, and others by microbial processes. Other congeners are very persistent. Consequently, the composition of the mixtures of PCBs that can be found in soil may substantially deviate from the technical mixtures. The most persistent congeners will be found in excess. It can therefore be expected that exposure of humans might occur to the most persistent congeners in soil.
Dioxin-like and non dioxin-like PCBs
From toxicology studies with individual PCB congeners it is known that some PCBs demonstrate a different toxicity profile than others. They show different target organs and metabolic behaviour.
A series of PCB congeners show "dioxin-like" toxicity. These PCBs bind to a cytosolic receptor, the *Ah* receptor that is known to bind chlorinated dibenzo-dioxins and –furans, starting a series of sequences that are responsible for the various adverse effects. The dioxin-like PCBs share a coplanar molecular configuration that is isostereomeric to 2,3,7,8-tetrachlorodibenzodioxin (TCDD). These PCBs are assigned with a Toxic Equivalency Factor (TEF) that relates their toxicity to that of TCDD, and are to be evaluated as dioxins. For the evaluation of the dioxin-like PCBs it is therefore referred to the evaluation of dioxins, furans and dioxin-like PCBs.

5.13.2. TOXICOLOGY

Toxicokinetics

Absorption
Data of oral intake of PCB mixtures in humans demonstrate a high degree of absorption. In young children absorption from mother's milk appears to be almost complete for tetra- and higher chlorinated congeners. In experimental animals such as monkeys absorption is also very high, with minor differences between congeners depending on the chlorine substitution pattern.
Data on the absorption of PCBs after inhalation in humans and laboratory animals are not reported. It is, however, stated in ATSDR (1998) that inhalation is a significant pathway for occupational exposure, leading to increased concentrations in adipose tissue. It can therefore be expected that absorption after inhalation will also be substantial.
Dermal absorption is demonstrated in laboratory animals. For Aroclor mixtures a percutaneous absorption in the order of 20% is reported.
Distribution
PCBs will be found in adipose tissue. High concentrations can be expected in fatty tissue in humans and in human milk. In the organs of humans concentrations are lower than in the adipose tissue. In experimental animals the liver is the target organ for PCBs.
It must be noted that the congener patterns in adipose fat, human milk, and liver are not identical to the pattern of congeners in food and other environmental samples. From this it is concluded that there is a selective retention of the different congeners, which might be due to differences in kinetics, including metabolism.
Metabolism
PCB congeners are metabolised in the liver into hydroxylated PCBs. Hydroxylation is favoured for chlorine at the para position. Two vicinal unsubstituted carbon atoms facilitate the metabolism. Sterical hindrance by a 3,5-dichloro-substitution, however, blocks metabolism. It can therefore be expected that the rate of metabolism is very different for the various congeners, and that some congeners are very hard to metabolise.
The metabolism of PCBs is induced by two enzyme systems One system is referred to as the 3-methylcholanthrene inducible enzymes, also known as cytochrome P448, or cytochrome P450 1A1 and 1A2. These are induced by the dioxin-like PCBs. The other system is known as phenobarbital (PB) inducible enzymes, or cytochrome P450 IIB1 and IIB2. This enzyme system is induced by the non dioxin-like PCBs.
Excretion
Excretion of both parent PCBs and the hydroxylated metabolites is mainly through the faeces. In urine only a small percentage of the metabolised congeners can be found. In humans who are accidentally exposed to PCB mixtures it has been observed that tetra- and some pentachlorinated PCBs were rapidly excreted whereas other pentachlorinated and the higher chlorine substituted congeners were slowly eliminated. For the latter PCBs half-lives in humans are reported to be in the order of months.
A specific way of excretion of PCBs is via milk. Both animals and humans show high concentrations of persistent PCB congeners in milk. A substantial secretion of PCBs will thus occur in dairy cattle and from breast-feeding of humans.
Biomarkers
Blood and adipose are suitable biomarkers for PCB exposure. It is preferred to evaluate the content on a lipid base. Using kinetic data of the various congeners in a one-compartment pharmacokinetic model provides the possibility to estimate previous exposure. The kinetic modelling is, however, only to be used if such an exposure was significantly greater than the background exposure at present.

Toxicity

Acute poisoning

Studies regarding lethality of PCB mixtures after inhalation, oral intake or dermal exposure of humans are not available. Vapours of Aroclor 1242 were not lethal in laboratory animals, but a broad range of lethal oral and dermal doses has been reported. The lethal doses depend of the type of PCB mixture and the animal species. In these studies the cause of death was unclear; there are no distinct pathological findings. A typical mark of a high dose exposure, however, is the "wasting syndrome", in which the animals loose body weight without a decreased food and water consumption (ATSDR 1998).

There are data about acute poisonings of humans from oral intake of PCB mixtures. In Japan and Taiwan a large number of humans were accidentally poisoned by the ingestion of consumption (rice) oil that was contaminated with a technical PCB mixture. It should be noted that the oil did not contain PCB congeners only; it is known that small quantities of compounds such as chlorinated dibenzofurans were present in the PCB mixtures. One can thus not relate all toxic effects to the PCB congeners only. The most prominent effect was chloracne: a dermal disorder with swelling of the eyelids, pigmentation of nails, and hyperkeratosis of the skin. The poisonings have also affected children born from exposed mothers. These babies had a dark brown skin and a decreased birth weight. In addition, neurological development was reported to be affected in children of mothers who were exposed to PCBs via fish consumption (IPCS 1993).

Chloracne is also reported in occupational exposed humans like electrical industry workers. This could be caused both by exposure from inhalation and dermal exposure. Other health effects are not consistent, in some cases changes in serum enzyme levels or liver abnormalities are reported, but confounding factors can not be excluded.

Genotoxicity and carcinogenicity

PCBs have little or no genotoxic potential. Some lower chlorinated PCB congeners interact with RNA and DNA after metabolic activation, but technical mixtures were negative in mutagenicity tests. Specific studies with several Aroclors, however, provided evidence that PCBs can enhance cell proliferation and promote carcinogenesis (Ahlborg et al. 1992, IPCS 1993).

There are a number of epidemiological studies investigating the relation between cancer and PCB exposure, both for occupational and accidental exposed humans. The overall conclusion of these studies suggests an association between cancer and exposure to PCB in humans. An increased risk in hepatobiliary cancer was consistently observed. However, the role of compounds other than PCBs can not be excluded, and thus the evidence must be considered to be limited.

In studies with laboratory animals, hepatocellular adenomas and carcinomas were found after oral exposure to technical PCB mixtures that contained a high degree of chlorination (60%). After an assessment of all available carcinogenicity data it was concluded that mixtures with less chlorine, such as Aroclor 1254 and 1242, do not demonstrate a carcinogenic potency (ATSDR 1998). If animals were treated with cancer initiators such as N-nitrosodiethylamine or 2-acetylaminofluorene, liver tumours were also found after dietary treatment with Aroclor 1254. Consequently these PCB mixtures appear to act as tumour promoters. According to IARC (1987) the PCBs are classified in group 2A: *probably carcinogenic to humans*, on the basis of *limited evidence for carcinogenicity to humans*, and *sufficient evidence for carcinogenicity to animals*.

Subchronic and chronic toxicity

Oral exposure

Hepatic effects are most prominent after subchronic and chronic oral exposure of laboratory animals like rats and monkeys to PCB mixtures. The effects include enzyme induction in the liver and in serum, liver enlargement, and alterations in lipid and vitamin A concentrations. Effects on serum enzymes were also found in some studies of humans who were exposed to PCBs. In experimental animals endocrine effects of thyroid and serum thyroxin levels were seen following PCB exposure. Immunotoxic effects are known to result from PCB exposure of rats and monkeys (such as reduced serum levels of immunoglobulins and decreased resistance to bacterial infection). Dermal effects resembling chloracne were reported in rhesus monkeys fed Aroclors. Studies with PCB congeners have demonstrated that some PCBs have effects on de developing nervous system and affect neurotransmitters (dopamine). Exposure of children *in utero* to PCBs is reported to lead to lower IQ scores. Neurobehavioural effects are also reported for experimental animals after exposure to PCB mixtures. Fi-

nally the reproduction of rats was reduced, and endocrine effects could be noticed in the offspring after maternal exposure to Arclor1254. In rats and guinea pigs dermal effects were not noticed.
For Aroclor 1016 a NOAEL of 0.007 mg/kg bw/day has been reported, with reduction in birth weight in monkeys after 22 months exposure as the critical effect.
In chronic oral studies with Aroclor 1242 and 1260 in rats LOAELs of 2 and 1 mg/kg bw/day, respectively, were found for mild hepatocellular hypertrophy and hepatic foci, and an increased incidence of follicular cell adenomas.
A LOAEL of 0.08 mg/kg bw/day was reported for lower birth weight and developmental effects after 18 months exposure of rhesus monkeys to Aroclor 1248. The NOAEL for these effects was 0.03 mg/kg bw/day.
For Aroclor 1254 in rhesus monkeys orally exposed for 72 months a LOAEL of 0.04 mg/kg bw/day was reported for dermal effects on nails and nailbeds. The NOAEL was 0.02 mg/kg bw/day. In offspring dermal effects were reported at 0.005 mg/kg bw/day. The dose of 0.005 mg/kg bw/day of Aroclor 1254 was reported as a LOAEL for decreased antibody response in rhesus monkeys after 23 months.
Inhalation exposure
There are very limited data on the inhalation of PCB congeners or technical mixtures. After semichronic and chronic inhalation exposure of rats and rabbits to Aroclor 1254 hepatic effects and reduced body weight were reported. The lowest marginal effect concentration for these effects was 1.5 mg/m^3 (ATSDR 1998).
Toxic mechanism of action
The non dioxin-like PCB congeners demonstrate interaction with neurotransmitters, estrogenic effects, and effects on the thyroid. They show cytochrome P450 IIB enzyme induction. The metabolic steps and the biochemical changes causing the interaction with the neurotransmitters and thyroxin are known in some detail, but it is not know how the PCB congeners start these effects. Consequently the toxic mechanism of action of the non dioxin-like PCB congeners is quite indefinite and needs to be elucidated.

5.13.3. EVALUATION

The effects of mixtures of non dioxin-like PCBs are to be evaluated preferably on the basis of the toxicological data of the technical mixtures. The technical mixtures of PCB do not show genotoxic properties. It has been demonstrated that the carcinogenic action of PCBs is based on promoting activities of PCB congeners. The adverse health effects of technical mixtures with non dioxin like-PCBs can thus be evaluated on the basis of NOAELs and uncertainty factors (UFs).
Aroclor 1016
In a subchronic study with Aroclor 1016 in monkeys a NOAEL of 7 µg/kg bw/day was reported for birth weight of offspring. A UF of 3 is considered sufficient for the extrapolation to chronic exposure as the effect relates to the offspring. With furhter UFs of 3 for extrapolation from monkeys to humans, and 10 for human variability, a TDI of 0.07 µg/kg bw/day for Aroclor 1016 is derived.
Aroclor 1248
For Aroclor 1248 there are no new relevant data since 1990, and thus the TDI of 0.09 µg/kg bw/day as derived by Vermeire et al (1991) is to be maintained.
Aroclor 1254
A LOAEL of 5 µg/kg bw/day for Aroclor 1254 has been reported for less serious immunological effects in monkeys (exposure during 23 months). A UF of 3 is applied to extrapolate to the NOAEL. As it was a semichronic study, an additional UF is needed for extrapolation to chronic exposure. After an exposure period of 23 months a steady state condition of uptake and elimination can be assumed, and thus a UF of 3 is considered sufficient for extrapolation to chronic exposure. A further factor of 3 is applied for the extrapolation of monkeys to humans, and a factor of 10 for human variability. This results in a TDI of 0.02 µg/kg bw/day for Aroclor1254.
The information about the exposure risk after inhalation is very limited. For chronic exposure of various experimental animals to Aroclor 1254 a LOAEC of 1.5 mg/m^3 was found for marginal effects (exposure 5 days per week, 7 hours per day). Adjusted for continuous exposure this equals to 0.3 mg/m^3.

A UF of 3 is used for extrapolation of the marginal effects to a NOAEC, and an additional UF of 100 is used for intra- and interspecies variation. This results in a TCA of 1 μg/m^3 for Aroclor 1254.

Environmental PCB mixtures

At present mixtures of PCBs are to be assessed on the basis of a chemical analysis of the seven indicator PCBs. These indicators are known to persist. From available data of congener-specific analysis of various technical mixtures it can be learned that the seven indicator PCBs are present in Aroclors 1016, 1242, and 1248 for about 20 to 30 % of the total concentration, and 40 to 50% for Aroclors 1254 and 1260. The historical contaminations with PCB mixtures in soil are hence better to be assessed as Aroclor 1254 than as mixtures with lower chlorine content (such as Aroclor 1016 or Aroclor 1248).

In conclusion, the TDI of Aroclor 1254 of 0.02 μg/kg bw/day is to be used for oral exposure of humans to mixtures of PCBs in soil. However, since the seven indicator PCBs contribute for 40 to 50% in Aroclor 1254, the TDI for the sum of the seven indicator PCBs in the total mixture must be set at 0.01 μg/kg bw/day (i.e., 50% of the TDI of Aroclor 1254).

Regarding inhalation exposure, a TCA of 1 μg/m^3 was derived for Aroclor 1254. Again based on the argument that the seven indicator PCBs contribute for 40 to 50% to Aroclor 1254, the TCA for the indicator PCBs is set at 0.5 μg/m^3 (i.e., 50% of the TCA or Aroclor 1254).

5.13.4. EVALUATION OF OTHER ORGANISATIONS

Aroclor 1016

US-EPA derived a RfD of 0.07 μg/kg bw/day for Aroclor 1016, is based on a NOAEL of 7 μg/kg bw/day for reproductive effects in monkeys with a UF of 100 (UFs of 3 were used each for inter- and intraspecies variation, a further factor of 3 for the extrapolation of a subchronic study, while a factor of 3 was applied for limitations in the database) (IRIS, revised 1996).

Aroclor 1248

US-EPA did not derive a RfD for Aroclor 1248; it was concluded that the database is inadequate for the derivation of an oral RfD (IRIS, revised 1996).

Aroclor 1254

US-EPA derived a RfD of 0.02 μg/kg bw/day for Aroclor 1254, based on a LOAEL of 5 μg/kg bw/day for dermal and immunological effects in monkeys, with a UF of 300. The UF is 10 for intraspecies variation and 3 for the extrapolation from rhesus moneys to humans. In addition a factor of 10 was used for the extrapolation of the LOAEL and the subchronic exposure time (IRIS, revised 1996).

ATDSR presented a MRL of 0.02 μg/kg bw/day for chronic oral exposure of PCBs, expressed as Aroclor 1254. This value is based on a LOAEL of 5 μg/kg bw/day in monkeys for decreased antibody response. A UF of 10 was used for extrapolation of the LOAEL to the NOAEL, a UF of 3 for interspecies extrapolation, and a UF of 10 for human variability (ATDSR 1998).

PCB mixtures

IARC (1987) classified PCB mixtures in group 2A: *probably carcinogenic to humans*. There is *limited evidence of carcinogenicity in humans* and *sufficient evidence of carcinogenicity in experimental animals*.

US-EPA presented cancer slope factors for PCB mixtures of 0.07, 0.4 and 2 (mg/kg bw/day)$^{-1}$ (cited in ATSDR 1998). According to ATSDR (1998) the different values apply to the various environmental samples. For food chain exposure, sediment and soil ingestion, and inhalation of dust, the value of 2 per mg/kg bw/day should be used. The value of 0.4 applies to drinking water and vapour inhalation. The lowest value of 0.07 was derived for PCB mixtures with a low percentage of dioxin-like, tumour promoting and persistent congeners.

The WHO did not propose a Drinking Water Quality Guideline for PCBs (WHO 1996).

Hassauer et al. (1993) advised the UBA (Germany) an oral "Orientierungswert" of 0.1 μg/kg bw/day for long term exposure of PCBs, based on a NOAEL of 0.01 mg/kg bw/day for foetotoxic effects in monkeys, with a UF of 100 and 100% absorption. In their proposal an inhalation "Orientierungswert" of 0.7 μg/m^3 was included for chronic inhalation on the basis of a LOAEC of 1.5 mg/m^3 for hepatotoxic effects in rats, with a UF of 1000 and 100% absorption.

5.13.5. BACKGROUND EXPOSURE

The present exposure of the general population to PCBs is mainly via the food. Animal fats such as meats and fish are of major importance the contribution from inhalation and other sources is negligible. Estimates of dietary intake range in the order of 1 to 15 µg/day, depending on the consumption pattern. The highest intake is to be expected for humans with a substantial consumption of fish (Ahlborg et al. 1992, IPCS 1993). Liem and Theelen (1997) presented a study of the PCBs in a series of duplicate diets of 1974, 1985, and 1994 in The Netherlands. The results showed a substantial decrease of the exposure to PCBs in that time period. The dietary intake of a series of 29 different PCB congeners in 1994 in The Netherlands was 0.02 µg/kg bw/day; the intake of the seven indicator PCBs was 0.01 µg/kg bw/day.

5.13.6. CONCLUSION

The non dioxin-like PCBs are to be evaluated on the basis of the seven indicator PCBs # 28, 52, 101, 118, 138, 153, and 180.

Compound	TDI	TCA	Background exposure
Polychlorinated biphenyls (sum of indicator congeners #28, 52, 101, 118, 138, 153 and 180) *)	0.01	0.5	0.01

TDI: tolerable daily intake (oral exposure); µg/kg bw/day
TCA: tolerable concentration in air (inhalation exposure); µg/m^3
Background exposure; µg/kg bw/day
*) these indicator PCBs represent the non-coplanar (non "dioxin-like") PCBs (cf. paragraph 5.13.3)

5.13.7. REFERENCES

Ahlborg UG, Hanberg A & Kenne K (1992):
Risk assessment of PCBs.
Karolinska Institute, Report Nord 1992:26; Stockholm, Sweden.

ATSDR (1998):
Toxicological Profile for Polychlorinated Biphenyls (Update).
Agency for Toxic Substances and Disease Registry, US Public Health Service, Atlanta (GA), USA.

Hassauer, M., Kalberlah, F., Oltmans, J. and Schneider, K. (1993) Basisdate Toxikologie für umweltrelevante Stoffe zur Gefahrenbeurteilung bei Altlasten.
Umwelt Bundes Amt, Berichte 4/93, Erich Schmidt Verlag, Berlin, Germany.

IARC (1987):
Overall evaluations of carcinogenicity - An updating of IARC monographs volumes 1 to 42; IARC Monographs, Supplement 7.
International Agency for Research on Cancer, Lyon, France.

IPCS (1993):
Environmental Health Criteria 140 - Polychlorinated Biphenyls and Terphenyls (2nd Edition).
World Health Organization, Geneva, Switzerland.

Liem AKD & Theelen RMC (1997):
Dioxins - chemical analysis, exposure and risk assessment.
PhD Thesis, Utrecht, The Netherlands.

Vermeire TG, Apeldoorn ME van, Fouw JC de & Janssen PJCM (1991):
Voorstel voor de humaan-toxicologische onderbouwing van C-toetsingswaarden.
National Institute of Public Health and the Environment, RIVM-report no. 725201005, February 1991; Bilthoven, The Netherlands.

WHO (1996):
Guidelines for drinking-water quality, 2nd ed. Volume 2, Health criteria and other supporting information.
World Health organization, Geneva, Switzerland.

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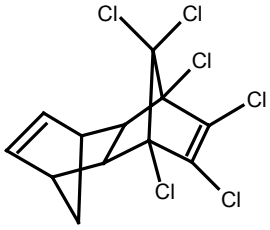
Final review: *A.G.A.C. Knaap (chair), G.J.A. Speijers, T.G. Vermeire*
Date: *05-07-2000*

Appendix 6 Pesticides

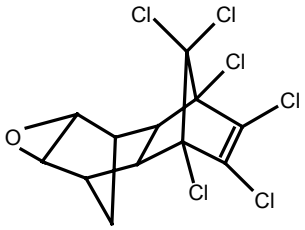
6.1. ALDRIN, DIELDRIN AND ENDRIN

6.1.1. INTRODUCTION

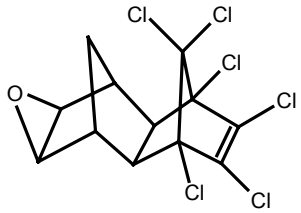
The MPRs (maximum permissible risk) for aldrin, dieldrin and endrin (the so-called drins) were evaluated in 1991 (Vermeire et al. 1991).
Regarding aldrin and dieldrin this evaluation considered chronic feeding studies with aldrin and dieldrin in dogs (Fitzhugh et al. 1964) and rats (Fitzhugh and Nelson 1963, Fitzhugh et al. 1964) as the pivotal ones. With aldrin these studies resulted in LOAELs of 25 µg/kg bw/day for 'questionable' (dogs) and 'minimal' (rats) 'effects in the liver'; with dieldrin the studies resulted in LOAELs of 25 µg/kg bw/day for 'liver changes' in dogs and 'minimal liver changes' in rats (quotes from JMPR 1967). From these LOAELs a TDI (tolerable daily intake) of 0.1 µg/kg bw/day for aldrin and dieldrin separately as well as for the sum of both compounds was derived (Vermeire et al. 1991), according to the acceptable daily intake (ADI) as developed by the JMPR (1967, 1970, 1977). Obviously a UF (uncertainty factor) of 250 was applied.
Regarding endrin, the evaluation of 1991 (Vermeire et al. 1991) concluded to a TDI of 0.2 µg/kg bw/day based on a chronic feeding study with rats (Treon et al. 1955) and a similar study with dogs (Jolley et al. 1969), which resulted in NOAELs for liver weight changes (dogs) and liver and kidney weight changes (rats) of 50 and 25 µg/kg bw/day, respectively, according to the ADI as developed by the JMPR (1970). Obviously UFs of 250 and 125, respectively, were applied.
Data for isodrin and telodrin allowing the estimation of a TDI were lacking.
Although Vermeire et al. (1991) considered inhalation exposure to drins at soil-contaminated sites conceivable, they were unable to derive a tolerable concentration in air (TCA) due to lack of data.
Background exposure was estimated to be 0.043 µg/kg bw/day for aldrin, dieldrin and endrin together (Vermeire et al. 1991).
Aldrin [82]), dieldrin [83]) and endrin [84]) belong to a group of chemically closely related persistent chlorinated pesticides (insecticides) which accumulate in food chains. Dieldrin is the epoxide of aldrin, formed in animals by biotransformation, and in the environment by chemical oxidation. Endrin is a stereoisomer of dieldrin. Drins were first synthesised in 1948; in the USA and in Western Europe the use of these pesticides was terminated some twenty years ago.



aldrin



dieldrin



endrin

[82]) 1,2,3,4,10,10-hexachloro-1,4,4α,5,8,8α-hexahydro-endo,exo-1,4:5,8-dimethanonaphtalene (CAS no. 309-00-2)
[83]) 1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4α,5,6,7,8,8α-octahydro-endo,exo-1,4:5,8-dimethanonaphtalene (CAS no. 60-57-1)
[84]) 1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4α,5,6,7,8,8α-octahydro-endo,endo-1,4:5,8-dimethanonaphtalene (CAS no. 72-20-8)

6.1.2. TOXICOLOGY

The drins are well absorbed, both after oral and inhalation exposure. Also percutaneous absorption occurs. Following absorption, aldrin is rapidly metabolised to dieldrin. Dieldrin in turn is further metabolised to polar metabolites via oxidation, hydroxylation, and conjugation; excretion is primarily in the faeces. Also endrin is metabolised via oxidation, hydroxylation, and conjugation, the metabolites are excreted in the faeces as well as in the urine (metabolite-dependent).
The toxicology of aldrin, dieldrin and endrin is quite comparable: all drins are neurotoxic and are potent inducers of microsomal liver enzymes. Chronic exposure to these compounds, both in humans and in experimental animals, results in stimulation of the central nervous system, probably by interaction with the neurotransmitter GABA (γ-aminobutyric acid). In addition, immunosuppression and adverse reproductive effects are seen. Regarding genotoxicity, most of the available evidence indicate that aldrin and dieldrin do not directly interact with DNA.
A 20-year follow-up study of a cohort of 570 workers who were involved in the manufacture of aldrin, dieldrin, endrin and telodrin in The Netherlands for at least one year indicated neurological disorders but no adverse hepatic effects. In general the neurological problems were reversible after removal of the source of exposure, but some mental problems remained (De Jong 1991). The value of this study, however, is limited because of the rather small number of subjects, uncertainty regarding exposure levels, and the potential exposure to to more than one of the drins and/or to other chemicals at the chemical manufacturing complex.
Results of carcinogenicity studies with aldrin and dieldrin do not permit an unambiguous conclusion. Epidemiological studies have been inadequate, but some studies in mice demonstrated the ability of aldrin and dieldrin to cause hepatocellular carcinomas, while several other studies in rats reported negative findings. Endrin did not cause cancer in animal studies, and there is no evidence that it can cause cancer in exposed humans. US-EPA classified aldrin and dieldrin in category B2: *probable human carcinogens*, and endrin in category D: *not classifiable as to its carcinogenicity to humans* (ATSDR 1992, 1996). IARC classified all three compounds in category 3: *unclassifiable as to carcinogenicity to humans* (IARC 1987).
In view of the lack of evidence for genotoxicity of the drins, their toxicity can be evaluated applying the threshold approach (ATSDR 1992, 1996; IARC 1987; IPCS 1992; IRIS 2000; JMPR 1967, 1970, 1977).

6.1.3. EVALUATION

There are no new studies that would warrant renewed MPR derivations, and considering that the ADIs as established by the JMPR in 1970 and 1977 (which served as the basis for the earlier MPR-evaluation by Vermeire et al., 1991, are as yet not re-evaluated, the previous MPRs are to be maintained. Remark: regarding the TDI for aldrin the use of a relatively small UF of 2.5 to compensate for the use of a LOAEL instead of a NOAEL is still considered acceptable in view of the rather marginal effects observed at this LOAEL.
According to Vermeire et al. (1991) inhalation exposure to drins at soil-contaminated sites is conceivable. Experimental data on toxic effects following inhalation exposure to aldrin, dieldrin and/or endrin, however, are not available, and hence this risk can only be estimated by route-to-route exposure. The available data on toxicokinetics of the three compounds indicate that they are well absorbed following both oral and inhalation exposure. Thus, the TDIs derived allow estimation of provisional TCAs (pTCAs) applying an adult breathing volume of 20 m^3/day and an adult body weight of 70 kg [pTCA = TDI×70÷20].
In the current re-evaluation isodrin and telodrin are left out of consideration due to lack of data.

Results:

Aldrin and dieldrin (sum of both compounds):	TDI	0.1 µg/kg bw/day	pTCA	0.35 µg/m^3
Endrin:	TDI	0.2 µg/kg bw/day	pTCA	0.70 µg/m^3

The TCAs are provisional because they are derived via route-to-route extrapolation.

6.1.4. EVALUATION BY OTHER ORGANISATIONS

US-EPA evaluated aldrin in 1988 and concluded to an oral reference dose (RfD ≈ TDI) of 0.03 µg/kg bw/day based on the LOAEL for liver toxicity of 25 µg/kg bw/day in the rat chronic feeding study of Fitzhugh et al. (1964), applying a UF of 1000 (including an additional factor of 10 for using a LOAEL) (IRIS 2000).
US-EPA evaluated dieldrin in 1990 and concluded to an oral RfD of 0.05 µg/kg bw/day based on the NOAEL for liver lesions of 5 µg/kg bw/day in the rat chronic feeding study of Walker et al. (1969), applying a UF of 100 (IRIS 2000).
US-EPA evaluated endrin in 1991 and concluded to an oral RfD of 0.3 µg/kg bw/day based on the NOAEL for mild histological liver lesions and occasional convulsions of 25 µg/kg bw/day in the dog chronic oral bioassay of the Velsicol Chemical Corporation (1969) [85]), applying a UF of 100 (IRIS 2000).
ATSDR evaluated aldrin and dieldrin in 1992 and concluded to a chronic-duration oral minimal risk level (MRL ≈ TDI) for aldrin of 0.03 µg/kg bw/day (UF = 1000), completely according to US-EPA, and a chronic-duration oral MRL for dieldrin of 0.05 µg/kg bw/day based on the NOAEL for increased serum alkaline phosphatase levels and decreased serum proteins of 5 µg/kg bw/day in the dog chronic feeding study of Walker et al. (1969), applying a UF of 100 (ATSDR 1992).
ATSDR evaluated endrin in 1996 and concluded to a chronic-duration oral MRL of 0.3 µg/kg bw/day, completely according to US-EPA (UF = 100) (ATSDR 1996).
US-EPA (IRIS 2000) and ATSDR (1992, 1996) concluded to insufficient data to allow the estimation of a tolerable concentration in air.
Regarding aldrin, Hassauer et al. (1993) advised the Bundes Umwelt Amt (Germany) to a "Orienterungswert" for long-term oral exposure of 0.025 µg/kg bw/day (based on the LOAEL of 25 µg/kg bw/day for hepatotoxicity in the chronic rat study of Fitzhugh et al. [1964] applying a UF of 1000), and a "Orienterungswert" for long-term inhalation exposure of 0.7 µg/m^3 (based on the NOAEL of 3 µg/kg bw/day for systemic toxicity and enzyme effects in the human study of De Jong [1991], applying route-to-route extrapolation assuming 100 % oral and 50 % inhalation absorption, and a UF of 30). They did not derive limit values for dieldrin or endrin.
The evaluations of the JMPR are summarised in paragraph 6.1.1 because these served as the basis for the previous MPR estimations. It must be noted, however, that JMPR (1970) did evaluate the rat chronic feeding study with dieldrin of Walker et al. (1969) which was the basis for the limit value estimations of ATSDR and US-EPA (see above), but JMPR did not feel the need for a renewal of its ADI for dieldrin on the basis of this study.

Tolerable daily intakes for prolonged exposure to aldrin, dieldrin and endrin as estimated by ATSDR (1992, 1996), US-EPA (1988, 1990, 1991), BUA (1993) and JMPR (1967, 1970, 1977)

Substance	ATSDR and US-EPA			BUA						JMPR		
	Oral	UF	Ref	Oral	UF	Ref	Inhal	UF	Ref	Oral	UF	Ref
Aldrin	0.03	1000	1	0.025	1000	1	0.7	30	2	0.1	250	1
Dieldrin	0.05	100	3	-	-	-	-	-	-	0.1	250	1
Endrin	0.3	100	4	-	-	-	-	-	-	0.2	125/250	4/5

Oral values are expressed in µg/kg bw/day, the inhalation value is expressed in µg/m^3

References:
1. Fitzhugh et al. 1964
2. De Jong 1991
3. Walker et al. 1969
4. Jolley et al. 1969 / Velsicol Chem. Corp. 1969
5. Treon et al. 1955

[85]) This is likely to be the same study as the study of Jolley et al. (1969) on the basis of which JMPR based its estimation of the ADI for endrin (JMPR 1970).

6.1.5. BACKGROUND EXPOSURE

Background exposure is predominantly through food intake. Since aldrin is rapidly converted to dieldrin, most studies indicate a negligible background intake of aldrin.
In 1991, Vermeire et al. estimated the background exposure of aldrin, dieldrin and endrin at 43 ng/kg bw/day for the three drins together (data from 1984-1985). Since drins are not in use anymore, the current background exposure is likely to be lower.
In the USA food survey studies carried out in the period 1986-1991 (FDA 1991, 1992) indicated (for children and adults) an intake of dieldrin of 1.6 ng/kg bw/day and an intake of endrin of <0.1 ng/kg bw/day. The current background exposure of drins in The Netherlands is thus likely to be below 40 ng/kg bw/day.

6.1.6. CONCLUSION

Compound	TDI	TCA	Background exposure
Aldrin	0.1 [a])	0.35 [a,b])	< 0.04 [c])
Dieldrin			
Endrin	0.2	0.7 [b])	

TDI: tolerable daily intake (oral exposure); µg/kg bw/day
TCA: tolerable concentration in air (inhalation exposure); µg/m^3
Background exposure; µg/kg bw/day
[a]) Separately as well as the sum of aldrin and dieldrin
[b]) Provisional because it is derived via route-to-route extrapolation
[c]) Sum of aldrin, dieldrin and endrin

6.1.7. REFERENCES

ATSDR (1992):
Toxicological profile for aldrin/dieldrin.
US Dept. of Health & Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta (GA), USA.

ATSDR (1996):
Toxicological profile for endrin and endrin aldehyde (update).
US Dept. of Health & Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta (GA), USA.

FDA (1991):
Food and Drug Administration Pesticide Program, 4th Annual Report - Residues in food 1990.
JAOAC 74, 121A-141A *(cited in ATSDR 1992).*

FDA (1992):
Food and Drug Administration Pesticide Program, 5th Annual Report - Residue monitoring 1991.
JAOAC 75, 135A-157A *(cited in ATSDR 1996).*

Fitzhugh OG & Nelson AA (1963):
Unpublished data from the US Food and Drug Administration *(cited in JMPR 1967).*

Fitzhugh OG, Nelson AA & Quaife ML (1964):
Chronic oral toxicity of aldrin and dieldrin in rats and dogs.
Food Cosmet Toxicol 2, 551-562 *(cited in ATSDR 1992, IRIS 2000 and JMPR 1967).*

Hassauer M, Kalberlah F, Oltmans J & Schneider K (1993):
Basisdate Toxikologie für umweltrelevante Stoffe zur Gefahrenbeurteilung bei Altlasten.
Umwelt Bundes Amt, Berichte 4/93, Erich Schmidt Verlag, Berlin, Germany.

IARC (1987):
Overall Evaluations of Carcinogenicity, Suppl. 7 - an Updating of IARC Monographs Volumes 1 to 42.
International Agency for Research on Cancer, World Health Organization, Lyon, France.

IPCS (1992):
Environmental Health Criteria 130 - Endrin.
International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland.

IRIS (2000):
Integrated Risk Information System (IRIS): summaries for aldrin, dieldrin, and endrin (all three dated May 1998).
US Environmental Protection Agency, Washington DC, USA.

JMPR (1967):
Pesticide residues in food.
Report of the FAO/WHO Joint Meeting on Pesticide Residues in Food, Geneva, November 1966.
WHO Food Add. Report no. 67.32; Geneva, Switzerland.

JMPR (1970):
Pesticide residues in food.
Report of the FAO/WHO Joint Meeting on Pesticide Residues in Food, Roma, November 1970.
WHO Technical Report Series 474; FAO Agricultural Studies 87; Roma, Italy (published in 1971).

JMPR (1977):
Pesticide residues in food.
Report of the FAO/WHO Joint Meeting on Pesticide Residues in Food, Geneva, December 1977.
FAO Plant Production and Protection Papers, 10 Suppl.; Roma, Italy (published in 1978).

Jolley WP, Stemmer KL, Grande F, Richmond J & Pfitzer EA (1969):
The effects exerted upon Beagle dogs during a period of two years by the introduction of 1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-1,4-endo,endo-5,8-dimethanonaphtalene into their daily diets.
Unpublished report, Kettering Laboratory, University of Cincinnatti (OH), USA *(cited in JMPR 1970).*

Jong G de (1991):
Long term health effects of aldrin and dieldrin - a study of exposure, health effects and mortality of workers engaged in the manufacture and formulation of the insecticides aldrin and dieldrin.
Toxicol Letters, Suppl 1991 *(cited in ATSDR 1992 and Hassauer et al. 1993).*

Treon JF, Cleveland FP & Cappel J (1955):
Toxicity of endrin for laboratory animals.
J Agr Food Chem 3, 842-848 *(cited in JMPR 1970).*

Velsicol Chemical Corporation (1969):
Effects exerted upon Beagle dogs during a period of two years by the introduction of 1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-1,4-endo,endo-5,8-dimethanonaphtalene into their daily diets.
Report, Kettering Laboratory, University of Cincinnatti (OH), USA *(cited in ATSDR 1996 and IRIS 2000).*

Vermeire TG, Apeldoorn ME van, Fouw JC de & Janssen PJCM (1991):
Voorstel voor de humaan-toxicologische onderbouwing van C-toetsingswaarden.
National Institute of Public Health and the Environment, RIVM-report no. 725201005, February 1991; Bilthoven, The Netherlands.

Walker AIT, Stevenson DE, Robinson J, Thorpe E & Roberts M (1969):
The toxicology and pharmacodynamics of dieldrin (HEOD) - two year oral exposures of rats and dogs.
Toxicol Appl Pharmacol 15, 345-373 *(cited in ATSDR 1992 and IRIS 2000).*

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Date:	*15-05-2000*

6.2. DDT AND ITS METABOLITES DDD AND DDE

6.2.1. INTRODUCTION

DDT [86,87]) and DDE [88]) were evaluated in 1991, and the MPR (maximum permissible risk) was set at a TDI (tolerable daily intake) of 20 µg per kg bw (body weight) per day for DDT, DDE, and for the sum of both compounds (Vermeire et al. 1991). This TDI was based on occupational health studies demonstrating that chronic exposure to at average 0.25 mg DDT per kg bw per day during 25 years did not result in any adverse affect, and thus could be considered the NOAEL for humans (Vermeire et al. 1991). Applying a UF (uncertainty factor) of 10 for intrahuman extrapolation a TDI of 20 µg/kg bw/day (rounded value) was derived, in accordance with the ADI (acceptable daily intake) for DDT, DDD [89]) and/or DDE (separately or in combination) as derived by JMPR (1984).
Inhalation exposure was considered to be irrelevant.
Background exposure results for the major part from food and water, and was estimated to be 0.1 µg/kg bw/day (at most) for the DDT complex (sum of DDT, DDE and DDD); these values were based on the food survey studies of Greve et al. (1987).
The insecticide DDT was widely used during World War II to protect troops and civilians from the spread of malaria, typhus and other vector-borne diseases. After the war DDT was widely used on a variety of agricultural crops and for the control of disease vectors as well. Although a great number of countries have restricted or banned the use of DDT since the early 1970s, many other countries, particularly the less developed ones, still use DDT. An alternative for the control of vector-borne diseases, attractive in terms of economy and efficacy, is not available (ATSDR 1993, WHO 1996).
DDT is insoluble in water but soluble in most organic compounds. Its presence is ubiquitous in the environment (even in the arctic). It is highly lipophilic and has been demonstrated to bioaccumulate. The breakdown products DDD and DDE are also present virtually everywhere in the environment and are more persistent than the parent compound (ATSDR 1993, WHO 1996).

6.2.2. TOXICOLOGY

The toxicology of DDT and its metabolites is reviewed here in some detail, because many of the limit values (cf. paragraph 6.2.4) are based on rather old studies which were not fully reviewed in the earlier evaluation (Vermeire 1991).

Toxicokinetics

DDT, DDD and DDE are absorbed following inhalation, oral and dermal exposure. Oral exposure is considered the most significant route of entry in humans, and results in preferential absorption by the intestinal lymphatic system, but quantitative data on humans are limited. All three compounds are readily distributed in the lymph and blood to all body tissues and ultimately stored in proportion to the lipid content of the tissue, regardless of the route of exposure. Excretion of DDT in the form of its metabolites is largely via the urine, although the parent compound may be excreted also via faeces, and breast milk (ATSDR 1993, IARC 1991).
The metabolism of DDT in humans appears qualitatively similar to that seen in rodents. DDT is primarily biotransformed to DDD and DDE, which are further metabolised (via a number of intermediates) to the major urinary metabolite DDA [2,2-bis(4-chlorophenyl)acetic acid] and conjugates thereof (ATSDR 1993, IARC 1991). The biological half-life of DDT is about one month in dogs, three

[86]) The term *'DDT'* refers to p,p'-DDT (see next footnote). The compound's structure, however, permits several isomeric forms, such as o,p'-DDT. The term DDT is also applied to commercial products consisting predominantly of p,p'-DDT, but also containing smaller amounts of otherr compounds, including p,p'- and o,p'-DDD and p,p'- and o,p'-DDE (see footnotes 3 and 4).
[87]) 1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane (dichlorodiphenyltrichloroethane, DDT), CAS no. 50-29-3.
[88]) 1,1-dichloro-2,2-bis(4-chlorophenyl)ethene (dichlorodiphenyldichloroethene, DDE), CAS no. 72-55-9.
[89]) 1,1-dichloro-2,2-bis(4-chlorophenyl)ethane (dichlorodiphenyldichloroethane, DDD, TDE), CAS no. 72-54-8.

months in monkeys and five weeks in rats (IARC 1991); regarding the biological half-lifes of the three compounds in humans their ranking is in the order DDE>DDT>DDD (ATSDR 1993).
Quantitatively marked species differences exist: mice produce more DDE than humans and other species, while humans produce more of the polar metabolite DDA (JMPR 1984, ATSDR 1993, WHO 1996).

Toxicity

Numerous toxicity studies on DDT and its breakdown products DDD and DDE have been published since the 1940s. Only the relevant ones resulting in well-defined adverse effects at relatively low doses are summarised here.
The vast majority of the reported toxicity data are dealing with effects upon oral exposure; data regarding effects following inhalation exposure are very limited and lack essential information on, e.g., exposure concentrations and doses.
Oral LD_{50} values for DDT in experimental animals vary from 113 to 800 mg per kg bw for rats, guinea pigs and rabbits. For DDD and DDE the LD_{50} values are in the same order of magnitude.
Human studies
Toxicity
Many medical and epidemiological studies have been carried out in humans occupationally involved in the production or use of DDT; most of these studies were done in the period 1940 - 1970. Generally the groups were relatively small-sized (less than 100 individuals). Main effects noted were on the nervous system, both central and peripheral, and on the liver. In most studies, however, the the exact duration and level of exposure cannot be quantified because the information is derived from case reports or epidemiological studies that do not adequately characterise exposure.
The study with the most detailed information is the one by Laws et al. (1967), who investigated 35 man employed from 11 to 19 years in a DDT production plant; the results were compared with general population data. Findings from medical histories, physical examinations, clinical laboratory tests and chest X-ray films did not reveal any adverse effects attributable to exposure to DDT. The fat storage of DDT (including metabolites) was 38-647 mg/kg, compared with an average of 8 mg/kg for the general population. Based on this fat storage and urinary DDA excretion the average daily intake of DDT by the 20 men with high occupational exposure was estimated at 18 mg/man/day (equalling 0.25 mg/kg bw/day) compared with an average of 0.028 mg/man/day (equalling 0.4 μg/kg bw/day) for members of the general population.
In a follow-up of this study (Laws et al. 1973), the liver function of 31 men involved in the earlier study was reported. Based on fat storage and excretion their exposure was equivalent to 3.6-18 mg/man/day (equalling 0.05-0.25 mg/kg bw/day) for periods ranging from 16-25 years (21 year at average). All tests were in the normal range for total protein, albumin, bilirubin, thymol turbidity, and sulfobromophtalein retention. The α-fetoprotein test was negative for all men. Two individuals had mild elevations of alkaline phosphatase, three had mildly elevated SGPT.
Carcinogenicity
Studies of workers exposed to DDT have not established an association between DDT exposure and the development of cancer. These studies had several confounding factors, of which the most common were exposure to multiple pesticides, inadequate follow-up times, and uncertain exposure concentrations. Thus, in a critical review ATSDR (1993) concluded that studies on the incidence of leukemia, non-Hodgkin lymphoma, multiple myeloma, and respiratory cancer all failed to demonstrate an association between DDT exposure and cancer development. Only a nested case-control mortality study of almost 6000 chemical manufacturing workers showed a weak association between DDT exposure and mortality from pancreatic cancer, from which it was concluded that DDT may be a risk factor for pancreatic cancer in humans after heavy and prolonged exposure (Garabrant et al. 1992).
Animal studies
In experimental animals the toxic effects upon prolonged exposure to DDT, DDD and/or DDE include hepatotoxicity, neurotoxicity, immunotoxicity, reproductive and developmental effects, and cancer.
Hepatotoxicity
The lowest dietary dose of DDT resulting in hepatotoxic effects was reported already in 1950: female rats exposed to DDT in the feed for 15-27 weeks showed cellular hypertrophy and cytoplasmic eo-

sinophilia in the liver at 0.25 mg/kg bw/day, the NOAEL in this study was 0.05 mg/kg bw/day (Laug et al. 1950). At higher dose levels of DDT, DDD and/or DDE, numerous other studies have demonstrated microsomal enzyme induction, increased liver weights, hypertrophy, hyperplasia, and cell necrosis, all dose-relatedly.

Neurotoxicity

DDT acts on the central nervous system, causing hyperexcitability, tremors and convulsions following oral exposure of humans to high doses. Similar effects were also seen in experimental animals: mice dietary exposed to 6.5 mg/kg bw/day (LOAEL) for 130-140 weeks showed tremors, the NOAEL in this study was 1.3 mg/kg bw/day (Turusov et al. 1973). The same was observed in rats, but at higher doses. Neurological effects were also noted in monkeys exposed to DDT administered by gavage during 2 - 6 months: loss of equilibrium occurred at a daily dose of 50 mg/kg bw/day, with a NOAEL of 5 mg/kg bw/day (Cranmer et al. 1972). In another study with monkeys exposed to DDT administered by gavage during 100 days, a decrease in brain lipids, CNS phospholipids, and cholesterol was noted at a LOAEL of 10 mg/kg bw/day (Sanyal et al. 1986).

Immunotoxicity

Adverse immunological effects were observed by Gabliks et al. (1975): rats dietary exposed to DDT during one month showed a decrease in number of mast cells at 1 mg/kg bw/day (LOAEL).

Reproduction toxicity

Reproductive effects occurred with a LOAEL of 0.35 mg/kg bw/day for decreased fertility and infertile pups of rats dietary exposed to DDT during 60 days (Green 1969), while Lundberg observed decreased implanted ova and increased persistent oestrus in mice dietary exposed to DDT during 12 weeks (Lundberg 1973), and decreased corpora lutea and implants in mice administered DDT by gavage during 28 days (Lundberg 1974); in both studies the LOAEL was 1.7 mg/kg bw/day.

Developmental toxicity

Developmental effects were reported in a study with pregnant rats dietary exposed to DDT during gestation and/or lactation: an increase in mortality of pups exposed perinatally via dams receiveing 25 mg/kg bw/day was reported, along with a decrease in growth of the pups after exposure via nursing from dams receiving 10 or 25 mg/kg bw/day. The NOAEL in this study was 1 mg/kg bw/day (Clement and Okey 1974). In a study with mice perinatally exposed to DDT during gestation and lactation, increased deaths (40% mortality in the pups before weaning) and decreased maze learning performance was seen at 26 mg/kg bw/day (LOAEL; Craig and Ogilvie 1974).

Genotoxicity

The genotoxicity of DDT, DDD and DDE was examined in a large number of assays, most of which were carried out in the 1970's. The data are summarized in IARC (1991), ATSDR (1993) and WHO (1996).

In vitro tests for gene mutations with DDT, DDD and DDE in bacterial systems, fungi, plant cells and mammalian cells were uniformly negative. The available *in vitro* tests for chromosome aberrations, practically all of which were carried out without metabolic activation, showed conflicting results with some negative results while others were weakly-positive.

A number of *in vivo* studies was carried out with DDT. A test for chromosome aberrations in bone marrow in rats was negative whereas the same test in mice was positive. Dominant lethal tests for DDT gave conflicting results with a weakly-positive response in two mouse studies but no effect in a further study in this species or in rats. In a single study in mice a weak-positive result was seen for the induction of chromosome aberrations in spermatocytes. No significant effect on sperm morphology was observed in several studies, but in a single study in rats a positive result was found. *In vivo* studies in insects showed no effect in two assays for sex-linked recessive lethal mutations, a positive response for dominant lethal mutations and conflicting results for the induction of aneuploidy.

For DDD no *in vivo* studies are available. DDE was tested in insects only, with a positive response for the induction of sex-linked recessive lethal mutations in one study and a negative result in another study (the heritable translocation test).

A consistent finding for DDT in a number of experiments, including an *in vivo* experiment in rats, is inhibition of gap-junctional intercellular communication (cf. elsewhere in this paragraph). This finding is significant because this effect is thought to play a role in the (non-genotoxic) induction of tumours by certain chemicals.

Taken together, the data on DDT's genotoxicity are inconclusive.

Carcinogenicity

DDT

Experimental animal studies on carcinogenicity are available for several species. Intermediate exposures with DDT in the food caused increased tumour incidence in mice but not in rats or hamsters. Mice observed for 50-105 weeks after cessation of treatment developed liver hepatomas following exposure to 32.5 mg DDT/kg bw/day for 15-30 weeks.

Chronic exposure (>1 year) to DDT caused cancer in multiple strains of mice. Liver neoplasms were seen in C57Bl/6, BALB/c and CF1 mice fed DDT at doses as low as 0.26 mg/kg bw/day for minimally 78 weeks; an increased incidence of pulmonary adenomas was seen in mice after chronic gavage administration at doses ranging from 1.3 to 32.5 mg/kg bw/day, and malignant lymphomas occurred in mice orally treated for 80 weeks at a dose of 10 mg/kg bw/day. One study with mice (administered 3-23 mg/kg bw/day for 2 years) was negative.

In one study in rats liver tumours developed in rats at a dose of 12.5 mg DDT per kg bw per day for 2 years. Other studies, however, failed to show a significant increase in tumour formation in rats after chronic DDT exposure: no increases were seen when administered to rats for 27 months at doses up to 25 mg/kg bw/day.

In studies with monkeys (with doses of 8-20 mg/kg bw/day for 5 years) and with dogs (with doses of 80 mg/kg bw/day for 49 months), tumour formation was not increased (ATSDR 1993).

In a multigeneration study in mice, increases in leukemia and pulmonary carcinomas were observed firstly in the F_2 generation (dietary exposure, perinatally - *in utero* - and through lactation, to 2.8 mg/kg diet, equivalent to 0.4 mg/kg bw/day) and with increasing frequency in each subsequent generation. In other multigeneration studies in mice, liver and pulmonary tumours were seen dose-relatedly in all generations (including the parental one); these tumours had a shorter latency period in the F_1 generation than in the parental generation, but tumour incidence was comparable and did not increase with consecutive generations (dietary exposure to 2 -250 mg/kg diet, equivalent to 0.3 - 40 mg/kg bw/day) (IARC 1991, ATSDR 1993).

DDT has been shown to act as a liver tumor promoter in rats initiated with 2-acetylaminofluorene, 2-acetamidophenanthrene or trans-4-acetylaminostilbene (Peraino et al. 1975, Scribner and Mottet 1981, Hilpert et al. 1983).

DDD

DDD induced liver tumours and lung adenomas in dietary exposed CF1 mice (250 mg/kg diet, equivalent to 40 mg/kg bw/day), and thyroid follicular cell tumours in dietary exposed Fischer-344 rats (850 - 3300 mg/kg diet, equivalent to 40 - 165 mg/kg bw/day), but was not tumourigenic in dietary exposed $B6C3F_1$ mice (78 weeks at 53-107 mg/kg bw/day) (IARC 1991, ATSDR 1993).

DDE

DDE via the diet produced liver tumours in mice at doses of 19-34 mg/kg bw/day for 30-78 weeks, and in hamsters at 40 mg/kg bw/day for 124 weeks, but not in rats at doses of 12-42 mg/kg bw/day for 78 weeks (ATSDR 1993).

Conclusion on carcinogenicity

Taken together it can be concluded that DDT has been shown to be carcinogenic in rodents, albeit that marked differences regarding the responses were found in the various studies. The increase in liver tumours in mice is the most consistent observation; apparently the mouse is particularly susceptible for the carcinogenicity of DDT. This susceptibility of the mouse may be the consequence of major species differences in the metabolism of DDT. Mice form more DDE than humans and other species; humans form more of the polar metabolite DDA. Indeed DDE has been considered to be the metabolite responsible for carcinogenicity in mice (JMPR 1984, WHO 1996).

In rats DDT was shown to act as a liver tumour promoter; initiation-promotion studies in other animals species could not be located.

In addition several expert groups have noted that in the studies showing carcinogenicity this occurred generally at doses higher than the doses at which systemic toxicity was observed.

Mechanism of action

DDT has been shown to be a powerful inducer of the cytochrome P450 system, which might explain its tumour-promoting activity. In addition the enzyme-inducing properties of DDT can be responsible

for changes in serum levels of endogenous compounds including hormones, which in turn may affect the reproductive system (JMPR 1984, ATSDR 1993).
DDT and a number of its metabolites are considered weakly hormone-disrupting substances capable of binding to, and activating oestrogen, androgen and progesterone receptors, which may also explain many of the reproductive effects seen in experimental animals (ATSDR 1993, Preziosi 1998). In turn, DDT's hormone-disrupting potency might also add to its tumour-promoting potency.
DDT acts on the CNS by interfering with the movements of ions through neuronal membranes: it delays the closing of Na^+ channels, prevent the full opening of K^+ gates, inhibits the transport of Ca^{++}, and interacts with a specific neuronal ATPase (ATSDR 1993). Together these effects result in maintaining the depolarisation of the nerve membrane, thus potentiating the release of transmitters leading to CNS excitation which in turn becomes manifest by hyperexcitability, tremors, and convulsions. Also this effect might add to DDT's tumour-promoting potency.

6.2.3. EVALUATION

The currently available data on the genotoxicity and carcinogenicity of DDT indicate its tumorigenic potential, but are inconclusive regarding its genotoxicity; mechanistic studies indicate its property to act as a promoting agent (cf. paragraph 6.2.2). In line with other (international) evaluations (cf. paragraph 6.2.4) the threshold approach is chosen for the derivation of a limit value.
The previous evaluation (Vermeire et al. 1991) adopted the TDI of 20 µg/kg bw/day as derived by JMPR (1984), who based its derivation on human studies which, however, were not cited (cf paragraph 6.2.1). This JMPR derivation is likely to be based on the studies of Laws et al. (1967, 1973; cf. paragraph 6.2.2) which involved 35 workers occupationally exposed during a period of at average 21 years. From the studies of Laws et al. a NOAEL of 0.25 mg/kg bw/day can be derived (cf. paragraph 6.2.2). If a MPR is to be derived from this NOAEL, additional UFs (uncertainty factors) should be used to cover the limitations of the studies (i.e., limited size, no well-defined control group, occupational exposure for approximately 20 years): a UF of 300 (composed of 10 for interspecies variation, 10 for limited size, and 3 for extrapolation to lifetime exposure) would be appropriate, resulting in a oral limit value of 0.8 µg/kg bw/day. However, in view of the limitations of the studies of Laws et al., preference is given to animal studies as the basis for the MPR derivation.
Reviewing all available data the hepatotoxic effects already noted in 1950 appear to represent the most sensitive endpoint, with a NOAEL of 0.05 mg/kg bw/day (Laug et al. 1950). In accordance with international evaluations (cf. paragraph 6.2.4) the MPR to be derived for DDT, DDD and DDE should thus be based on this study. Applying a UF of 100 (10 for extrapolation from animals to humans, 10 for intrahuman variations) results in a TDI of 0.5 µg/kg bw/day. This value is close to the limit value that can be derived from the studies of Laws et al. (1967, 1973) if the above UFs are used.
The limited data on the toxicity of DDD and DDE indicate a similar pattern of toxicity at exposure levels comparable with those of DDT (ATSDR 1993), and thus the TDI derived for DDT also holds for DDD and DDE, including the sum of DDT, DDD and DDE.
Although DDT is present in the atmosphere world-wide (WHO 1996, 2000), the reported air concentrations are low and do not significantly contribute to the background exposure (cf. paragraph 6.2.5). Due to the rather low volatility significant exposure via ambient at sites of soil contamination is not expected. Thus the derivation of a TCA (tolerable concentration in air) is not necessary.

6.2.4. EVALUATIONS BY OTHER ORGANISATIONS

In 1963 JMPR allocated an acceptable daily intake (ADI) for DDT of 5 µg/kg bw/day, which was changed into 10 µg/kg bw/day in 1965, and again back to 5 µg/kg bw/day in 1969 (JMPR 1984). JMPR (1984) concluded to no significant risk of DDT producing tumours in humans. In 1994 JMPR re-evaluated the toxicology of DDT and allocated an ADI of 20 µg/kg bw/day, based on a study in workers exposed for 25 years at an average dosage of 0.25 mg/kg bw/day, which dose was without

any adverse effect (NOAEL) (JMPR 1984); obviously a UF of approximately 10 was applied [90]). This limit value was adopted as the MPR by Vermeire et al. in 1991 (cf. paragraph 6.2.1) [91]).
In 1996 US-EPA (IRIS 2000) derived a RfD for DDT of 0.5 µg/kg bw/day, based on the NOAEL for liver lesions of 0.05 mg/kg bw/day of the 27 week rat feeding study of Laug et al. (1950), applying a UF of 100.
ATSDR (1993) derived a intermediate-duration MRL (exposure of 2 weeks to 1 year) for DDT of 0.5 µg/kg bw/day (using the same study as US-EPA).
Also Hassauer et al. (1993) advised the BundesUmweltAmt (Germany; BUA) to an "Orienterungswert" for long-term oral exposure to DDT of 0.5 µg/kg bw/day, based on the same study as US-EPA.
Neither US-EPA, nor ATSDR or Hassauer et al. derived limit values for long-time inhalation exposure, due to lack of data.
None of the organisations mentioned above derived limit values for DDD or DDE, due to lack of data.
IARC (1991) classified DDT in category 2B: *possibly carcinogenic to humans* (based on *sufficient evidence* for its carcinogenicity in experimental animals, and *inadequate evidence* for its carcinogenicity in humans). US-EPA classified DDT, DDD, and DDE in category B2: *probable human carcinogens* (based on *sufficient evidence* for their carcinogenicity in experimental animals, and *inadequate evidence* for their carcinogenicity in humans). Applying the linearised multistage procedure this organisation derived oral slope factors for carcinogenic risks of 0.34 per [mg/kg bw/day] for DDT, 0.24 per [mg/kg bw/day] for DDD, and 0.34 per [mg/kg bw/day] for DDE; for DDT an inhalation unit risk of 9.7×10^{-5} per [µg/m^3] was derived by route-to-route extrapolation (IRIS 2000).

6.2.5. BACKGROUND EXPOSURE

Daily intake of DDT from food has been measured in several countries, and indicates a mean dietary intake by the average adult of < 2 µg/day, equalling approximately 30 ng/kg bw/day (WHO 1996). However, in countries still actively applying DDT as an insecticide the daily intake may be substantially higher. The food survey study of Greve et al. (1987) indicated a background exposure in The Netherlands from dietary intake of 0.1 µg/kg bw/day at most.
Concentrations of DDT in air in non-agricultural areas have been reported to be in the range of <1 - 2.4 ng/m^3, in agricultural communities concentrations were 1 - 22 ng/m^3. In communities with anti-mosquito fogging programmes concentrations may be much higher, 8.5 µg/m^3 being the highest level recorded (WHO 1996). Taking a concentration of 2.4 ng/m^3 as a reasonable average, this level would cause an additional intake (assuming 100% absorption) of 0.8 ng/kg bw/day, which is negligible compared to the average intake by food.

6.2.6. CONCLUSION

Compound	TDI	TCA	Background exposure
DDT	0.5 [a])	n.r.	< 0.1 [b])
DDD	0.5 [a])	n.r.	
DDE	0.5 [a])	n.r.	

TDI: tolerable daily intake (oral exposure); µg/kg bw/day
TCA: tolerable concentration in air (inhalation exposure); µg/m^3
Background exposure; µg/kg bw/day
[a]) Holds also for the sum of DDT, DDD and DDE
[b]) Background exposure to the sum of DDT, DDD and DDE
n.r. not relevant

[90]) The study or studies on which this derivation was based were not cited, but are probably the epidemiological studies of Laws et al. (cf. paragraph 2.2.1).
[91]) Note added after finalisation of this document: in 2000 the JMPR allocated a pTDI for DDT of 10 µg/kg bw/day.

6.2.7. REFERENCES

ATSDR (1993):
Toxicological profile for 4,4'-DDT, 4,4'-DDE, 4,4'-DDD (update).
US Dept. of Health & Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta (GA), USA.

Clement J & Okey A (1974):
Reproduction in female rats born to DDT-treated parents.
Bull Environm Contam Toxicol 12, 373-377 *(cited in ATSDR 1993)*.

Craig G & Ogilvie D (1974):
Alteration of T-maze performance in mice exposed to DDT during pregnancy and lactation.
Environm Physiol Biochem 4, 189-199 *(cited in ATSDR 1993)*.

Cranmer M, Peoples A & Chadwick R (1972):
Biochemical effects of repeated administration of p,p'-DDT on the squirrel monkey.
Toxicol Appl Pharmacol 21, 98-101 *(cited in ATSDR 1993)*.

Gabliks J, Al-Zubaidy T & Askari E (1975):
DDT and immunological responses - 3. Reduced anaphylaxis and mast cell population in rats fed DDT.
Arch Environm Health 30, 81-84 *(cited in ATSDR 1993)*.

Garabrant DH, Held J, Langholz B, et al. (1992):
DDT and related compounds and risk of pancreatic cancer.
J Natl Cancer Inst 84, 764-771 *(cited in ATSDR 1993)*.

Green V (1969):
Effects of pesticides on rat and chick embryo.
In: Hemphill D (ed): Trace substances in environmental health 2, 183-209.
Proc. Univ. Missouri, 3rd Annual Conference; St Louis, USA *(cited in ATSDR 1993)*.

Greve PA, Harten DC van, Heusinkveld HAG, Janssen GE, Verschraagen C & Tonkelaar EM den (1987):
Bestrijdingsmiddelen in duplicaat 24-uurs voedingen, deelrapport I: organochloorbestrijdingsmiddelen.
National Institute of Public Health and the Environment, RIVM-report no. 388474001, 1987; Bilthoven, The Netherlands.

Hassauer M, Kalberlah F, Oltmans J & Schneider K (1993):
Basisdate Toxikologie für umweltrelevante Stoffe zur Gefahrenbeurteilung bei Altlasten.
Umwelt Bundes Amt, Berichte 4/93, Erich Schmidt Verlag, Berlin, Germany.

Hilpert D, Romen W & Neumann HG (1983):
The role of partial hepatectomy and of promoters in the formation of tumors in non-target tissues of trans-4-acetylaminoxtilbene in rats.
Carcinogenesis 4, 1519-1525 *(cited in IRIS 2000)*.

IARC (1991):
Monographs on the evaluation of carcinogenic risks to humans, vol. 53: occupational exposures in insecticide application, and some pesticides.
International Agency for Research on Cancer, World Health Organization, Lyon, France.

IRIS (Integrated Risk Information System), 2000:
- Summary for p,p'-DDT; oral RfD assessment dated February 1996, carcinogenicity assessment dated May 1991.
- Summary for p,p'-DDD; carcinogenicity assessment dated August 1988.
- Summary for p,p'-DDE; carcinogenicity assessment dated August 1988.

US Environmental Protection Agency, Washington DC, USA.

JMPR (1984):
Pesticide residues in food - evaluations 1984.
Joint FAO/WHO Meeting on Pesticide Residues, Roma (Italy); September/October 1984.

Laug EP, Nelson AA, Fitzhugh OG & Kunze FM (1950):
Liver cell alteration and DDT storage in the fat of the rat induced by dietary levels of 1-50 ppm DDT.
J Pharmacol Exptl Therap 98, 268-273 *(cited in JMPR 1984, ATSDR 1993, IRIS 2000)*.

Laws ER Jr, Curley A & Biros FJ (1967):
Men with intensive occupational exposure to DDT - a clinical and chemical study.
Arch Environm Health 15, 766-775 *(cited in WHO 1979 and ATSDR 1993).*

Laws ER Jr, Madrey WC, Curley A & Burse VW (1973):
Long-term occupational exposure to DDT.
Arch Environm Health 27, 318-321 *(cited in WHO 1979 and ATSDR 1993).*

Lundberg C (1973):
Effects of long-term exposure to DDT on the oestrus cycle and the frequency of implanted ova in the mouse.
Environm Physiol Biochem 3, 127-131 *(cited in ATSDR 1993)*.

Lundberg C (1974):
Effect of DDT on cytochrome P-450 and oestrogen-dependent functions in mice.
Environm Physiol Biochem 4, 200-204 *(cited in ATSDR 1993)*.

Peraino C, Fry RJM, Staffeldt E & Christopher JP (1975):
Comparative enhancing effects of phenobarbital, amobarbital, diphenylhydantoin and dichlorodiphenyltrichloroethane of 2-acetylaminofluorene-induced hepatic tumorgenesis in the rat.
Cancer Res 35, 2884-2890 *(cited in IRIS 2000).*

Preziosi P (1998):
Endocrine disruptors as environmental signallers - an introduction.
In: Wright AN & Fischli AE, eds: Natural and anthropogenic environmental oestrogens, the scientific basis for risk assessment.
Pure & Appl Chem, vol 70 no 9, September 1998.

Sanyal S, Agarwal N & Subrahmanyam D (1986):
Effect of acute sublethal and chronic administration of DDT (chlorophenothane) on brain lipid metabolism of rhesus monkeys.
Toxicol Letters 34, 47-54 Environm Physiol Biochem 3, 127-131 *(cited in ATSDR 1993)*.

Scribner JD & Mottet NK (1981):
DDT acceleration of mammary gland tumors induced in the male Sprague-Dawley rat by 2-acetamidophenanthrene.
Carcinogenesis 2, 1235-1239 *(cited in IRIS 2000).*

Turusov V, Day N, Tomatis L, et al. (1973):
Tumors in CF-1 mice exposed for six consecutive generations to DDT.
J Natl Cancer Inst 51, 983-997 *(cited in ATSDR 1993)*.

Vermeire TG, Apeldoorn ME van, Fouw JC de & Janssen PJCM (1991):
Voorstel voor de humaan-toxicologische onderbouwing van C-toetsingswaarden.
National Institute of Public Health and the Environment, RIVM-report no. 725201005, February 1991; Bilthoven, The Netherlands.

WHO (1979):
Environmental Health Criteria 9: DDT and its derivatives.
World Health Organization and United Nations Environmental Programme, WHO, Geneva, Switzerland.

WHO (1996):
Guidelines for drinking-water quality, 2nd. ed., vol. 2: Health criteria and other supporting information - DDT; pp 638-644.
World Health Organization, Geneva, Switzerland.

WHO (2000):
Draft report of the meeting on health risks of persistant organic pollutants from long-range transboundary air pollution.
WHO-UNECE Task Force on Health Aspects of Long Range Transboundary Air Pollution; Bilthoven, The Netherlands, May 10, 2000.

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6.3. α-, β-, γ-, AND δ-HEXACHLOROCYCLOHEXANE

6.3.1. INTRODUCTION

The MPR (maximum permissible risk) for HCHs (α-, β- and γ-hexachlorocyclohexane) was evaluated in 1991 and set at a TDI (tolerable daily intake) of 1 μg per kg bw (body weight) per day for α-HCH and γ-HCH, respectively, as well as for the sum of both compounds, and at a TDI of 0.02 μg/kg bw/day for β-HCH (Vermeire et al. 1991).
The TDI for α-HCH was based on the LOAEL for leucocytopenia and liver changes of 10 mg/kg feed and a NOAEL of 2 mg/kg feed (equivalent with 0.5 and 0.1 mg/kg bw/day, respectively) in a 90-day oral study with rats (Slooff and Matthijssen 1988). An uncertainty factor (UF) of 100 was used to derive the TDI.
For β-HCH two semi-chronic oral studies on reproduction in rats were considered, both of which resulted in a NOAEL for infertility of 0.4 mg/kg feed, equivalent with 0.02 mg/kg bw/day (Slooff and Matthijssen 1988). A UF of 1000 was used to derive the TDI.
The TDI for γ-HCH was based on a LOAEL for liver and kidney damage of 10 mg/kg feed and a NOAEL of 2 mg/kg feed (equivalent with 0.5 and 0.1 mg/kg bw/day, respectively) in a 90-day oral study with rats (different from the α-HCH studies) (Slooff and Matthijssen 1988). A UF of 100 was used to derive the TDI.
Data for δ-HCH were lacking.
Inhalation exposure was considered to be relevant for α- and γ-HCH, for these isomers a TCA (tolerable concentration in air) of 0.25 μg/m^3 was derived, based on the NOAEL of 0.1 mg/m^3 for hepato- and nephrotoxicity in a 90-day inhalation study with rats exposed to γ-HCH during 6 h/day, 7 days/week, which was corrected for continuous exposure to a NOAEL of 25 μg/m^3 (Slooff and Matthijssen 1988). A UF of 100 was used to derive the TDI.
Background exposure results for the major part from food, and was estimated to be 0.03 μg/kg bw/day (at most) for α- and γ-HCH, and 0.014 μg/kg bw/day (at most) for β-HCH (Vermeire et al. 1991); these values were based on the food survey studies of Greve et al. (1987).
Alpha-, β- and δ-HCH are by-products in the manufacture of γ-HCH (better known as lindane), which has been used as a broad-spectrum insecticide since the early 1950's. The HCHs are rather persistent chlorinated cyclohexanes with a tendency to accumulate in food chains. In most Western countries the use of lindane has been limited or terminated.

6.3.2. TOXICOLOGY

In rats HCHs are rapidly and almost completely absorbed from the gastrointestinal tract. There are indications that HCHs are also well absorbed upon inhalation and dermal exposure. The biotransformation involves dechlorination, mainly producing a number of chlorophenols. Also chlorinated hydroxybenzenes and -cyclohexenes, and various conjugates are formed. The biological half-life in rats is the order of 1-18 days, dependent on the isomer.
IARC classified all three isomers in category 2B: *possibly carcinogenic to humans* (IARC 1987). US-EPA classified α-HCH in category B2: *probable human carcinogen*, and β-HCH in category C: *possible human carcinogen*; γ-HCH has as yet not been classified (IRIS 2000).

α-HCH

Oral exposure to α-HCH results in liver enzyme induction, increased liver weight, histological changes in the liver, kidney dysfunction and immunosuppression. There are no indications for α-HCH being mutagenic. Carcinogenicity studies revealed equivocal results: in some mouse studies hyperplastic nodules and hepatocellular carcinomas were found, while others (mice, rats) were negative. Further research indicated that the α-HCH induced tumorgenicity has a non-genetic mechanism: it was suggested to act as a promoting agent, possibly involving induction of the mixed function oxidase system.

β-HCH

Beta-HCH accumulates more strongly than the other two isomers. Its toxicity profile is comparable with that of α- and γ-HCH, but is expressed at lower dosages. In addition some weak estrogenic effects were described, the uterus being the target organ. There are no indication for mutagenic potential, and of two limited carcinogenicity studies (mice), one showed hyperplastic changes in the liver and an in-

crease in benign and malignant liver tumours, but the other study was negative; research directed to the mechanism of this suggested a tumour-promoting effect of β-HCH, possibly involving induction of the mixed function oxidase system.

γ-HCH

The toxicity of γ-HCH is partly comparable with α-HCH. Its toxicity is also primarily expressed in the liver and kidney, but next to these it exerts neuro- and immunotoxicity.

Meera et al. (1992) studied the immunomodulary effects of γ-HCH in a 24 week study with female Swiss mice and found a dose-dependent biphasic response (stimulation followed by suppression) in cell-mediated and humoral immune function, and an increase in thymus medulla size accompanied by a decreased cellular population in thymus cortex (also dose-dependent). The LOAEL in this study was 0.012 mg/kg bw/day, for reduced activity of lymphoid follicles with prominent megakaryocytes and delayed hypersensitivity to immune challenge. It must be noted, however, that in some short-term rat and mouse studies carried out in the 1970s and 1980s immunotoxic effects were only seen at doses approximately 10-100 times higher than the LOAEL observed by Meera et al. (1992).

A two-year oral toxicity and carcinogenicity study with rats resulted in a number of effects including neurotoxicity (convulsions), haematological effects, hepato- and nephrotoxicity; the NOAEL for the most sensitive endpoints (hepato- and nephrotoxic effects, decreased survival) was 0.47 mg/kg bw/day. Carcinogenicity was not observed (Amyes 1990 as cited in JMPR 1997). Numerous mutagenicity studies did not demonstrate any mutagenic potential. Gamma-HCH was suggested to act as a promoting agent, possibly involving induction of the mixed function oxidase system.

Gamma-HCH is not teratogenic, and did not have adverse effects on reproduction or maturation in a 3-generation study in rats; foetal toxicity was seen at doses which also resulted in maternal toxicity.

δ-HCH

Data on δ-HCH are limited to one acute oral study in rats (100 mg/kg bw by gavage), resulting in a significant decrease in mRNA expression from brain calmodulin genes (Barrón et al 1995 as cited in ATSDR 1999).

6.3.3. EVALUATION

α-HCH and β-HCH

There are no relevant new data for α- and β-HCH that warrant a change in the TDIs (both compounds, 1 and 0.02 μg/kg bw/day, respectively) and TCA (α-HCH, 0.25 $\mu g/m^3$) as previously estimated by Vermeire et al. in 1991 (inhalation exposure to β-HCH was - and still is - considered not relevant).

γ-HCH

The oral exposure study of Meera et al. (1992; cf. paragraph 6.3.2) clearly indicates immunotoxic effects at levels lower than known in 1991. Thus for γ-HCH a TDI of 0.04 μg/kg bw/day is derived, based on the LOAEL of 12 μg/kg bw/day obtained in the cited study of Meera et al. with a UF of 300 (10×10 for intra- and interspecies variability, an additional UF of 3 is considered sufficient to compensate for the use of a LOAEL instead of a NOAEL in view of the rather marginal toxic responses at the LOAEL). JMPR criticised this study due to the purity of the preparation used (~97%), but this argument is considered invalid because there are no indications for impurities that would cause such a substantial higher toxicity of the substance tested.

Data that would allow the estimation of a TCA for γ-HCH are not available, but in view of the proposed 25-fold reduction of the newly proposed TDI compared with the previous one, it is obviously not justified to maintain the previously derived TCA, and thus the TCA for γ-HCH has to be estimated via route-to-route extrapolation. Considering that the compound is well-absorbed via both the oral and the inhalation route, assuming similar end-points, and assuming an adult body weight of 70 kg and a breathing volume of 20 m^3 per day, the corresponding TCA is 0.14 $\mu g/m^3$ (TDI×[70÷20]).

δ-HCH

The one study (acute oral toxicity for rats) available for δ-HCH does not provide data which allow the derivation of a TDI.

6.3.4. EVALUATION BY OTHER ORGANISATIONS

α-HCH

ATSDR (1999) estimated a chronic-duration MRL (minimum risk level) for oral exposure of 8 µg/kg bw/day based on a NOAEL of 0.8 mg/kg bw/day for liver effects in rats with a UF of 100.

Hassauer et al. (1993) advised the Bundes Umwelt Amt (Germany; BUA) to "Orienterungswerte" for long-term oral exposure of 0.1 µg/kg bw/day and 0.17 µg/m^3 for long-term inhalation exposure. The oral value is based on the NOAEL of 0.1 mg/kg bw/day for hepato- and nephrotoxicity in a subchronic oral study with rats, with a UF of 1000; the inhalation value is taken from the γ-HCH evaluation with an additional UF of 3.3 (100 × 3.3 in total; reasoning for the additional UF is not given).

Neither ATSDR (1999) nor US-EPA (IRIS 2000) derived MRLs or RfCs for inhalation exposure, due to lack of reliable data.

β-HCH

ATSDR (1999) estimated an intermediate duration MRL (exposure during 15-365 days) for oral exposure of 0.6 µg/kg bw/day, based on a LOAEL of 0.18 mg/kg bw/day for liver effects in rats with a UF of 300.

Hassauer et al. (1993) advised the BUA to "Orienterungswerte" for long-term oral exposure of 0.02 µg/kg bw/day and 0.03 µg/m^3 for long-term inhalation exposure. The oral value is based on the NOAEL of 0.02 mg/kg bw/day for hepato- and nephrotoxicity in a subchronic oral study with rats, with a UF of 1000, the inhalation value is taken from the γ-HCH evaluation with an additional UF of 16 (100×16; reasoning for the additional UF is not given).

Neither ATSDR (1999) nor US-EPA (IRIS 2000) derived MRLs or RfCs for inhalation exposure, due to lack of reliable data.

γ-HCH

ATSDR (1999) estimated an intermediate duration MRL for oral exposure of 0.01 µg/kg bw/day based on a LOAEL of 12 µg/kg bw/day for immunological/lymphoreticular effects in female mice in a 24-week feeding study (Meera et al. 1992) with a UF of 1000 (including a UF of 10 to compensate for the use of a LOAEL).

JMPR (1997) derived a temporary ADI (acceptable daily intake) of 0–1 µg/kg bw/day based on the NOAEL of 0.5 mg/kg bw/day for hepatotoxic effects and decreased survival in a two-year toxicity/carcinogenicity study in rats; a UF of 500 was applied. JMPR criticised the immunotoxicity study of Meera et al. (1992) due to the disputable purity of the γ-HCH used (cf. paragraph 6.3.3), and derived the ADI as "temporarily" awaiting confirmatory studies of the immunotoxicity in mice.

US-EPA (IRIS 2000) assigned in 1988 only γ-HCH a RfD (oral reference dose) of 0.3 µg/kg bw/day based on the NOAEL of 0.33 mg/kg bw/day for liver and kidney toxicity in an oral subchronic study with rats, applying a UF of 1000.

Hassauer et al. (1993) advised the BUA to "Orienterungswerte" for long-term oral exposure of 0.33 µg/kg bw/day and 0.56 µg/m^3 for long-term inhalation exposure. The oral value is based on the NOAEL of 0.33 mg/kg bw/day for hepato- and nephrotoxicity in a subchronic oral study with rats, with a UF of 1000. The inhalation value is taken from the NOAEL of 0.1 mg/m^3 for hepato- and nephrotoxicity in a subchronic inhalation study with rats, converted to oral intake by rats (resulting in 16 µg/kg bw/day), applying a UF of 100 for human intake (resulting in 0.16 µg/kg bw/day), and reconverting to human inhalation (resulting in 0.56 µg/m^3).

δ-HCH

Other organisations did not derive a TDI (or any other limit value) for δ-HCH.

Tolerable daily intakes for prolonged exposure to α-, β-, and γ-HCH as estimated by ATSDR, BUA, US-EPA and JMPR

Compound	ATSDR (1999) [1])	JMPR (1997) [1])	BUA (1993)		US-EPA (1988) [1])
	Oral	Oral	Oral [2])	Inhalation [2])	Oral
α-HCH	8 [3])	-	0.1	0.17	-
β-HCH	0.6 [4])	-	0.02	0.03	-
γ-HCH	0.01 [4])	0 - 1 [5])	0.33	0.56	0.3 [6])

Oral values: µg/kg bw/day; inhalation values: µg/m^3

[1]) ATSDR, JMPR and US-EPA did not derive limit values for (prolonged) inhalation exposure
[2]) Orienterungswert (for long-term oral and inhalation exposure, respectively)
[3]) MRL (minimum risk level) for chronic duration (365 days and longer)
[4]) MRL (minimum risk level) for intermediate duration (15-365 days)
[5]) Temporary ADI (acceptable daily intake)
[6]) RfD (reference dose)

6.3.5. BACKGROUND EXPOSURE

In 1991 Vermeire et al. estimated the background exposure at 0.03 µg/kg bw/day (at most) for α- and γ-HCH, and 0.014 µg/kg bw/day (at most) for β-HCH, based on Dutch food survey studies reported in 1987 Greve et al. 1987).
IPCS (1991, 1992) reports values of 0.03 µg/kg bw/day for α-HCH and 0.006 µg/kg bw/day for γ-HCH (data from Britain in the late 1970s).
Hassauer et al. (1993) presents values of 1-3 µg/kg bw/day for the sum of all isomers except γ-HCH, and at 1-5 µg/kg bw/day for γ-HCH.
ATSDR (1999) estimated the intake in the US at 8, <1 and 2 ng/kg bw/day for α-, β-, and γ-HCH, respectively (data obtained in de mid-1980s).
Obviously the various estimations differ considerably. As these estimates date at best from the mid-1980s, current background exposures may be expected to be lower due to the banned or drastically limited use of HCHs. Since Vermeire et al. (1991) already presented their values noting that these were the upper limits, the current background exposure is estimated to be < 0.03, < 0.01 and < 0.03 µg/kg bw/day for α-, β-, and γ-HCH, respectively.

Summary of estimated background exposures

Reference	α-HCH	β-HCH	γ-HCH
Vermeire et al. (1991)	≤ 0.03	≤ 0.014	≤ 0.03
IPCS (1991, 1992)	0.03	-	0.006
Hassauer et al. (1993)	1-3	1-3	1-3
ATSDR (1999)	0.008	< 0.001	0.002

6.3.6. CONCLUSION

Compound	TDI	TCA	Background exposure
α-HCH	1	0.25	< 0.03
β-HCH	0.02	-	< 0.01
γ-HCH	0.04	0.14	< 0.03

TDI: tolerable daily intake (oral exposure); µg/kg bw/day
TCA: tolerable concentration in air (inhalation exposure); µg/m^3
Background exposure; µg/kg bw/day

6.3.7. REFERENCES

Amyes SJ (1990):
Lindane: combined oncogenicity and toxicity study by dietary administration to Wistar rats for 104 weeks.
Unpublished report LSR no. 90/CIL002/0839 from Life Sciences Research Ltd., UK *(cited in JMPR 1997)*.

ATSDR (1999):
Toxicological profile for alpha-, beta-, gamma- and delta-hexachlorocyclohexane (update).
US Dept. of Health & Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta (GA), USA.

Barrón S, Serratosa J & Tusell JM (1995):
Regulation of c-*fos* expression by convulsants and hexachlorocyclohexane isomers in primary cultures of cortical neurons.
J Neurochem 64, 1708-1714 *(cited in ATSDR 1999)*.

Greve PA, Harten DC van, Heusinkveld HAG, Janssen GE, Verschraagen C & Tonkelaar EM den (1987):
Bestrijdingsmiddelen in duplicaat 24-uurs voedingen, deelrapport I: organochloorbestrijdingsmiddelen.
National Institute of Public Health and the Environment, RIVM-report no. 388474001, 1987; Bilthoven, The Netherlands.

Hassauer M, Kalberlah F, Oltmans J & Schneider K (1993):
Basisdate Toxikologie für umweltrelevante Stoffe zur Gefahrenbeurteilung bei Altlasten.
Umwelt Bundes Amt, Berichte 4/93, Erich Schmidt Verlag, Berlin, Germany.

IARC (1987):
Overall Evaluations of Carcinogenicity, Suppl. 7 - an updating of IARC Monographs volumes 1 to 42.
International Agency for Research on Cancer, World Health Organization, Lyon, France.

IPCS (1992):
Environmental Health Criteria 123 - Alpha- and beta-hexachlorocyclohexanes.
International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland.

IPCS (1991):
Environmental Health Criteria 124 - Lindane.
International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland.

IRIS (2000):
Integrated Risk Information System (IRIS): summaries for alpha-, beta- and gamma-hexachlorocyclohexanes (all three dated May 1998).
US Environmental Protection Agency, Washington DC, USA.

JMPR (1997):
Pesticide residues in food - evaluations 1997, part II - toxicological and environmental.
Joint FAO/WHO Meeting on Pesticide Residues, Roma (Italy) / Geneva (Switzerland).

Meera P, Rao PR, Shanker R & Tripathi O (1992):
Immunomodulatory effects of γ-HCH (lindane) in mice.
Immunopharmacol Immunotoxicol 14, 261-282.

Vermeire TG, Apeldoorn ME van, Fouw JC de & Janssen PJCM (1991):
Voorstel voor de humaan-toxicologische onderbouwing van C-toetsingswaarden.
National Institute of Public Health and the Environment, RIVM-report no. 725201005, February 1991; Bilthoven, The Netherlands.

Profile compilation:	*A.J. Baars*
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6.4. CARBAMATES: CARBARYL AND CARBOFURAN

6.4.1. CARBARYL

6.4.1.1. INTRODUCTION

Carbaryl was evaluated within the scope of this project as a compound of the group of carbamate pesticides by Vermeire et al. in 1991. A TDI (tolerable daily intake) of 10 μg per kg bw (body weight) per day for oral intake was derived. This value is the ADI (acceptable daily intake) of carbaryl derived by the WHO in 1973. A TCA (tolerable concentration in air) was not derived.
For the update additional literature, published since 1991, was reviewed. This included a review of the IPCS (1994), and evaluations of the FAO/WHO Joint Meeting of Pesticides Residues (JMPR 1997, JMPR draft 2000).
Carbaryl is the common name for 1-naphtyl-N-methyl carbamate. It is also known under various trade names, as carbaryl is produced and used as a pesticide. Carbaryl is used as a broad spectrum contact and ingestion insecticide to control various pests. It is used for protection of cotton (about 40 % of total), vegetables and fruits. Besides it is used on cattle, poultry and pets to control insects, ticks and lice (IPCS 1994).
It can be expected that the natural occurrence in soil is negligible. A diffuse type of soil contamination with carbaryl can be found due to it use in agricultural areas. Higher concentrations can be expected in dumps of industrial and household waste.

6.4.1.2. TOXICOLOGY

Toxicokinetics

Studies with laboratory animals have demonstrated that 50 to 80% of the dose is rapidly absorbed after inhalation and oral intake. Absorption in the stomach is low compared with that through the intestines, but some vehicles facilitate the rate of gastrointestinal absorption.
Dermal absorption was studied in human volunteers. The results showed almost complete penetration of carbaryl. After a few days about 60% of the applied dose is percutaneously absorbed. Some solvents can also facilitate dermal penetration.
After a single oral dose given to rats, carbaryl is found in blood, muscle, brain, spleen and liver. Following chronic exposure, however, carbaryl was only found in intestines, liver, and kidney.
Carbaryl is biotransformed in the liver. By hydrolysis 1-naphtol is formed and in addition various hydroxy-carbaryl compounds are formed by hydroxylation. The principal metabolite in humans is 1-naphtol. The intermediates are conjugated with sulphates and glucuronides, producing water soluble compounds. *In vitro* data indicate that the cytochrome P450 enzyme system is involved in the metabolism of carbaryl.
The water soluble conjugates of carbaryl are excreted in the urine. A small percentage is excreted in faeces. In laboratory animals more than 90% of the initial oral dose is eliminated within 3 days.
Studies with lifestock have demonstrated that excretion of carbaryl and its metabolites in milk and eggs is less than 1% of the initial dose (IPCS 1994, JMPR 1997).

Toxicity

Acute poisoning
Acute toxicity was investigated in experimental animals tests after oral and inhalation exposure. Carbaryl is considered moderately toxic. The toxic signs observed were typical for cholinesterase inhibition, such as salivation within minutes after administration, and death within a few days. The same effects were noticed in laboratory animals after inhalation exposure.
The clinical picture of carbaryl intoxication of humans results from accumulation of acetylcholinesterase. The symptoms include salvation, broncho-restriction, abdominal cramps and bradycar-

dia. At low doses the effects are reversible. At high dose levels effects on the nervous system, like anxiety, convulsions, coma, and eventually death, can also be noticed (IPCS 1994).

Genotoxicity and carcinogenicity

IPCS (1994) provided an overview of the results of genotoxicity tests of carbaryl. These tests include various endpoints *in vitro* and *in vivo*. Virtually all these tests demonstrated negative results, and it was concluded that carbaryl is not a genotoxic compound.

In a two year toxicity/carcinogenicity study with CD-1 mice, carbaryl (administered via the diet) was found to be carcinogenic even at the lowest dose-level (100 ppm, equal to 15 mg/kg bw/day). The incidence of renal tubular cell neoplasia and vascular tissue neoplasia (haemangiosarcomas) was increased. The LOAEL in this study was 15 mg/kg bw/day. In a chronic study with rats an increased incidence was observed for thyroid follicular cell adenoma and transition cell hyperplasia in the kidney. An epidemiological study on carbaryl production workers exposed for a period of maximally 18 years showed no increase in cancer mortality (IPCS 1994, JMPR 1997).

Subchronic and chronic toxicity

Carbaryl was tested in semi-chronic and chronic oral studies in various laboratory animals. Effects on the kidney in dogs appeared to be at the most sensitive effects with a NOAEL of 1.8 mg/kg bw/day in a one year toxicity study. In a one year study with rats a NOAEL of 2 mg/kg bw/day was reported for effects on thyroid and the reproductive organs of both male and female animals. In developmental studies a NOAEL of 2 mg/kg bw/day was reported with birth defects. Maternal toxicity was observed at a LOAEL of 5 mg/kg bw/day.

Inhalation exposure was investigated in a few semichronic studies. Cholinergic reactions were observed in cats with a NOAEC of 30 mg/m^3 after an exposure period of 30 days, and 16 mg/m^3 after an exposure period of 120 days. The dosing regime was not reported. In a semichronic study with rats (7 hours per day for 5 days per week) a NOAEC of 10 mg/m^3 was reported for carbaryl-containing dust (IPCS 1994).

In controlled studies with human volunteers oral single doses of about 2.8 mg/kg bw produced moderate symptoms of cholinesterase inhibition. At 0.13 mg/kg bw/day for a period of six weeks a small increased ratio of amino acid nitrogen to creatinine in the urine was found. This effect might represent a renal effect, but the change was reversible. No inhibition or other effects were noticed at 0.06 mg/kg bw/day (JMPR 1997).

6.4.1.3. EVALUATION

Carbaryl is not considered a genotoxic compound. Consequently a TDI can be derived from a NOAEL and uncertainty factors (UFs).

In the draft reassessment of the JMPR (2000) an ADI is derived of 3 µg/kg bw/day, using a LOAEL of 15 mg/kg bw/day in the long term toxicity-carcinogenicity study in mice, with a UF of 100 for inter- and intraspecies variation, and a factor of 10 for extrapolation of a LOAEL. An additional factor of 5 was used for its carcinogenicity in this animal study. This approach is adopted for the derivation of the TDI. The available human data support this value, as a NOAEL of 0.06 mg/kg bw/day for carbaryl was found in a six-week volunteer study. At slightly higher doses cholinesterase inhibition was observed which was reversible. The difference between this human NOAEL and the TDI on the basis of animal studies is a factor of 20. This factor can be considered sufficient for the variation of human sensitivity and the extrapolation to a life time exposure, as carbaryl is rapidly eliminated.

For inhalation exposure the NOAEC of 10 mg/m^3 from semichronic exposure of rats is taken. Corrected for continuous exposure this is equivalent to 3 mg/m^3. A UF for extrapolation to chronic exposure is not considered necessary, as the substance is rapidly eliminated, but a UF of 3 is to be used for the restricted database. Using a factor of 100 for inter- and intraspecies variation a TCA of 10 µg/m^3 for carbaryl is derived.

6.4.1.4. EVALUATIONS BY OTHER ORGANISATIONS

The US-EPA derived a RfD of 0.1 mg/kg bw/day, based on a NOEL of 200 ppm in the diet (9.6 mg/kg bw/day) in a chronic rat feeding study. The critical effects were kidney and liver toxicity. A UF of 100 was used to account fore interspecies and intrahuman variability (IRIS 2000).
The JMPR (1997) derived an ADI for humans of 3 µg/kg bw/day in 1996. This value was based on a LOAEL of 15 mg/kg bw/day in the carcinogenicity study in mice, using a UF of 100 for inter- and intraspecies variation, 10 for extrapolation to a NOAEL, and an additional factor of 5 for the incidence of vascular tumours. The draft report of 2000 is to be evaluated later.

6.4.1.5. BACKGROUND EXPOSURE

It can be expected that background exposure of the general population to carbaryl is resulting from the ingestion of foods. IPCS (1994) presented data of the intake of carbaryl from food in the USA; the latest estimates are based on the period of 1980 to 1984 and added up to 0.12 mg/day, which equals 2 µg/kg bw/day. This estimate is to be used for The Netherlands, but it should be noted that the value might be outdated.

6.4.1.6. CONCLUSION

TDI: 3 µg/kg bw/day; TCA: 10 µg/m^3; background exposure in The Netherlands: 2 µg/kg bw/day.

6.4.2. CARBOFURAN

6.4.2.1. INTRODUCTION

Carbofuran was evaluated within the scope of this project as a compound of the group of carbamates pesticides by Vermeire et al. in 1991. A TDI (tolerable daily intake) of 10 µg per kg bw (body weight) per day for oral intake was derived. This value is the ADI (acceptable daily intake) of carbofuran derived by the WHO in 1980. A TCA (tolerable concentration in air) was not derived.
For the update additional literature, published since 1991, was reviewed. This included a re-evaluation of the JMPR (1997) and the WHO (1996, 1998).
Carbofuran is the common name for 2,3-dihydro-2,2-dimethylbenzofuran-7-yl-methyl carbamate. It is also known under various trade names, as carbofuran is produced and used as a pesticide. It is an acaricide, insecticide, and nematocide, and used for protection of various vegetables, cereals, and fruits.
It can be expected that the natural occurrence of carbofuran in soil is negligible. A diffuse type of soil contamination can be found due to it use in agricultural areas. Higher concentrations can be expected in dumps of industrial and household waste.

6.4.2.2. TOXICOLOGY

Toxicokinetics

Studies with laboratory animals indicate that carbofuran is readily absorbed after oral intake.
Data on absorption after inhalation or dermal application could not be found. Carbofuran is rapidly metabolised to hydroxy-(methyl)-carbofuran. Besides it can be biotransformed into 7-phenol, which is further metabolised to various conjugates. Analyses of residues in rats have demonstrated that the metabolism of carbofuran takes place in the liver; the metabolites are predominantly excreted via the urine. A small percentage of the total excretion of the parent compound and metabolites can be found in the faeces. In rats and mice most of the dose is eliminated within 24 hours (WHO 1996, JMPR 1997).

Toxicity

Acute poisoning
In experimental animals acute toxicity was determined after oral and inhalation exposure. Carbofuran is considered highly toxic. The toxic signs observed were typical for cholinesterase inhibition, such as salivation, cramps and trembling, and sedation within minutes after administration, and eventually death (JMPR 1997).
In humans involved in the application and formulation of carbofuran the same effects of cholinesterase inhibition are reported: following small doses the effects were reported to be mild and reversible, whereas at higher doses convulsions and coma were observed. In a study with human volunteers the same type of mild effects were noticed at a single dose of 0.1 mg/kg bw/day. No effects were observed at 0.05 mg/kg bw/day (WHO 1996).
Genotoxicity and carcinogenicity
JMPR (1997) presented a review of the tests for the genotoxicity of carbofuran. In virtually all *in vitro* test systems the results were negative. Positive results are only reported for sister chromatid exchange in Chinese hamster ovary cells and mouse lymphoma cells. In *in vivo* test systems, the results were negative.
In a two year study with rats and mice no treatment-related pathological changes were observed, and there was no evidence of compound-related increases in tumour incidences.
On the basis of the available studies it was concluded by WHO (1996) that carbofuran appears to be neither carcinogenic nor mutagenic.
Subchronic and chronic toxicity
In a 14 day oral study and a 13 week oral study with beagle dogs, effects indicating cholinesterase inhibition were noticed at the lowest dose tested: 0.45 mg/kg bw/day. In a subsequent four-week study no effects were observed at 5 ppm in the diet (equivalent to 0.22 mg/kg bw/day). In a one-year study in beagle dogs the cholinesterase inhibition was noticed with a marginal effect level of 10 ppm in the diet (equivalent to 0.3 mg/kg bw/day). Other adverse effects were not observed at this dose level. It can therefore be concluded that 0.22 mg/kg bw/day can be used as the NOAEL for cholinesterase inhibition for chronic exposure in dogs. US-EPA (IRIS 2000) derived from the latter study a NOEL of 0.5 mg/kg bw/day (20 ppm in the diet).
In a two year oral study with mice and rats the NOAEL for cholinesterase inhibition in erythrocytes was reported to be 1 mg/kg bw/day. In a similar study with mice cholinesterase inhibition in the brain was observed; here the NOAEL was 3 mg/kg bw/day.
In reproduction studies with rats the NOAELs for reproductive and developmental effects were in the range of 1.2 to 1.7 mg/kg bw/day, for both parental and pup toxicity. Effects reported refer to body weight and clinical signs of neurotoxicity, maternal inhibition of cholinesterase in blood and liver, and some evidence of delayed pup development. In a developmental toxicity study with rabbits a NOAEL of 0.6 mg/kg bw/day was reported for maternal toxicity (WHO 1996, JMPR 1997).
No reports of inhalation or dermal exposure studies with carbofuran could be located.

6.4.2.3. EVALUATION

Carbofuran is not considered a genotoxic compound. Consequently a TDI can be derived on the basis of a NOAEL and uncertainty factors (UFs).
The evaluation is based on the proposal for the ADI of carbofuran as derived by the JMPR (1997) and WHO (1998); the most sensitive adverse effect of carbofuran exposure was considered to be cholinesterase inhibition. The NOAEL for this effect is 0.22 mg/kg bw/day in the most sensitive animal species, the dog, for both short term and long term exposure. A UF of 100 is to be applied for inter- and intraspecies variation, which results in a TDI for carbofuran of 2 µg/kg bw/day.
Due to lack of data a TCA can not be derived.

6.4.2.4. EVALUATIONS BY OTHER ORGANISATIONS

US-EPA derived a RfD of 5 µg/kg bw/day, based on a NOEL of 0.5 mg/kg bw/day in a one-year dog feeding study. The evaluated effects were RBC and cholinesterase inhibition, and testicular and uterine effects. A UF of 100 was used to account fore inter- and intraspecies differences (IRIS 2000).
The JMPR reviewed the toxicology of carbofuran in 1996. An ADI of 2 µg/kg bw/day was allocated on the basis of the NOAEL for erythrocyte acetylcholinesterase inhibition of 0.22 mg/kg bw/day in a four-week study in dogs. A UF of 100 was applied for inter- and intraspecies variation (JMPR 1997).
The WHO proposed a Drinking Water Quality Guideline of 7 µg/L. It was based on an ADI of 2 µg/kg bw/day that was derived at the re-evaluation by the JMPR in 1996 (WHO 1998).

6.4.2.5. BACKGROUND EXPOSURE

It can be expected that background exposure of the general population to carbofuran is resulting from the ingestion of foods. The JMPR (1999) calculated the daily intake of carbofuran via food by Europeans to be 0.037 mg/day, this equals to 0.6 µg/kg bw/day. This estimate is to be used for The Netherlands.

6.4.2.6. CONCLUSION

TDI: 2 µg/kg bw/day; TCA: not derived due to lack of data; background exposure in The Netherlands:0.6 µg/kg bw/day

6.4.3. SUMMARY

Compound	TDI	TCA	Background exposure
Carbaryl	3.0	10	2.0
Carbofuran	2.0	n.d.	0.6

TDI: tolerable daily intake (oral exposure); µg/kg bw/day
TCA: tolerable concentration in air (inhalation exposure); µg/m^3
Background exposure; µg/kg bw/day
n.d.: not derived (due to lack of data)

6.4.4. REFERENCES

IPCS (1994):
Environmental Health Criteria 153: Carbaryl.
World Health Organization, Geneva, Switzerland.

IRIS (Integrated Risk Information System, US-EPA), 2000:
- Summary for carbaryl; oral RfD assessment dated March 1988.
- Summary for carbofuran; oral RfD assessment dated September 1987.
US Environmental Protection Agency, Washington DC, USA.

JMPR (1997):
Evaluations 1996, Part II, Toxicological.
WHO/PCS 97.1, World Health Organization, Geneva, Switzerland.

JMPR (1999):
Report Pesticide Residues in Food - 1999.
FAO plant production and protection paper 153, Rome, Italy.

JMPR (2000):
Draft Working paper A for a joint FAO/WHO meeting on pesticide residues: carbaryl.
World Health Organization, Geneva, Switzerland; September 2000.

Vermeire TG, Apeldoorn ME van, Fouw JC de & Janssen PJCM (1991):
Voorstel voor de humaan-toxicologische onderbouwing van C-toetsingswaarden.
National Institute of Public Health and the Environment, RIVM-report no. 725201005, February 1991; Bilthoven, The Netherlands.

WHO (1996):
Guidelines for drinking-water quality, 2nd ed. Volume 2, Health criteria and other supporting information.
World Health Organization, Geneva, Switzerland.

WHO (1998):
Guidelines for drinking-water quality, 2nd ed. Addendum to Volume 1, recommendations
World Health Organization, Geneva, Switzerland.

Profile compilation:	*R.M.C. Theelen*
Profile review:	*A.J. Baars*
Final review:	*A.G.A.C. Knaap (chair), G.J.A. Speijers, T.G. Vermeire, P.J.C.M. Janssen*
Date:	*30-10-2000*

6.5. DITHIOCARBAMATES: MANEB

6.5.1. INTRODUCTION

Maneb was evaluated as a compound of the group of dithiocarbamates pesticides within the scope of this project by Vermeire et al. in 1991. They presented a TDI (tolerable daily intake) of 50 µg per kg bw (body weight) per day for oral intake of the ethylenebisdithiocarbamates maneb, mancozeb and zineb. The value was adopted from the ADI (acceptable daily intake) of maneb derived by the JMPR in 1980. It was derived from a NOAEL of 12.5 mg/kg bw/day in a rat study, with a UF (uncertainty factor) of 250. In the Dutch legal framework for the evaluation of soil contamination, however, a TDI of 20 µg/kg bw/day for maneb is to be used (Staatscourant, 24 February 2000). Vermeire et al. did not derive a TCA (tolerable concentration in air).
For the update additional literature, published since 1991, was reviewed. This included a review of JMPR (1994), and CICAD (1999).
Maneb is the common name for ethylene-bis-(dithiocarbamate)-manganese. Since maneb is a pesticide, it is also known under many trade names. Maneb is primarily used as a fungicide for application on edible crops (CICAD 1999).
It can be expected that the natural occurrence in soil is negligible. A diffuse type of soil contamination with maneb can be found due to it use on agricultural areas. Higher concentrations can be expected in dumps of pesticide waste.

6.5.2. TOXICOLOGY

Toxicokinetics

Studies with laboratory animals have demonstrated that 50 to 70% of the dose is absorbed after oral intake. Dermal absorption in animals is less than 10%. In the absorption process maneb is split up, and manganese is excreted separately. The carbamate residue is then found in bone, blood, muscle, and most other organs (WHO 1996). In rats maneb is metabolised into ethylenethiourea or ethylenediamine by separation of carbon disulfide. Ethylenethiourea is biotransformed into oxalic acid and urea, whereas ethylenediamine is converted to formate. Almost 90% of all absorbed maneb was eliminated in the urine within 24 hours, most of it as metabolites; only a small percentage is excreted as the parent compound (JMPR 1994).

Toxicity

Acute poisoning
Tests of acute toxicity were performed in experimental animals using oral and inhalation exposure. Maneb is considered moderately toxic. The toxic signs observed were ataxia, hyperactivity followed by inactivity, loss of muscle tone, and alopecia.
Studies with human volunteers indicate that maneb is a dermal sensitizer. Exposed humans developed exanthema and renal failure, but in all cases they fully recovered (WHO 1996).
Genotoxicity and carcinogenicity
JMPR (1994) provided an overview of the results of genotoxicity tests of maneb. These tests include gene mutation assays, *in vivo* chromosomal abberation tests, DNA-repair tests and sister chromatid exchange. Nearly all tests demonstrated negative results, and it was concluded by the JMPR that maneb is not a genotoxic compound.
Maneb was found to be carcinogenic in mice. The incidence of hepatocellular adenomas was significantly increased after 79 weeks at dietary concentrations of 2400 ppm of technical maneb (90% purity), equivalent to a dose of 45 mg/kg bw/day. In a long term study with rats, however, there was no evidence of carcinogenicity (JMPR 1994).
Subchronic and chronic toxicity
Maneb was tested in semichronic and chronic oral studies, and reproduction and teratogenicity studies in various laboratory animal species. Effects on thyroid weight and thyroid follicular cell hyperplasia were most prominent in rats, dogs and monkeys. The NOAEL in these studies ranged from 5 to 20

mg/kg bw/day for the different species. In a semichronic study with rats a LOAEL of 10 mg/kg bw/day was reported, with a NOAEL of 5 mg/kg bw/day. In a chronic rat study, however, a NOAEL of 20 mg/kg bw/day was found for these thyroid effects.
Inhalation exposure was investigated in a nose-only subchronic and semichronic study with rats, 6 hours per day, for five days a week. Only body weight was affected with a NOAEC of 10 mg/m^3 in the semichronic study, but no other compound-related effects were found by the highest dose of 100 mg/m^3 tested in both studies. A study of the metabolite ETU in the urine indicated that maneb was rapidly eliminated, and the treated animals fully recovered within a short time (JMPR 1994).
Studies with maneb in humans could not be located.
Mechanism of action
Studies of dithiocarbamates and the thyroid showed that exposure resulted in a reduced assimilation of iodine. It was concluded that dithiocarbamates or its metabolites possess an anti-thyroid effect and inhibit the synthesis of thyroxin (IPCS 1988).

6.5.3. EVALUATION

Maneb is not considered a genotoxic compound. Consequently a TDI can be derived from a NOAEL and UFs.
Animal data indicate a NOAEL for semichronic oral exposure of 5 mg/kg bw/day for the most sensitive endpoint, i.e., effects on the thyroid. The NOAEL in a chronic study for these effects, however, was 20 mg/kg bw/day (which may have to do with the rapid elimination of maneb and/or with species and strain differences), and thus an additional UF for extrapolation to chronic exposure is not necessary. Using a UF of 100 for intra- and interspecies variation results in a TDI of 50 µg/kg bw/day.
For inhalation exposure the NOAEC of 10 mg/m^3 from semichronic exposure of experimental animals is taken as the pivotal value. Corrected for continuous exposure this equals to 1.8 µg/m^3. Maneb was rapidly eliminated and full recovery was noticed at the end of the exposure. Consequently an additional UF to extrapolate to chronic exposure is not necessary; a UF of 100 is to be used for inter- and intraspecies variation to establish the limit value. This results in a TCA for maneb of 18 µg/m^3.

6.5.4. EVALUATIONS BY OTHER ORGANISATIONS

The US-EPA derived a RfD for maneb of 5 µg/kg bw/day. It was based on a NOEL of 5 mg/kg bw/day in a 6 months monkey feeding study, the critical effect was increased thyroid weight. A UF of 100 was used to account fore interspecies and intraspecies variability, and 10 for extrapolation from a subchronic study to chronic exposure (IRIS, revised 1992).
The JMPR (1994) derived an ADI for maneb of 50 µg/kg bw/day, based on a NOAEL of 5 mg/kg bw/day for thyroid effects in rats, using a UF of 100 for inter- and intraspecies variation. It was noted, however, that for maneb a group-ADI of 30 µg/kg bw/day should be used for humans in a mixture with mancozeb, metiram, and zineb, because of the similarity of chemical structures of these compounds and comparable toxic profiles. The derivation of this value was not reported.

6.5.5. BACKGROUND EXPOSURE

It can be expected that the background exposure of the general population to maneb is resulting from the ingestion of vegetable foods. According to Vermeire et al. (1991) the intake of maneb, mancozeb and zineb is 0.75 µg/kg bw/day.
In The Netherlands residues of dithiocarbamates are generally less than 0.1 mg per kg product (VWS 1997), the available data do not provide an estimate for the intake of maneb solely. If a daily intake of 500 g vegetable foods is assumed this would lead to an intake of less than 50 µg dithiocarbamates per person per day, or 0.8 µg/kg bw/day of maneb, mancozeb and zineb. This is quite similar to the previous estimate of Vermeire et al. It is thus concluded that the estimate for the background exposure of total of maneb, mancozeb and zineb in The Netherlands of 0.75 µg/kg bw/day can be maintained.

6.5.6. CONCLUSION

Compound	TDI	TCA	Background exposure
Maneb	50	18	0.75

TDI: tolerable daily intake (oral exposure); µg/kg bw/day
TCA: tolerable concentration in air (inhalation exposure); µg/m^3
Background exposure; µg/kg bw/day

6.5.7. REFERENCES

CICAD (1999):
Manganese and its compounds. Concise International Chemical Assessment Document no 12.
World Health Organization, Geneva, Switzerland.

IPCS (1988):
Environmental Health Criteria 78 - Dithiocarbamate pesticides, ethylenethiourea, and propylenethiourea: a general introduction.
World Health Organization, Geneva, Switzerland.

JMPR (1994):
Evaluations 1993, Part II Toxicological; WHO ICPS 94.4.
World Health Organization, Geneva, Switzerland.

Vermeire TG, Apeldoorn ME van, Fouw JC de & Janssen PJCM (1991):
Voorstel voor de humaan-toxicologische onderbouwing van C-toetsingswaarden.
National Institute of Public Health and the Environment, RIVM-report no. 725201005, February 1991; Bilthoven, The Netherlands.

VWS (1997):
Veterinaire Milieuhygienewijzer
Veterinaire Hoofd Inspectie voor de Volksgezondheid, Rijswijk, The Netherlands.

WHO (1996):
Dithiocarbamates (maneb, zineb, mancozeb):
WHO/FAO data sheets on pesticides no. 94, WHO/PCS/DS/ 96.66.
World Health Organization, Geneva, Switzerland.

Profile compilation: *R.M.C. Theelen*
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Date: *31-10-2000*

6.6. TRIAZINES: ATRAZINE

6.6.1. INTRODUCTION

Atrazine was evaluated within the scope of this project as a compound of the group of triazine pesticides by Vermeire et al. in 1991. A TDI of 2 µg/kg bw/day for oral intake of all triazines was derived. This value was the ADI of simazine as derived by the US-EPA in 1989. It was based on a NOAEL of 0.52 mg/kg bw/day in a chronic rat study with an uncertainty factor (UF) of 300.
In the report of Vermeire et al. (1991) an ADI for atrazine of 5 µg/kg bw/day was presented that was derived by the US-EPA in 1988, and an ADI of 0.7 µg/kg bw/day that was derived by the WHO in 1987. In the Dutch legal framework for the evaluation of soil contamination finally a TDI of 5 µg/kg bw/day was presented for atrazine (Koolenbrander 1995).
For the update additional literature, published since 1991, was reviewed. This included a review of the IARC (1999), and an evaluation of the WHO (1996a, b).
According to IUPAC atrazine is the common name for 6-chloro-N-ethyl-N-isopropyl-1,3,5-triazine-2,4-diamine. It is also known under many trade names, as atrazine is produced and used as a broad spectrum herbicide. Atrazine is used for the control of weeds in crops of vegetables, fruits and forestry. In some countries its use is restricted (WHO 1996a, b; IARC 1999).
It can be expected that the natural occurrence in soil is negligible. A diffuse type of soil contamination with atrazine can be found due to it use on agricultural areas. Higher concentrations can be expected in dumps of pesticide waste.

6.6.2. TOXICOLOGY

Toxicokinetics

Atrazine is readily and almost completely absorbed from the gastrointestinal tract; in a single dose study with rats 80% was absorbed. Dermal absorption in the rat is limited, amounting to less than 2% after 20 hours exposure. The doses are mainly retained in the erythrocytes, liver, spleen and kidneys. Studies with rats including *in vitro* experiments with rat liver cells, and in pigs have demonstrated that atrazine is metabolised to dealkylated products. A minor pathway is the conjugation with glutathione. The parent compound and metabolites are excreted in the urine; a minor fraction can be found in the faeces. Unchanged atrazine has been found in the urine of workers occupationally exposed to atrazine (WHO 1996a, b).

Toxicity

Acute poisoning
Studies of acute toxicity are reported for experimental animals after oral, dermal, and inhalation exposure. Atrazine is considered moderately toxic. The toxic signs reported are initial excitation followed by depression with reduced respiratory rate, motor incoordination, spasms, and hyperthermia. Lung oedema and haemorrhages of liver and spleen have been observed at autopsy of animals.
Regarding intoxication of humans one lethal case is reported due to dermal exposure from spillage. In the cases of accidental exposure ocular and dermal irritation, chest pain, dizziness and nausea have been reported (WHO 1996b.)
Genotoxicity and carcinogenicity
In a large range of studies *in vivo* and *in vitro* in bacteria, *Drosophila* and mammalian cells, across all genotoxic endpoints (gene mutation assays, chromosomal effects assays, other genotoxic effects, and cell transformation assays), predominantly negative results were obtained. Tests for induction of micronuclei and SCEs in rats and mice dosed for 13 weeks with atrazine-containing drinking water were also negative (IARC 1999). The weight of evidence to date is that atrazine is not genotoxic, in line with the WHO who, based on available data, also concluded that atrazine is not a genotoxic compound (WHO 1996b).
Atrazine was tested for carcinogenicity after oral administration to rats and mice. Increased incidences of mammary tumours (fibroadenomas, adenocarcinomas) were observed only in intact female Spra-

gue-Dawley rats, not in Fischer 344 rats, CD-1 mice, and ovariectomized Sprague-Dawley rats; the NOAEL for this increased mammary tumour incidence was 0.5 mg/kg bw/day. Atrazine does not increase the incidences of other tumour types (IARC 1999). This species difference in the induction of mammary gland tumours can be explained by the finding that atrazine affects neuroendocrine pathways of the hypothalamus to accelerate the onset of reproductive senescence in female Sprague-Dawley rats but not in Fischer 344 rats. Besides, atrazine does not have intrinsic oestrogenic activity (IARC 1999).
IARC (1999) presented also an overview of carcinogenicity case-control studies of humans exposed to atrazine. The incidences of ovarian tumours, lymphatic and haematopoietic malignancies, and colon cancer were investigated in the various studies, but generally the results were inconclusive. IARC (1999) concluded to inadequate evidence in humans for the carcinogenicity of atrazine, and sufficient evidence in experimental animals. It was noted, however, that the mechanisms by which atrazine increases the incidence of mammary gland tumours in Sprague-Dawley rats is not relevant to humans.
In the evaluation it was stated that the mammary tumours in experimental animals associated with exposure to atrazine involve a hormonally mediated mechanism, but it was considered not relevant for humans (IARC 1999).
Subchronic and chronic toxicity
A two-week oral study in female rats showed that 100 mg atrazine/kg bw/day influenced serum concentrations of oestrogen, LH, prolactin, and progesteron.
In a one-year oral study with dogs various haematological effects with cardiac toxicity were reported with a NOAEL of 5 mg/kg bw/day.
In a chronic oral study with rats a NOAEL was reported of 70 mg/kg diet (equivalent to 3.5 mg/kg bw/day) based on reduced body weight and non-neoplastic effects. Haematological effects were observed at 1000 mg/kg in the diet.
In a two-generation rat reproduction study a statistically significant increase in relative testis weight was found in both generations, with a NOAEL of 0.5 mg/kg bw/day.
Atrazine was not teratogenic, but embryotoxicity was demonstrated with a NOAEL of 5 mg/kg bw/day (WHO 1996a).
Mechanism of action
Atrazine appears to disrupt the neuroendocrine pathways that regulate ovulation in Sprague-Dawley rats. Although the mechanism of this has yet not been elucidated, it probably does not involve a direct oestrogenic action of atrazine or binding of atrazine (and/or its metabolites) to the oestrogen receptor (IARC 1999).
Mild anaemia was sufficiently common to indicate that inhibition of haematopoiesis was an effect of atrazine treatment at higher doses used in toxicology studies: anaemia, altered haematological parameters and/or haematopoietic system toxicity were noted in short-term, subchronic, and chronic studies.
Other, albeit less-consistent non-neoplastic toxicological findings with dietary atrazine included possible testicular effects, i.e., small testes at high doses in a semichronic weanling rat study and a dog study, and small and/or cyanotic testes reported in one of a number of chronic rat studies.

6.6.3. EVALUATION

Atrazine is not considered a genotoxic compound. Consequently a TDI can be derived from a NOAEL and UFs.
Atrazine affects hormonal factors although it is not an endocrine disruptor itself. The increase in relative testis weight in male rats in the reproduction study, with a NOAEL of 0.5 mg/kg bw/day, is a pivotal effect in males, while in female rats (Sprague-Dawley only) an increase in mammary gland tumour incidence was observed, with a NOAEL of 0.5 mg/kg bw/day. These NOAELs of 0.5 mg/kg bw/day are used to derive a TDI for both sexes. A UF of 100 is to be used for interspecies and intraspecies variation. Thus a TDI of 5 μg/kg bw/day for atrazine is derived.

6.6.4. EVALUATIONS BY OTHER ORGANISATIONS

IARC classified atrazine in group 3 as *not classifiable as to its carcinogenicity to humans*, with inadequate evidence in humans for the carcinogenicity of atrazine, and sufficient evidence in experimental animals (IARC 1999).
The US-EPA derived a RfD for atrazine of 35 µg/kg bw/day. It was based on a NOEL of 70 ppm in the diet (3.5 mg/kg bw/day) in a chronic rat feeding study. The critical effect was decreased body weight. A UF of 100 was used to account fore interspecies and intrahuman variability (IRIS, revised 1993).
The WHO derived a drinking water guideline of 2 µg/L for atrazine on the basis of a TDI of 0.5 µg/kg bw/day. This value was derived from a NOAEL of 0.5 mg/kg bw/day from a carcinogenicity study with rats with a UF of 100 for inter- and intraspecies extrapolation and an additional factor of 10 to reflect potential neoplasia (WHO 1996a).

6.6.5. BACKGROUND EXPOSURE

No data about the exposure of the general population of The Netherlands to atrazine could be located. Due to its use and its chemical properties it can be expected that food is the major source of exposure of the general population to atrazine. According to IARC (1999) no atrazine residues were found in a survey of various foods (with a limit of detection of 50 µg/kg). It is therefore concluded that the background exposure to atrazine is negligible.

6.6.6. CONCLUSION

Compound	TDI	Background exposure
Atrazine	5	negligible

TDI: tolerable daily intake (oral exposure); µg/kg bw/day
Background exposure; µg/kg bw/day

6.6.7. REFERENCES

IARC (1999):
Some chemicals that cause tumours of the kidney or urinary bladder in rodents and some other substances.
IARC Monographs Volume 73, International Agency for Research on Cancer, Lyon, France.

Koolenbrander J (1995):
Urgentiesystematiek van bodemsanering: de handleiding.
SDU, Den Haag, The Netherlands.

Vermeire TG, Apeldoorn ME van, Fouw JC de & Janssen PJCM (1991):
Voorstel voor de humaan-toxicologische onderbouwing van C-toetsingswaarden.
National Institute of Public Health and the Environment, RIVM-report no. 725201005, February 1991; Bilthoven, The Netherlands.

WHO (1996a):
Guidelines for drinking-water quality, 2nd ed. Volume 2, Health criteria and other supporting information.
World Health Organization, Geneva, Switzerland.

WHO (1996b):
Atrazine.
WHO/FAO data sheets on pesticides no. 82, WHO/PCS/DS/ 96.82.
World Health Organization, Geneva, Switzerland.

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Profile review: *A.J. Baars*
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Date: *01-11-2000*

Appendix 7 Other organic compounds

7.1. PYRIDINE

7.1.1. EVALUATION

For the re-evaluation of pyridine, the following national and international reviews were consulted:
- Toxicological profiles of the US Agency for Toxic Substances and Disease Registry;
- IRIS files of the US Environmental Protection Agency;
- Environmental Health Criteria of the WHO's International Programme on Chemical Safety;
- Evaluations of carcinogenicity of the WHO's International Agency for Research on Cancer;
- Criteria documents of the RIVM;
- Other relevant information available in the compounds database of the library of the RIVM's Centre for Substances & Risk Assessment.

New relevant information regarding pyridine could not be located. Consequently the MPRs as derived by Vermeire et al. in 1991 are to be maintained.

Compound	TDI	TCA	Background exposure	Odour threshold
Pyridine	1.0	120	*)	120

TDI: tolerable daily intake (oral exposure); µg/kg bw/day
TCA: tolerable concentration in air (inhalation exposure); µg/m^3
Background exposure; µg/kg bw/day
Odour threshold; µg/m^3
*) No data available; assumed to be negligible

7.2.2. REFERENCES

Vermeire TG, Apeldoorn ME van, Fouw JC de & Janssen PJCM (1991):
Voorstel voor de humaan-toxicologische onderbouwing van C-toetsingswaarden.
National Institute of Public Health and the Environment, RIVM-report no. 725201005, February 1991; Bilthoven, The Netherlands.

Author: A.J. Baars
Date: 01-06-2000

7.2. TETRAHYDROFURAN

7.2.2. EVALUATION

For the re-evaluation of tetrahydrofuran, the following national and international reviews were consulted:

- Toxicological profiles of the US Agency for Toxic Substances and Disease Registry;
- IRIS files of the US Environmental Protection Agency;
- Environmental Health Criteria of the WHO's International Programme on Chemical Safety;
- Evaluations of carcinogenicity of the WHO's International Agency for Research on Cancer;
- Criteria documents of the RIVM;
- Other relevant information available in the compounds database of the library of the RIVM's Centre for Substances & Risk Assessment.

New relevant information regarding tetrahydrofuran could not be located. Consequently the MPRs as derived by Vermeire et al. in 1991 are to be maintained.

Compound	TDI	TCA	Background exposure	Odour threshold
Tetrahydrofuran	10 [1])	35	[2])	60×10^3 - 150×10^3

TDI: tolerable daily intake (oral exposure); µg/kg bw/day
TCA: tolerable concentration in air (inhalation exposure); µg/m^3
Background exposure; µg/kg bw/day
Odour threshold; µg/m^3
[1]) TDI is provisional because it is derived from the TCA via route-to-route extrapolation
[2]) No data available; assumed to be negligible

7.2.3. REFERENCES

Vermeire TG, Apeldoorn ME van, Fouw JC de & Janssen PJCM (1991):
Voorstel voor de humaan-toxicologische onderbouwing van C-toetsingswaarden.
National Institute of Public Health and the Environment, RIVM-report no. 725201005, February 1991; Bilthoven, The Netherlands.

Author: A.J. Baars
Date: 01-06-2000

7.3. TETRAHYDROTHIOPHENE

7.3.1. EVALUATION

For the re-evaluation of tetrahydrothiophene, the following national and international reviews were consulted:

- Toxicological profiles of the US Agency for Toxic Substances and Disease Registry;
- IRIS files of the US Environmental Protection Agency;
- Environmental Health Criteria of the WHO's International Programme on Chemical Safety;
- Evaluations of carcinogenicity of the WHO's International Agency for Research on Cancer;
- Criteria documents of the RIVM;
- Other relevant information available in the compounds database of the library of the RIVM's Centre for Substances & Risk Assessment.

New relevant information regarding tetrahydrothiophene could not be located. Consequently the MPRs as derived by Vermeire et al. in 1991 are to be maintained.

Compound	TDI	TCA	Background exposure	Odour threshold
Tetrahydrothiophene	180 [1])	650	[2])	3000

TDI: tolerable daily intake (oral exposure); µg/kg bw/day
TCA: tolerable concentration in air (inhalation exposure); µg/m^3
Background exposure; µg/kg bw/day
Odour threshold; µg/m^3
[1]) TDI is provisional because it is derived from the TCA via route-to-route extrapolation
[2]) No data available; assumed to be negligible

7.3.2. REFERENCES

Vermeire TG, Apeldoorn ME van, Fouw JC de & Janssen PJCM (1991):
Voorstel voor de humaan-toxicologische onderbouwing van C-toetsingswaarden.
National Institute of Public Health and the Environment, RIVM-report no. 725201005, February 1991; Bilthoven, The Netherlands.

Vermeire TG (1993):
Voorstel voor de humaan-toxicologische onderbouwing van C-(toetsings)waarden - Addendum op RIVM rapport nr. 725201005
National Institute of Public Health and the Environment, RIVM report no. 715801001, May 1993; Bilthoven, The Netherlands.

Author: A.J. Baars
Date: 01-06-2000

7.4. CYCLOHEXANONE

7.4.1. EVALUATION

For the re-evaluation of cyclohexanone, the following national and international reviews were consulted:

- Toxicological profiles of the US Agency for Toxic Substances and Disease Registry;
- IRIS files of the US Environmental Protection Agency;
- Environmental Health Criteria of the WHO's International Programme on Chemical Safety;
- Evaluations of carcinogenicity of the WHO's International Agency for Research on Cancer;
- Criteria documents of the RIVM;
- Other relevant information available in the compounds database of the library of the RIVM's Centre for Substances & Risk Assessment.

New relevant information regarding cyclohexanone could not be located. Consequently the MPRs as derived by Vermeire et al. in 1991 are to be maintained.

Compound	TDI	TCA	Background exposure
Cyclohexanone	4600	136	*)

TDI: tolerable daily intake (oral exposure); µg/kg bw/day
TCA: tolerable concentration in air (inhalation exposure); µg/m^3
Background exposure; µg/kg bw/day
*) No data available; assumed to be negligible

7.4.2. REFERENCES

Vermeire TG, Apeldoorn ME van, Fouw JC de & Janssen PJCM (1991):
Voorstel voor de humaan-toxicologische onderbouwing van C-toetsingswaarden.
National Institute of Public Health and the Environment, RIVM-report no. 725201005, February 1991; Bilthoven, The Netherlands.

Author: A.J. Baars
Date: 01-06-2000

7.5. PETROL/GASOLINE

7.5.1. EVALUATION

For the re-evaluation of petrol/gasoline the following national and international reviews were consulted:

- Toxicological profiles of the US Agency for Toxic Substances and Disease Registry;
- IRIS files of the US Environmental Protection Agency;
- Environmental Health Criteria of the WHO's International Programme on Chemical Safety;
- Evaluations of carcinogenicity of the WHO's International Agency for Research on Cancer;
- Criteria documents of the RIVM;
- Other relevant information available in the compounds database of the library of the RIVM's Centre for Substances & Risk Assessment.

New relevant information regarding petrol/gasoline could not be located. Consequently the MPRs as derived by Vermeire et al. in 1991 are to be maintained.

Compound	TDI	TCA	Background exposure
Petrol/gasoline	3100	71	*)

TDI: tolerable daily intake (oral exposure); µg/kg bw/day
TCA: tolerable concentration in air (inhalation exposure); µg/m^3
Background exposure; µg/kg bw/day
*) No data available; assumed to be negligible

7.5.2. REFERENCES

Vermeire TG, Apeldoorn ME van, Fouw JC de & Janssen PJCM (1991):
Voorstel voor de humaan-toxicologische onderbouwing van C-toetsingswaarden.
National Institute of Public Health and the Environment, RIVM-report no. 725201005, February 1991; Bilthoven, The Netherlands.

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7.6. TOTAL PETROLEUM HYDROCARBONS (TPH)

7.6.1. INTRODUCTION

A human-toxicological MPR (maximum permissible risk) for 'minerale olie' (see remark in paragraph 7.6.2 under 'Introduction and definition') was established in 1993 (Vermeire 1993), while in 1995 a MPR was derived for high boiling aromatic solvents [92]) (Janssen et al. 1995).
Regarding 'minerale olie' (Vermeire 1993), the relevant exposure was considered to be oral. There were only very limited toxicity data; the available studies did not allow for the estimation of a NOAEL or LOAEL. However, a dietary dose of 5 % for rats (equivalent to 2500 mg/kg bw/day) during full life-span was not harmful. Applying a safety factor of 100 resulted in a MPR of 25 mg/kg bw/day.
Remark: According to the present state-of-the-art however, this approach (i.e., the assumption of a dietary dose of 5 % being not harmful) is not considered very reliable anymore.
Regarding 'high boiling aromatic solvents' (Janssen et al. 1995), oral, inhalatory and dermal exposures were all considered relevant. Toxicity data were scarce, basis for the TDI estimation was a 12 months inhalatory study in the rat which resulted in a NOAEL of 450 mg/m^3 (corrected for exposure time: 80 mg/m^3). Applying a safety factor of 100 resulted in a TCA of 0.8 mg/m^3, and via route-to-route extrapolation to a provisional MPR of 0.17 mg/kg bw/day.
The present report deals with an approach to evaluate mineral oil contaminated areas by splitting up the oil mixture in a limited number of fractions of hydrocarbon compounds, which are then each evaluated on the basis of their physical-chemical and toxicological characteristics. Only carcinogenic oil compounds (like, e.g., benzene and most polycyclic aromatic hydrocarbons) need to be evaluated separately; these carcinogenic risk evaluations can be found elsewhere in this report.
Relevant routes to be considered in cases of soil contamination: oral and inhalation.

7.6.2. CHARACTERISATION OF TOTAL PETROLEUM HYDROCARBONS

Introduction and definition
The present report is largely based on data collected, discussed and published by the Oil Companies' European Organization for Environment, Health and Safety (CONCAWE), the US Total Petroleum Hydrocarbon Criteria Working Group (TPHCWG), and the US Agency for Toxic Substances and Disease Registry (ATSDR), supplemented by recent literature. Its goal is to evaluate the current knowledge, aiming at an improvement of the scientific basis as compared to the earlier reports.
In the present report 'total petroleum hydrocarbons' (TPH) is defined as all petroleum hydrocarbons with 6 or more carbon atoms (which equals the definition used by Vermeire (1993)).
Remark: The Dutch term 'minerale olie' (which is now replaced by TPH) should not be confused with the English term 'mineral oil', which in general characterises the particular petroleum hydrocarbon products also known as 'medicinal white oils'.

Properties and use of total petroleum hydrocarbons
Total petroleum hydrocarbons (TPH) are principally composed of carbon and hydrogen but may also contain oxygen, sulphur and nitrogen; hydrocarbons containing the latter two elements are referred to as heterocyclic compounds.
TPH originate from crude oils. According to the IPCS (1982) these petroleum crude oils can be broadly devided into paraffinic, asphaltic, and mixed crude oils. Paraffinic crude oils are composed of aliphatic hydrocarbons (paraffins), paraffin wax (longer chain aliphatics), and high grade oils. Naphta is the lightest of the paraffinic fraction, followed by kerosene fractions. Asphaltic crude oils contain larger concentrations of cycloaliphatics and high viscosity lubricating oils. Petroleum solvents are the product of crude oil distillation and are generally classified by boiling point range. Lubricants, greases,

[92]) High boiling aromatic solvents is the residu that remains after evaporation of the more volatile constitutents from gasoline or other petroleum products, and is rich in C3- and C4-alkylated benzenes. The composition of these mixtures resembles that of high-boiling aromatic solvents derived from petroleum; the latter are commonly denoted as *high-boiling aromatic solvents* (HBAS) or as *high-flash aromatic naphta* (various commercial products). In general the boiling range is 155-210 °C.

and waxes are high boiling point fractions of crude oils. The heaviest, solid fraction of crude oils are the residuals or bitumen.
An important feature of the TPH analytical methods is the use of the *equivalent carbon number* index (EC). The EC represents equivalent boiling points for hydrocarbons (HCs) and is based on equivalent retention times on a boiling point gaschromatographic column (a non-polar capillary column), normalised to n-alkanes. In other words, the EC number of a compound X represents the number of carbon atoms that an imaginary n-alkane should have in order to present exactly the same boiling point as compound X. Thus, the EC numbers of n-alkanes equals their number of carbon atoms, while the EC numbers start to differ from the number of carbon atoms for the branched alkanes and the unsaturated and aromatic HCs. Some examples: n-hexane (C_6H_{14}), being a n-alkane, naturally has EC 6.0, 2,2-dimethylbutane (C_6H_{14}) has EC 5.37, methylcyclopentane (C_6H_{14}) has EC 6.27, cis-2-hexene (C_6H_{12}) has EC 6.14, and benzene (C_6H_6) has EC 6.5.
Characterisation according to EC numbers is thus the physical characteristic that is the basis for separating petroleum (and other) components in chemical analysis, and it is also typically the way by which analytical laboratories routinely report carbon numbers for HCs evaluated by (boiling point) gas chromatographic analysis.

7.6.3. TOXICOLOGY

Introduction
The toxicology of some mixtures such as diesel fuel, fuel oils and gasoline, and chemicals such as benzene, 1,3-butadiene, toluene and xylenes has been extensively evaluated by regulatory and governmental agencies and institutes such as the US Agency for Toxic Substances and Disease Registry (ATSDR), the International Agency for Research on Cancer (IARC), the International Programme on Chemical Safety (IPCS), the US Environmental Protection Agency (USEPA), the UK Health and Safety Executive (UKHSE), and the RIVM. The toxicological information of many constituents is limited. In 1997 the TPHCWG, examining information on 254 chemicals in the C3-C26 range, identified approximately 65 compounds as possible surrogates for other petroleum hydrocarbons and for which useful toxicological information was available (TPHCWG 1997a,b), which was essentially confirmed and adoped by the ATSDR (1998). In addition the CONCAWE has started to publish some 11 reports summarising the available information on toxicity etc. of a number of principal oil products; since 1992, nine of these reports have appeared (CONCAWE 1992a-c, 1993, 1994, 1995, 1997, 1998).

Acute exposure
In general, low molecular weight petroleum distillates are poorly absorbed from the gastrointestinal tract and do not cause appreciable systemic toxicity by ingestion unless inhalation occurs, in which case primary effects include pulmonary damage and transient CNS depression or excitation. Inhalation exposure to volatile petroleum hydrocarbons such as low molecular weight aromatics and aliphatics including petrol may result in cardiac arrhythmias and CNS depression. Case reports of renal and haematological effects have also been recorded from acute high exposure. Gases such as methane, ethane and propane may cause asphyxiation in confined spaces.
Dermal effects from short-term exposure to relatively high concentrations of solvents may include irritant and defatting effects, and exposure to lubricating oils, greases and waxes may result in skin disorders such as primary irritation, oil acne, hyperkeratosis and photosensitivity.
Testing the acute oral toxicity of 19 selected petroleum hydrocarbons in rats resulted in LD_{50} values from 4700 mg/kg bw (‘heavy fuel oil’ #6, containing 1.2% S) to 17500 mg/kg bw (‘home heating oil’ 50% #2). Of the 19 petroleum hydrocarbons evaluated six did not induce mortality at 23000 mg/kg bw, and lubricating oils did not induce mortality at 5000 mg/kg bw. The selection included unleaded petrol, five middle distillates (three #2 fuel oils, four #6 fuel oils) and seven lubricating oils (5 paraffinic and 2 naphtenic base stocks).
The middle distillates (HCs with carbon numbers of approximately 6-20) proved to be the most irritating and toxic of the streams examined. Heavy fuel oils produced the most severe eye irritation while the middle distillates produced the most severe dermal irritation. Contact with diesel fuel resulted in dermal blisters while paraffinic and naphtenic oils were the least reactive. Only #6 heavy fuel oil (0.8% S) demonstrated dermal sensitising potential with mild reactions being produced.

The category of heavy fuel oils was shown to have a dermal LD_{50} in the rabbit of >2000 to >5000 mg/kg bw.

Subacute and subchronic exposure

The scarce data available are restricted to inhalation studies and indicate mainly nephrotoxic and pulmonary effects. Rats exposed to jet fuel (JP-5) vapour for 60 days developed slight nephropathy at an exposure level of 2900 mg/m^3 (male rats only); in a 90-days study with rats and dogs exposed to vapour concentrations of 150 and 750 mg/m^3 jet fuel (JP-5), male rats showed dose-related slight nephropathy; the same effects were seen in a 12-months study with rats exposed to jet fuel (JP-5) vapour at concentration levels of 1000 and 5000 mg/m^3 (6 h/day, 5 days/wk). A further a 90-days study with rats and mice continuously exposed to marine diesel fuel vapour in the concentration range of 150-750 mg/m^3 resulted also in dose-dependant nephropathy in male rats only. Exposure of rats to vaporised unleaded gasoline for 3 months (6 h/day, 5 days/wk) at concentrations levels of 90, 1250 or 9950 mg/m^3 resulted likewise in male rat nephropathy. The toxic effects in male rat kidney observed with various HCs are the result of a complex accumulation process that starts with the interaction of HC metabolites and alpha-2μ-globulin. The accumulation causes tubular cell damage and increased cellular proliferation, which enhances the probability of tumour development. When alpha-2μ-globulin is not produced in substantial amounts (such as in in female rats, mice, or other animal species including man), neither the nephrotoxicity nor the subsequent carcinogenesis occurs.

Rats exposed to aerosolised diesel fuel concentrations of 1300-6000 mg/m^3 (either for 2 h, 3 times per week during 3 weeks, or once per week for a total of 6 hours over 9 weeks) did not show signs of neurotoxicity, but showed an increase in focal accumulation of free cells in the lungs, thickening and hypocellularity of alveolar walls, and a decreased total lung capacity. Reductions in respiratory rate, pulmonary hyperaemia, leucocytosis, monocytosis and decreased erythrocyte sedimentation rate were observed in a study in which rats, mice, rabbits and cats were exposed to kerosene aerosol concentrations of 50-120000 mg/m^3 for up to 4 weeks (the kerosenes used were characterised as standard lighting grade, and export grades A and B). Histological examination revealed inflammatory changes in the respiratory tracts. Rats exposed to an aerosol of solvent-extracted paraffin oil for 9 days at concentrations of 50, 500 or 1500 mg/m^3 developed dermal irritation and clinical signs of CNS depression at the two highest dose levels, accompanied by microscopic evidence of inflammation and irritation in pulmonary tissue at the highest dose level. A 4 weeks study with rats exposed to aerosol concentrations of 50, 210 or 1000 mg/m^3 (6 h/day, 5 days/wk) of solvent-extracted 100 SUS oil or washed white oils showed a dose-related increase of lung weights associated with accumulations of foamy alveolar macrophages, but no clinical signs of toxicity.

Developmental and reproductive toxicity

Heavy fuel oils showed maternal and foetal toxic effects in rats (19 days dermal exposure starting at day 0 of gestation) at doses of 8 and 30 mg catalytically cracked clarified oil per kg bw per day, respectively (LOAELs). In similar experiments, clarified slurry oil had a LOAEL of 30 mg/kg bw/day, for heavy coker oil this value was 125, and for heavy vacuum gas oil it was 500 mg/kg bw/day (both maternal and foetal toxicity).

In a study to evaluate adverse reproductive effects, dermal application of clarified slurry oil to rats showed non-reproductive toxic effects in males and females with NOAELs of 1 and 10 mg/kg bw/day, respectively, while the reproductive NOAEL rats was >250 mg/kg bw/day (both sexes).

No abnormal development was seen in the offspring of rats dermally exposed to three lubricating oil basestocks (up to 2000 mg/kg bw/day) on days 0-19 of gestation. Gavage administration to rats of 5 ml/kg bw/day of a highly refined white oil on days 6-19 of gestation did not produce any sign of teratogenicity. The same dose regimen applied for 13 weeks after which treated male and female rats were allowed to breed, did not show any abnormality in the offspring.

Diesel fuel (inhalatory exposure) or gas oils (dermal application) did not show foetotoxic or teratogenic effects in rats at dose levels below the level(s) at which maternal toxicity was observed (maternal LOAELs varying between 30 and 1000 mg/kg bw/day). Rats exposed to kerosene (760 or 2600 mg/m^3, 6 h/day, days 6-15 of gestation) did not show adverse effects in the dams or the progeny. Similar results were obtained in a study with jet fuel A (0, 700 and 2800 mg/m^3).

Carcinogenicity
Human epidemiological studies have demonstrated the association of petroleum hydrocarbon exposures with various adverse health outcomes. Exposure to mineral oils that have been used in a variety of occupations, including mulespinning, metal machining and jute processing, has been associated strongly and consistently with the occurrence of squamous-cell cancers of the skin, and especially of the scrotum. Occupational exposure to twelve petroleum-derived liquids suggested increased risk of cancers from exposure to automotive and aviation petrol, mineral spirits, diesel fuel, and lubricating and cutting oils. Oil and gas field work seemed to be associated with acute myelogenous leukaemia, but this was not found in more updated studies. An increased risk of renal adenocarcinomas was seen for refinery and petrochemical workers and from occupational exposures to gasoline.
Environmental exposures within residential localities have been reported to increase bone, brain and bladder cancer deaths of children and adolescents living in a residential area near three large petroleum and petrochemical complexes. Also neurophysiological and neurological impairment in residents (with up to 17 years residence) adjacent to an oil processing and Superfund site was reported.
Dermal carcinogenic potential of petroleum hydrocarbons was demonstrated by an increased incidence of squamous cell carcinomas and fibrocarcinomas in male mice treated with dewaxed heavy paraffin distillate in lifetime skin painting studies. Petroleum distillates with boiling points below those of polycyclic aromatic hydrocarbons (generally responsible for dermal carcinogenic responses) were reported to have weak tumorigenic activity, a finding that was supported in three other studies.
The carcinogenic risk evaluation of a number of TPH as reported by IARC (1987, 1989) resulted in classification of benzene and untreated/mildly treated mineral oil as *'carcinogenic to humans'* and of unleaded gasoline, residuel fuel oils, marine diesel fuel, 1,2-butadiene, benzo(a)pyrene, benzo(b)-fluoranthrene, and dibenzo(a,h)anthracene as *'probably/possibly carcinogenic to humans'*.

7.6.4. APPROACHES TO ASSESS THE RISK OF TPH IN CONTAMINATED AREAS

Introduction
In order to develop human health-based TDI(s) as the starting point for estimating cleanup levels for petroleum hydrocarbons in contaminated areas, three principally different approaches are conceivable: (1) the use of toxicity data for the whole mixture or parent product (e.g., diesel fuel, gasoline, jet fuel, etc.), (2) the identification and quantification of all component chemicals followed by a full risk assessment of these components, and (3) the use of an indicator and/or surrogate approach to assess the toxicity and risk posed by the mixture.
Ideally any hazard assessment should be based on the compounds (that is: all individual compounds) to which the receptor of concern is exposed. On the other hand, utilising data on the actual mixture present would account accurately for the interactive effects of all compounds in the mixture. However, such data are currently not available, and therefore these approaches are impractical and in fact unusable. The data which are available, are: (1) data on some whole mixtures or parent products, (2) data on some individual compounds, namely important indicators such as benzene and benzo(a)pyrene, and (3) data on some fraction-specific mixtures.
Toxicity data on whole mixtures or parent products are only available for some gasolines, some jet fuels, and medicinal white oil. Thus for other parent products (such as bunker fuel, diesel, lube oils, etc.) a whole mixture approach is not possible at all. Moreover, once released in the environment the parent product separates into fractions based on differences in fate and transport. Thus the mixture to which a receptor is exposed will vary with space, time, and by media. Finally, there are no toxicity data on weathered fraction-specific mixtures or mixtures of parent compounds (such as mixtures of diesel and gasoline). Hence, a whole mixture approach is not appropriate for a weathered release, but is only feasible for the hazard assessment of a fresh release of a single, known product for which toxicity data are available.
Recently (1994-1998) a number of approaches were reported, all of which recognised the need to be based upon reliable scientific data and at the same time recognised the necessity to be feasible in generally encountered polluted situations. All apply the indicator/surrogate principle outlined above; these include the methods developed by the Massachusetts Department of Environmental Protection (MDEP-USA) (Hutcheson et al. 1996), the method described by Staats et al. (1997), the results of efforts of the TPHCWG (TPHCWG 1997a,b) (the TPHCWG is a USA consortium of state regulatory

agencies, academia, Department of Defence, Department of Energy, USEPA, ATSDR, petroleum, power and transportation industries and consulting firms), and finally the recent draft report of the ATSDR (1998).
Comparing these approaches, the one developed by Hutcheson et al. (1996) virtually offers the advantage of being rather simple to execute. It only discriminates between 4 subgroups, 3 of which are concerned with saturated HCs (alkanes, cycloalkanes and isoalkanes), the 4th one covering all aromatic compounds. However, this approach is considered to be an oversimplification of the complex composition of the contaminations seen in practice. Moreover, the scientific basis of two out of the four RfDs [93]) is rather weak.
The method as developed by Staats et al. (1997) is not only more detailed but also has a better scientific basis, and offers the possibility to discriminate between soils contaminated with neat petroleum products of known composition and (weathered) soils contaminated with unknown TPH. However, as with Hutcheson et al., also this method required a detailed chemical analysis, and if this analysis does not allow a risk assessment based on one or more neat petroleum products, then also here rather few surrogates/indicator data are available to serve as the basis for risk assessment, again resulting in an oversimplification of the complex composition of the contaminations seen in practice.
In contrast with Hutcheson et al. (1996) and Staats et al. (1997) the TPHCWG approach (1997a,b) discriminates between an reasonable number of groups (defined as 'fractions') and thus allows a more detailed risk assessment while still being feasible in practice. The approach has its scientific basis in an in-depth evaluation of the available toxicity data. In short, the TPHCWG-methodology (see Figure 1) evaluates as the first step individual carcinogenic indicators to which the receptor is exposed, which is consistent with USEPA methodology for carcinogens. If these indicators are not present, or are present below levels of concern, the remaining mass of petroleum is evaluated using fraction-specific surrogates. The fraction-specific composition of the mixture to which the receptor is exposed is determined, and surrogate RfDs/RfCs are utilised to determine the risk or to develop cleanup goals. The use of fraction-specific surrogates accounts for the effect of fate and transport on the whole mixture or parent products in that changes in the relative mass of each fraction at the receptor are accounted for in the risk assessment. This TPHCWG approach is described in further detail below.

The TPHCWG approach
Recently the TPHCWG (1997a,b) extensively evaluated the toxicity data on individual TPH compounds. Petroleum is known to consist of thousands of individual HCs and related compounds. Of these, some 250 are actually identified. Of these 250 identified compounds only 95 had toxicity data. Of these 95, only 25 have sufficient data to develop toxicity criteria. Most of these 25 have USEPA-derived RfDs/RfCs or slope factors.
Considering the scarce data available and the need to assess the risks of petroleum mixtures, there is no other choice than to use the indicator/surrogate approach. Based on the uncertainties discussed above, the TPHCWG decided to choose for a combination of data on individual compounds *(indicators)* and fraction-specific mixtures *(surrogates)* as the hazard assessment methodology.
Firstly, the ***indicator approach*** is used to assess the hazard of (human) carcinogenic compounds (such as benzene and certain PAHs).
Secondly, if possible and applicable, the ***whole product approach*** is applied (this will only rarely be possible).
Finally, the ***surrogate approach*** is applied. This TPHCWG approach is outlined in Figure 1.
Remark: This latter approach (i.e., the surrogate approach) is outlined in more detail below. The current report does not deal with the first steps (i.e., the indicator approach for carcinogenic risks, and the whole product approach) in evaluating TPH-contaminated areas.
Over 200 HCs were considered in the development of fraction-specific characteristics. Because the fate and transport of a chemical in the environment largely defines its exposure potential to the receptors of organisms at risk, partition modelling according to ASTM standards was applied to each chemical in order to quantify, individually, the chemical's relative ability to leach from soil to groundwater and to volatilise from soil to air. Based on these results the chemicals were grouped into

[93]) Reference Dose (RfD) and Reference Concentration (RfC) are terms introduced by the US-EPA as 'neutral' replacements of the ADI/TDI and TCA, respectively.

6 aliphatic and 7 aromatic fractions, using one order of magnitude in relevant physical-chemical parameters as the cut-off point. Within each fraction the HCs are grouped according to their EC (equivalent carbon) numbers (EC-numbers are based on equivalent retention times on a boiling point gaschromatographic column; see paragraph 7.6.2). The ATSDR (1998) adopted these fractions, but see below for a remark regarding the exact classification of aromatic compounds with ECs of approximately 8.

To evaluate the potential human health effects, the original number of fractions was reduced to seven (4 aliphatic and 3 aromatic fractions), mainly due to the limited toxicity data available and the similarity in toxic effects. The toxicity data available on fraction-specific mixtures cover the aliphatic fractions of TPH and the aromatic fraction >EC5 - EC8; data on the >EC8 - EC16 and >EC16 - EC35 aromatic fractions consist of mixture data on the EC8 - EC11 range only. In addition, there are no data on petroleum components with >EC35. However, since compounds >EC20 are not volatile or soluble in groundwater, they are likely to remain at the release site; moreover, compounds >EC35 are likely to possess low bioavailability by the oral, inhalatory and dermal route. The RfDs/RfCs for aliphatic fractions are at least one order of magnitude greater than those for the aromatic fractions. This is a result of both a difference in uncertainty and potency. The TPH fraction-specific RfDs and RfCs are summarised in Table 1.

Of the aliphatic >EC5-EC8 fraction, n-hexane is the only compound for which the USEPA has developed a RfD. Because of its unique toxicity, however, the use of the n-hexane RfD of 0.06 mg/kg bw/day as basis for the fraction-specific RfD would considerably overestimate the risks of HCs in this fraction. The composition of petroleum products containing n-hexane is well known and ranges from 0.05% to 7.0% in some gasolines and up to 15.7% in sweetened naphta. Thus, generally the levels of n-hexane are low (approx. 2 % in gasolines). The available datasets on n-heptane and on solvent mixtures containing hexane isomers allowed the conclusion that n-heptane can be considered an appropriate surrogate for the EC6-EC8 HCs (with the exception of hexane), and consequently the TPHCWG recommended a RfD for the EC6-EC8 aliphatics of 5 mg/kg bw/day [94]). In all studies an uncertainty factor (UF) of 100 (10 for animal to human, 10 for most sensitive) was applied to arrive at the RfDs/RfCs.

Toxicity data on individual components in the aliphatic >EC8-EC16 fraction are minimal. The data that were utilised were studies on jet fuel JP-8 (EC9-EC16) and studies on dearomatised petroleum streams (10 studies in total) which together cover the entire range of the fraction. Although data on n-nonane are available, the data on petroleum streams were preferred based on the fact that these are data on mixtures rather than on an individual compound at the low end of the fraction. The UFs used in these studies varied from 1000 (which includes an additional factor of 10 to compensate for the use of subchronic studies) to 5000 in one study (the additional factor of 5 was applied to compensate for the use of a LOAEL instead of a NOAEL).

The RfDs for the aliphatic >EC16-EC35 and >EC35 fractions were based on an recent and extensive BIBRA study in which Fischer rats were exposed to various white mineral oils (these are complex mixtures of highly refined mineral HCs, predominantly branched chain alkanes and alkenes with one or more saturated cyclic structures, and no aromatics or other contaminants, extensively used as food additives and in cosmetics and pharmaceutical products). The RfD for the EC17-EC35 fraction (2 mg/kg bw/day) is based on the NOAEL for low molecular weight oils for liver granulomas (200 mg/kg bw/day) and a UF of 100. The RfD for the >EC35 fraction (20 mg/kg bw/day) is based on the NOAEL for high molecular weight oils for liver granulomas (2000 mg/kg bw/day) and a UF of 100. An recent similar study in Japan showed comparable results.

In petroleum products of the aromatic >EC5-EC8 range, seven compounds were identified. RfDs are available for six of these: ethylbenzene, styrene, toluene, m-, o- and p-xylene. The values range from 0.1 to 2.0 mg/kg bw/ day. On reviewing the toxicity and compositional information of this fraction, the TPHCWG considered a RfD of 0.2 mg/kg bw/day appropriate. RfCs are available for three compounds: toluene, ethylbenzene and styrene, ranging from 0.4 to 1.0 mg/m^3; the TPHCWG recommended a RfC of 0.4 mg/m^3 for this fraction. The UFs range from 100 (xylenes) to 1000 (toluene, eth-

[94]) Only in the rare cases of a release of high purity n-hexane the RfD of n-hexane (i.e., 0.06 mg/kg bw/day) should be used.

ylbenzene and styrene), the additional factor of 10 for these latter ones compensates for the use of subchronic studies.
In the aromatic >EC8-EC16 fraction 77 compounds have been identified; RfDs have been developed for 8 of these (all with ECs > 9), ranging from 0.03 to 0.3 mg/kg bw/day. There are also data available on a mixture within this range: naphtalene/methylnaphtalenes; for this mixture a RfD of 0.03 mg/kg bw/day was developed. After reviewing the information, a fraction-specific RfD of 0.04 mg/kg bw/day was considered to be appropriate (of the 8 available individual RfDs, 4 were 0.04 mg/kg bw/day, the only exceptions are fluorene and the naphtalene/methylnaphtalenes mixture with values of 0.03 mg/kg bw/day). Inhalation data for the EC9-EC16 fraction are extremely limited, there are RfCs for isopropylbenzene (0.09 mg/m^3) and naphtalene (0.0013 mg/m^3), but these compounds are not at all representative for this fraction. In addition there are several inhalation studies on EC9 aromatic mixtures that allowed the development of an RfC, resulting in values ranging from 0.2 to 1.3 mg/m^3. The TPHCWG determined the more conservative value (0.2 mg/m^3) to be representative of this entire fraction. The UFs range from 100 (biphenyl), via 1000 (naphtalene, fluorene), to 3000 (isopropylbenzene, methylnaphtalene, anthracene); the additional factor of 10 (naphtalene, fluorene) originates from the use of subchronic studies, the additional factor of 3 (isopropylbenzene, methylnaphtalene, anthracene) compensates for the inadequate databases.
There are no previous developed RfDs for aromatic HCs in the >EC16-EC35 range, and a literature review did not result in data which allowed for the development of a RfD. Thus the TPHCWG considered the RfD for pyrene ($C_{16}H_{10}$), i.e., 0.03 mg/kg bw/day, to be the best option as a surrogate for the fraction-specific RfD. Pyrene is considered a conservative surrogate because its carbon number is lower than any of the compounds in this fraction. The UF was 3000 (which includes a factor of 10 to compensate for the use of a subchronic study, and a modifying factor of 3 for lack of adequate toxicity data in a second species and reproductive/developmental data).
The TPHCWG approach is based on some implicit assumptions. It assumes:
(1) that the toxicity of the fraction as tested does not significantly change with weathering in the environment,
(2) that the composition of the fraction will not vary significantly from the surrogate tested, and
(3) that the interaction of the various fractions can be assumed to be additive.
These uncertainties warrant a careful use of the methodology. Comments are presented below.

The ATSDR toxicological profile for TPH
Late 1998 the ATSDR published the draft of its toxicological profile for TPH (ATSDR 1998). In its approach to the health assessment of TPH, ATSDR has drawn on the experience of others that have been developing approaches to health based assessment of TPH, particularly on Hutcheson et al. (1996) and the TPHCWG (1997a,b).
The ATSDR adopted the TPH fraction approach as developed by the TPHCWG, considering this approach the most useful. However, the ATSDR adjusted the classification of compounds into appropriate fractions, because xylene and styrene were misclassified on the basis of actual rather than equivalent carbon index numbers (these compounds have ECs of 8.5-8.81 and should thus belong in the TPHCWG >EC8 - EC16 category). Hence, the aromatic >EC5 -EC8 fraction has beeen redefined as an >EC5 - EC9 fraction, so that it includes all the BTEXs. Consequently, the aromatic >EC8 - EC16 fraction has then been redefined as an >EC9 - EC16 fraction.

Comments
As outlined above, the TPHCWG approach (1997a,b) discriminates between a reasonable number of fractions, thus allowing a more detailed risk assessment while still being feasible in practice. With respect to the underlying assumptions (uncertainties) of the approach as such, careful consideration of these learns that they are to a certain extent irrelevant:
Regarding weathering, there are no toxicity data on weathered products. Whittaker and Pollard (1997) recently suggested the use of certain marker compounds in oil and oil products to determine the origin of a crude oil contamination and the state of weathering. They propose oil weathering indices based on petroleum microbiology, in particular on the differential rates at which oil components are metabolised and transformed. Microbial catabolism of n-alkanes proceeds via successive oxidation and cleavage of the terminal methyl groups of a hydrocarbon molecule. Branched or cyclic compounds experience

slower biotransformation rates due to the presence of secondary, tertiary and quaternary carbon atoms that render these compounds more difficult to metabolise. Thus in terms of oil class fractions, the open chain alkanes are generally the most labile oil components, followed by aromatic compounds, then polar resins, and finally the highly condensed bitumen compounds.
However, although this methodology allows - to a certain extent - the determination of the origin of a crude oil or a particular petroleum product (such determinations are performed in The Netherlands by the RIZA), it only allows a determination of the 'weathering status' in relation to this origin. If e.g. in the past a spillage of a particular jet fuel occurred, the use of marker compounds makes it possible to estimate the weathering of this spillage. In contrast, if the origin of a contamination (that is, the product or its composition at the time it was spilled) is not known, the methodology is unable to identify the weathering status. Assuming that the risk assessment of any petroleum-contaminated site inevitably always starts with a full chemical analysis of the contamination aiming at a classification according to the fractions as defined by the TPHCWG, this presents the actual composition in terms of these fractions, by which the question if and to what extent weathering has occurred, becomes irrelevant.
The same argument holds for the second assumption, i.e. that the composition of the fraction will not vary significantly from the surrogate tested. Again assuming that a chemical analysis will always precede the actual risk assessment makes this assumption irrelevant.
The third assumption (the interaction of the various fractions are assumed to be additive) is more serious. Current knowledge, however, does not present clear and scientifically based indications that interactions other than addition of effects should be applied. Unfortunately the TPHCWG does not explain how and when interaction, and thus additivity, becomes an inportant issue in the evaluation of contaminated areas. The ATSDR, however, does pay some attention to the question how to account for exposure to more than one fraction. Their approach is based on the assumption of additivity (in accordance with the TPHCWG), an approach which is claimed to be reasonable for compounds or fractions that affect the same system or target organ. The ATSDR then defines a 'hazard index', being the sum of the ratios of monitored level of exposure to the accepted level of exposure for each of the constitutents of a mixture:

$HI = \Sigma E_i/AL_i$

HI : hazard index
E_i : actual exposure level to the i^{th} component
AL_i : accepted exposure level for the i^{th} component

A proposal to handle this 'hazard index'-approach in the Dutch situation is developed in paragraph 7.6.6.

7.6.5. BACKGROUND EXPOSURE

No data are available regarding the daily oral or inhalatory background exposure to TPH. Oral exposure can be assumed to be negligible, in agreement with Vermeire (1993). Inhalatory background exposure might be expected only from rather volatile TPH-based compounds. However, only for a few neat petroleum products some limited data are available, like e.g., gasoline (petrol) fumes and exhausts, and TPH-based solvents used in industry and households, like e.g., Stoddard solvent ('white spirit' or 'turpentine').
Gasolines are mixtures of volatile HCs (C3-C11, composed of 30-90% alkanes and 5-55% aromatics with a boiling range of 30-260 °C). Regarding gasoline fumes and exhausts, air concentrations measured in Germany in the mid-seventies indicate arithmetric mean values for non-methane HCs ranging from 42 (rural areas) to 756 (city streets with heavy traffic) $\mu g/m^3$ (BUA 1998), with an average value of approximately 300 $\mu g/m^3$. Since the indoor concentration will hardly differ from the outdoor concentration, this figure results in a background exposition of the average population of 86 µg/kg bw/day for an adult of 70 kg with a breathing volume of 20 m^3/day. The MAC-value for gasoline in air (Dutch occupational limit value, 8 h/day, 40 h/week) is 240 mg/m^3 (MAC 1997).
Stoddard solvent (a mixture of saturated aliphatic and alicyclic C7-C12 HCs with a maximum content of 25% aromatics and a boiling range of 130-230 °C) was reviewed by the IPCS (1996): no estimations were reported with regard to the background exposure of the general population. Painters and industrial workers were reported to be exposed to widely varying concentrations of white spirit. A reasonable time-weight average exposure level (8 h/day) of indoor painting appeared to be approximately

150 mg/m^3 (IPCS 1996). Assuming a 14 days 8 h/day exposure per year for the general population (amateur painting and cleaning) this results in a mean daily exposure of 550 µg/kg bw/day for an adult of 70 kg bw (breathing volume 20 m^3/day) [95]). Alternatively, a time-weight average air concentration can be estimated to be approximately 2 mg/m^3 [96]). The MAC-value for Stoddard solvent in air (Dutch occupational limit value, 8 h/day, 40 h/week) is 575 mg/m^3 (MAC 1997).
The estimations presented above are probably rather conservative, taken into account that the measurements were done in the mid-eighties (Stoddard solvent) and the mid-seventies (gasoline), and that since then the use of alkyd paints has decreased in favour of water-soluble paints, and vehicle engines have improved considerably the efficiency with which gasoline is burned. Moreover, the estimations apply to two neat petroleum products only. Nevertheless, apparently the background exposition is already in the order of magnitude of the MPRs for the light TPH fractions (cf. paragraph 7.6.6 and Table 2). On the other hand, the data indicate air concentrations well below the occupational limit values.

7.6.6. CONCLUSION

Based on current knowledge and in view of the complexity of the vast majority of petroleum-contaminated areas the TPHCWG methodology (after correction of the mistake noted by ATSDR (1998)) offers at present the best possible methodology to perform a human health based risk assessment giving an optimal reliability while at the same time being feasible in practice. Basically, a tiered approach is applied, as outlined in Figure 1. Detailed site history information is followed by specific chemical analysis with particular emphasis on the carcinogenic indicator compounds, like e.g., benzene and selected PAHs. If these are present, indicating a hazard for human carcinogenic health effects, further investigation is needed, followed by the appropriate measures (this first step is not further discussed in the present report). If these indicator compounds are not present in concentrations causing concern, the possibility to apply a whole product approach is considered (which will only be possible in cases of very recent spillages with known products). Finally, a TPH fraction-specific analysis is made, and the resulting concentrations are compared with fraction-specific MPRs as summarised in Table 2. If necessary, the appropriate measures are taken.
This approach ultimately leads to 7 (human) MPR values for TPH fractions. It explicitly excludes carcinogenic risks (meaning that carcinogenic effects are expected to be evaluated first), as well as the risks that can be estimated applying - if possible - the whole product approach. Only after these two steps have been considered and have shown to be not applicable, the non-carcinogenic risks according to the fraction-approach are to be considered. These MPRs are summarised in Table 2, and replace the earlier MPR for 'minerale olie' (Vermeire 1991).
Remark (1):
There is one change compared to the recommendations of the TPHCWG. The TPHCWG suggests for the aliphatic >EC5 - EC8 fraction a RfD of 5 mg/kg bw/day. The reasoning for this, however, is quite unclear. They review a large number of studies with n-heptane (C_7H_{16}), concluding to a RfD of 2 mg/kw bw/day, and then calculate a RfD of 5 mg/kg bw/day by route-to-route extrapolation using a RfC of 18.4 mg/m^3 which resulted from an inhalatory study with commercial hexane. Furthermore they review seven studies with various petroleum products, in all of which the RfDs varied between 1.5-2.0 and (one with cyclohexane, one with methylcyclohexane), but do not develop a RfD from these data. The proposed RfD of 2 mg/kg bw/day, based on six studies with n-heptane and seven studies with different petroleum products, has evidently a better scientific basis.
Remark (2):
From these human-toxicological MPRs as summarised in Table 2 the corresponding SRCs (severe risk concentrations) for the various TPH-fractions can be calculated using the CSOIL model. Given a contaminated area in which exposure to more than one fraction is under discussion, the approach should be as follows, depending on the specific situation:
1. *If the SRC for one or more fractions is exceeded, the appropriate measures should be considered or taken.*

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[95]) (14 × 8/24 × 20 × 150) ÷ (365 × 70) = 548 µg/kg bw/day.
[96]) (14 × 8/24 × 150) ÷ 365 = 1.92 mg/m^3.

2. *If (and only if) none of the fraction-specific SRCs is exceeded, an overall site-specific contamination index should be calculated assuming additivity, according to the following formula:*

$$\text{site-specific contamination index} = \Sigma \frac{\text{measured level}_i}{\text{SRC}_i}$$

If this index is ≥ 1, the appropriate measures should be considered or taken (ATSDR 1998).

A serious objection to this approach is the question whether or not it is correct to assume additivity. However, as already outlined in paragraph 7.6.4, current knowledge does not present clear and scientifically based indications that interactions other than addition of effects can be applied. Thus, at present there simply is no better way of meaningful dealing with this problem. This approach is also followed by the ATSDR (1998) as the default assumption if no other (more detailed) information is available.

Remark (3):

It should be noted that the chemical analysis of contaminates sites, which the proposed method requires, should include the HCs with equivalent carbon numbers 6 - 10. This implies an extension of the current methodology according to NEN 5733, which defines 'mineral oil' as the sum of all alkanes (including branched alkanes) with carbon numbers 10 - 40, requiring additional analysis of the amount of aromatic and/or polycyclic aromatic HCs if their presence is indicated. The NEN 5733 definition finds its basis in a GC-FID analysis and refers to the detector signal between n-decane ($C_{10}H_{22}$) and n-tetracontane ($C_{40}H_{82}$).

7.6.7. COMPARISON WITH EARLIER DERIVED MPRs

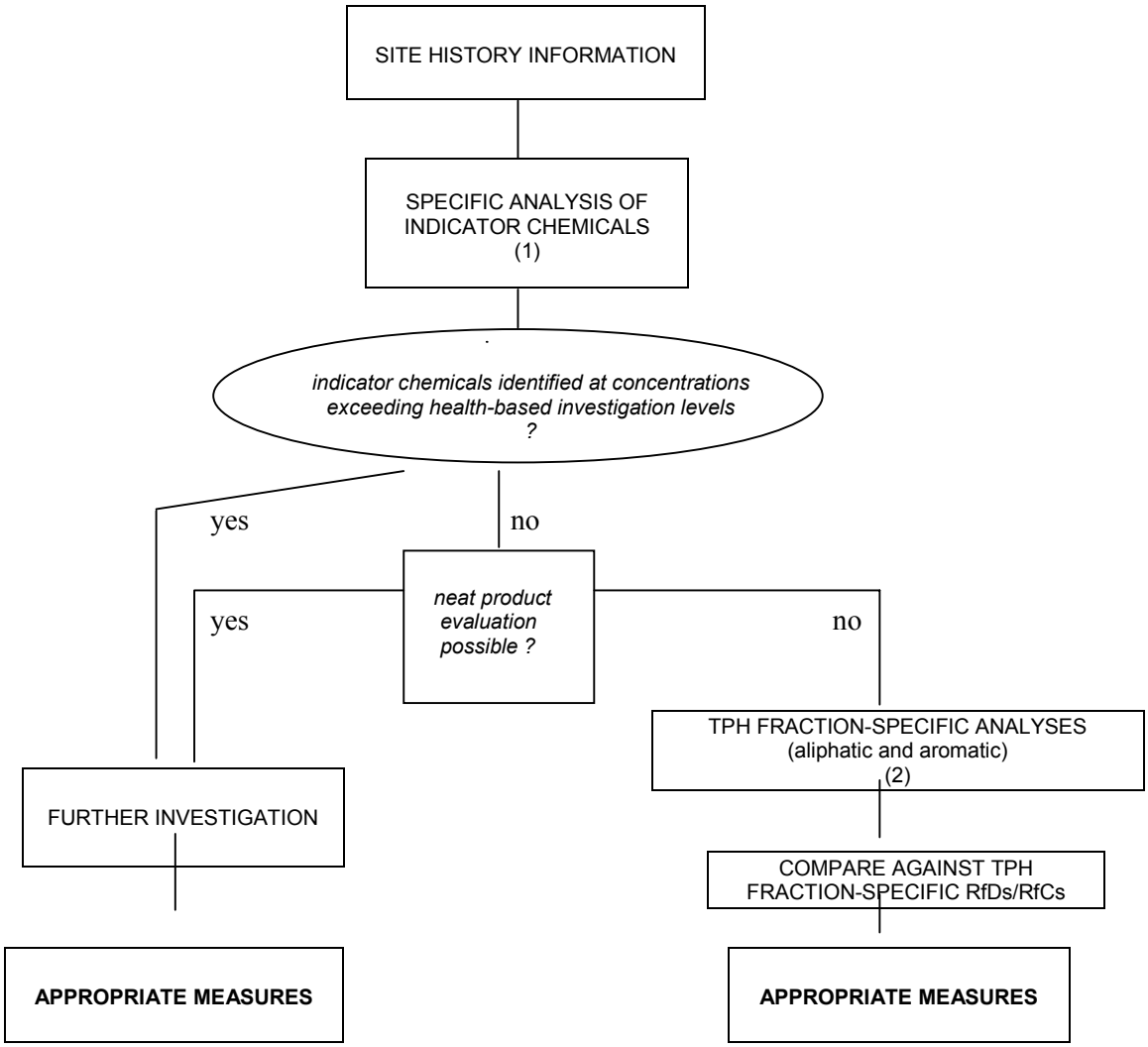
Next to the earlier referred MPRs for 'minerale olie' and HBAS (see paragraph 7.6.1), a number of MPRs for individual TPH components were derived in the years 1991-1996 (Vermeire et al. 1991, Vermeire 1993, Janssen et al. 1995, Janssen et al. 1998). The accompanying TDIs, TCAs and cancer risks are summarised in Table 3, together with the TDIs/TCAs as estimated in the present report (cf. Table 2), and arranged according to the present TPH fractions.

The earlier derived MPRs are mostly limited to the aliphatic >EC5-EC8 and the aromatic >EC5-EC9 fractions; in the aromatic >EC16-EC35 fraction almost all MPRs are related to the carcinogenic risk.

A comparison of the available values shows good agreement. The only significantly differing value is the TCA for gasoline of 71 μg/m^3, which is very low compared to the TCA range of the aliphatic/aromatic EC5-EC16 fractions. However, this particular TCA was developed in 1991, and was based upon two studies published in 1978 and 1979 (cited in IARC 1989), reporting interstitial fibrosis in lung parenchyma of female rats in semichronic studies. In more recent studies, however, these effects were not reported (cf. paragraph 7.6.3, CONCAWE 1992b, and TPHCWG 1997b). Moreover, also the Dutch occupational limit value of 240 mg/m^3 is considerably higher than the above cited TCA (MAC 1997). Hence it seems justified not to use the 1991 TCA for gasoline of 71 μg/m^3 any more, unless there are important reasons to do so in, e.g., specific gasoline-contaminated areas.

7.6.8. FIGURES AND TABLES

Figure 1 Schematic outline of the TPHCWG methodology (1997)



1. Chemicals indicating carcinogenic hazards (specific analysis), e.g.: lead, benzene, 1,3-butadiene, and the PAHs benzo-(a)pyrene, benzo(a)anthracene, dibenzo(a,h)anthracene, benzo(k)fluoroanthrene, benzo(b)fluoroanthrene, benzo(j)fluoro-anthrene, dibenzo(a,h)acridine, dibenzo(a,j)acridine, dibenzo(a,e)pyrene, dibenzo(a,h)pyrene, dibenzo(a,i)pyrene, dibenzo-(a,l)pyrene, indeno(1,2,3-cd)pyrene, 5-methylchrysene; **if necessary also:** ethylbenzene, toluene, xylene, n-hexane.

2. TPH fraction-specific analyses (aromatic and aliphatic):

aliphatic >EC5 - EC8	aromatic >EC5 - EC9
aliphatic >EC8 - EC16	aromatic >EC9 - EC16
aliphatic >EC16 - EC35	aromatic >EC16 - EC35
aliphatic >EC35	

EC: Equivalent carbon number index. The EC is based on equivalent retention times on a boiling point gaschromato-graphic column (non-polar capillary column) in order to normalise to n-alkanes (cf. paragraph 7.6.2).

Remark: *In this figure the classification of the fractions has been corrected and redefined according to the remark in paragraph 7.6.4: 'aromatic >EC5 - EC8' is now 'aromatic >EC5 - EC9'.*

Table 1 TPH fraction-specific RfDs and RfCs of the TPHCWG-method (1997b)

TPH fraction [1])	Oral RfD (mg/kg bw/day)	Inhalation RfC (mg/m^3)	Critical effect (studies) [2])
aliphatic >EC5-EC8	5.0	18.4	neurotoxicity (6 studies n-heptane; 10 studies commercial hexane)
aliphatic >EC8-EC16	0.1	1.0	hepatic & haematological changes (5 studies on JP-8 and dearomatised petroleum streams)
aliphatic >EC16-EC35	2.0	NA [3])	hepatic granulomas (1 extensive study on 5 white mineral oils)
aliphatic >EC35	20	NA	hepatic granulomas (1 extensive study on 3 white mineral oils)
aromatic >EC5-EC8	0.20	0.4	hepato- & nephrotoxicity (based on the available RfDs/RfCs in this range) [4])
aromatic >EC8-EC16	0.04	0.2	decreased body weight, increased liver and kidney weight (based on 8 RfDs and 2 RfCs, respectively)
aromatic >EC16-EC35	0.03	NA	nephrotoxicity (1 study on pyrene)

[1]) EC : Equivalent carbon number index. The EC is based on equivalent retention times on a boiling point gaschromatographic column (non-polar capillary column), in order to normalise to n-alkanes (cf. paragraph 7.6.2).
[2]) Between brackets the toxicity studies from which RfDs/RfCs were developed according to USA-EPA methodology.
[3]) NA : not available (and not applicable due to extremely low volatilisation).
[4]) RfD : six out of the seven compounds in this range (ethylbenzene, styrene, toluene, o-, m-, p-xylene).
RfC : toluene, ethylbenzene, styrene.

Remark: see critical note in paragraph 7.6.4 on a mistake in the aromatic fraction >EC5 - EC8 in this table.

Table 2 Human toxicological MPRs for TPH fractions

TPH fraction	TDI [1]) (µg/kg bw/day)	TCA [2]) (µg/m^3)	UF [3])
aliphatic >EC5 - EC8	2000 [4])	18400	100
aliphatic >EC8 - EC16	100	1000	1000 and 5000, respectively
aliphatic >EC16 - EC35	2000	NA [5])	100
aliphatic >EC35	20000	NA	100
aromatic >EC5 - EC9	200	400	100 and 1000, respectively
aromatic >EC9 - EC16	40	200	100 and 3000, respectively
aromatic >EC16 - EC35	30	NA	1000

Based on TPHCWG (1997b, cf. Table 1) and ATSDR (1998)

EC: Equivalent carbon number index. The EC is based on equivalent retention times on a boiling point gaschromatographic column (non-polar capillary column), in order to normalise to n-alkanes (cf. paragraph 7.6.2).

[1]) TDI (tolerable daily oral intake): equal to the estimated (TPHCWG) RfDs (see Table 1), except for aliphatics >EC5 - EC8; see paragraph 7.6.6.

[2]) TCA (tolerable concentration in air): equal to the estimated (TPHCWG) RfCs (see Table 1).

[3]) UF (uncertainty factor) applied, for explanation see paragraph 7.6.4.

[4]) The TDI of 2 mg/kg bw/day of n-heptane is preferred instead of the rather feebly-argued RfD of 5 mg/kg bw/day (which was calculated from the RfC by route-to-route extrapolation) as recommended by the TPHCWG for this fraction (Table 1; see also paragraph 7.6.5).

[5]) NA: not available (and not applicable due to extremely low volatilisation).

Remarks:

A. These human MPR values replace the earlier MPR for 'minerale olie' (Vermeire, 1993).

B. These human MPR values for TPH fractions explicitly exclude both carcinogenic risks (meaning that carcinogenic effects are expected to be evaluated first), as well as the risks that can be estimated applying - if possible - the whole product approach (see Figure 1). Only after these two steps have been considered and have shown to be not applicable, the non-carcinogenic risks according to the fraction-approach are to be considered.

Table 3 Comparison of the present TDIs/TCAs with earlier derived values

TPH fraction / compound	EC	MPR values 1991/1996		MPR values 1999/2000	
		Oral (µg/kg bw/day)	Inhalation (µg/m^3)	Oral (µg/kg bw/day)	Inhalation (µg/m^3)
Aliphatic >EC5-EC8				TDI 2000	TCA 18400
Hexane	6	pTDI 23	pTCA 200		
Heptane	7	TDI 3100			
Octane	8	TDI 3100			
Aliphatic >EC8-EC16 --				TDI 100	TCA 1000
Aliphatic >EC15-EC35 --				TDI 2000	NA
Aliphatic >EC35 --				TDI 20000	NA
Aromatic >EC5-EC9				TDI 200	TCA 400
Benzene	6.5	TDI 4.3; CR_{oral} 170	TCA 30; CR_{inhal} 1200	CR_{oral} 3.3	CR_{inhal} 20
Toluene	7.58	TDI 430	TCA 3000	TDI 223	TCA 400
Ethylbenzene	8.5	TDI 136	TCA 77	TDI 100	TCA 770
Xylenes	8.7	TDI 10	TCA 54	TDI 150	TCA 870
Styrene	8.83	TDI 77	TCA 800	TDI 120	TCA 900
Aromatic >EC9-EC16				TDI 40	TCA 200
Naphtalene	11.69	TDI 50	-	TDI 40	-
HBAS	±10.1	pTDI 170	TCA 800		
Aromatic >EC16-EC35				TDI 30	-
Dodecylbenzene	±18.5	TDI 5	NA		
Phenanthrene	19.36	CR_{oral} 20	-	TDI 40	-
Anthracene	19.43	TDI 50	-	TDI 40	-
Pyrene	20.80	CR_{oral} 20	-	CR_{oral} 500	-
Fluoranthene	21.85	CR_{oral} 20	-	CR_{oral} 50	-
Benzo(a)anthracene	26.37	CR_{oral} 20	-	CR_{oral} 5	-
Chrysene	27.41	CR_{oral} 2	-	CR_{oral} 50	-
Benzo(k)fluoranthene	30.14	CR_{oral} 20	-	CR_{oral} 5	-
Benzo(a)pyrene	31.34	CR_{oral} 2	-	CR_{oral} 0.5	-
Benzo(ghi)perylene	34.01	CR_{oral} 20	-	TDI 30	-
Indeno(1,2,3cd)pyrene	35.01	CR_{oral} 20	-	CR_{oral} 5	-
PAHs total	-	CR_{oral} 6.3	-	-	-
Others					
Gasoline	-	TDI 3100	TCA 71		
TPH	-	TDI 25000	-		

TDI tolerable daily intake (p: provisional).
TCA tolerable concentration in air.
CR quantitative carcinogenic risk assessment (oral and inhalation, respectively).
EC equivalent carbon number index. The EC is based on equivalent retention times on a boiling point gaschromatographic column (non-polar capillary column), in order to normalise to n-alkanes.
NA not applicable.
HBAS high boiling aromatic solvents, also known as 'aromatic nafta' or 'high-flash aromatic naphta', is a mixture that remains after evaporation of the more volatile constituents from gasoline or other petroleum products. Generally this mixture is rich in C3- and C4-alkylated benzenes, i.e., trimethylbenzenes, methylethylbenzenes, tetramethylbenzenes and methylpropylbenzenes. Its boiling range is approximately 155-210 °C; the ECs range from 9.6 - 10.7 (average approximately 10.1).
Gasoline gasolines are mixtures of volatile HCs (C3-C11, composed of 30-90% alkanes and 5-55% aromatics) with a boiling range of 30-260 °C.
TPH 'minerale olie' in the 1993 report.

7.6.9. REFERENCES

BUA (Gesellschaft Deutscher Chemiker - Beratergremium für Umweltrelevante Altstoffe / AdvisoryCommittee on Existing Chemicals of Environmental Relevance of the German Chemical Society) (1998):
BUA Report 200: Gasoline.
S. Hirzel Wissenschaftliche Verlagsgesellschaft, Stuttgart, Germany.

ATSDR (Agency for Toxic Substances and Disease Registry) (1998):
Draft toxicological profile for total petroleum hydrocarbons.
US Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta (Georgia), USA.

CONCAWE (the Oil Companies' Organization for Environmental and Health Protection) (1992a):
Liquefied petroleum gas.
Product Dossier No. 92/102; CONCAWE, Brussels, Belgium.

CONCAWE (the Oil Companies' Organization for Environmental and Health Protection) (1992b):
Gasolines.
Product Dossier No. 92/103; CONCAWE, Brussels, Belgium.

CONCAWE (the Oil Companies' Organization for Environmental and Health Protection) (1992c):
Bitumen and bitumen derivatives.
Product Dossier No. 92/104; CONCAWE, Brussels, Belgium.

CONCAWE (the Oil Companies' Organization for Environmental and Health Protection) (1993):
Petroleum coke.
Product Dossier No. 93/105; CONCAWE, Brussels, Belgium.

CONCAWE (the Oil Companies' Organization for Environmental and Health Protection) (1994):
Kerosenes/jet fuels.
Product Dossier No. 94/106; CONCAWE, Brussels, Belgium.

CONCAWE (the Oil Companies' Organization for Environmental and Health Protection) (1995):
Gas oils (diesel fuels/heating oils).
Product Dossier No. 95/107; CONCAWE, Brussels, Belgium.

CONCAWE (the Oil Companies' Organization for Environmental and Health Protection) (1997):
Lubricating oil basestocks.
Product Dossier No. 97/108; CONCAWE, Brussels, Belgium.

CONCAWE (the Oil Companies' Organization for Environmental and Health Protection) (1998):
Heavy fuel oils.
Product Dossier No. 98/109; CONCAWE, Brussels, Belgium.

Hutcheson MS, Pedersen D, Anastas ND, Fitzgerald J & Silverman D (1996):
Beyond TPH - health-based evaluation of petroleum hydrocarbon exposures.
Regulatory Toxicol Pharmacol 24: 85-101.

IARC (1987):
Monographs on the Evaluation of Carcinogenic Risks to Humans, Suppl. 7, Overall evaluations of carcinogenicity - an updating of IARC monographs volumes 1 to 42.
International Agency for Research on Cancer, Lyon, France.

IARC (1989):
Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 45 - Occupational exposures in petroleum refining; crude oil and major petroleum fuels.
International Agency for Research on Cancer, Lyon, France.

IPCS (International Programme on Chemical Safety) (1982):
Environmental Health Criteria 20 - Selected petroleum products.
World Health Organization, Geneva, Switzerland.

IPCS (International Programme on Chemical Safety) (1996):
Environmental Health Criteria 187 - White Spirit (Stoddard Solvent).
World Health Organization, Geneva, Switzerland.

Janssen PJCM, Van Apeldoorn ME, Van Koten-Vermeulen JEM & Mennes WC (1995):
Human-toxicological criteria for serious soil contamination - compounds evaluated in 1993 and 1994.
National Institute of Public Health and the Environment, RIVM report nr. 715810009, August 1995; Bilthoven, The Netherlands.

Janssen PJCM, Van Apeldoorn ME, Van Engelen JGM, Schielen PCJI & Wouters MFA (1998):
Maximum permissible risk levels for human intake of soil contaminants: fourth series of compounds.
National Institute of Public Health and the Environment, RIVM report nr. 711701004, March 1998; Bilthoven, The Netherlands.

MAC (Maximum Allowable Concentrations in Air) (1997):
Nationale MAC-lijst 1997-1998 van het Ministerie van Sociale Zaken & Werkgelegenheid (National MAC-list 1997-1998 of the Ministry of Social Affairs & Labour).
SDU Publishers, The Hague, The Netherlands (in Dutch).

Staats DA, Mattie DR & Fisher JW (1997):
Petroleum-related risk factors and soil screening levels.
Human Ecol Risk Assessm 3: 659-681.

TPHCWG (Total Petroleum Hydrocarbons Criteria Working Group, Toxicology Technical Action Group) (1997a):
Selection of representative TPH fractions based on fate and transport considerations.
TPHCWG Series Volume 3; Amherst Scientific Publishers, Amherst (MA), USA.

TPHCWG (Total Petroleum Hydrocarbons Criteria Working Group, Toxicology Technical Action Group) (1997b):
Development of fraction specific reference doses (RfDs) and reference concentrations (RfCs) for total petroleum hydrocarbons.
TPHCWG Series Volume 4; Amherst Scientific Publishers, Amherst (MA), USA.

Vermeire TG (1993):
Voorstel voor de humaan-toxicologische onderbouwing van C-(toetsings)waarden - Addendum op rapportnr. 725201005.
National Institute of Public Health and the Environment, RIVM rapport nr. 715801001, May 1993; Bilthoven, The Netherlands (in Dutch).

Vermeire TG, Van Apeldoorn ME, De Fouw JC & Janssen PJCM (1991):
Voorstel voor de humaan-toxicologische onderbouwing van C-(toetsings)waarden.
National Institute of Public Health and the Environment, RIVM rapport nr. 725211005, February 1991; Bilthoven, The Netherlands (in Dutch).

Whittaker M & Pollard SJT (1997):
A performance assessment of source correlation and weathering indices for petroleum hydrocarbons in the environment.
Environm Toxicol Chem 16: 1149-1158.

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