Canadian Environmental Protection Act

Priority Substances List
Assessment Report

Aniline

Government of Canada / Gouvernement du Canada
Environment Canada / Environnement Canada
Health Canada / Santé Canada

Canada

CANADA'S GREEN PLAN

Canadian Environmental Protection Act

PRIORITY SUBSTANCES LIST ASSESSMENT REPORT

ANILINE

Government of Canada
Environment Canada
Health Canada

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TABLE OF CONTENTS

Synopsis

Although aniline is not produced in Canada, aniline and aniline hydrochloride are imported for use as intermediates in the production of chemicals for the synthesis of rubber and polymers. The amounts imported will likely decline as aniline is replaced by other substances in the production of rubber. Approximately 1.1 tonnes of aniline may be released into the Canadian environment each year from various stages of its commercial life cycle; however, the aniline released is not expected to persist. Information was not identified on the concentrations of aniline in air, surface waters, biota, soil, or sediment within Canada.

The predicted concentration of aniline in surface waters in Canada is approximately 130 000 times less than the effects threshold estimated for the most sensitive aquatic species identified *(Daphnia magna)*. The predicted concentration of aniline in ambient air in Canada is approximately 14 orders of magnitude less than the lowest level identified that adversely affected trees. Information on the toxicity of aniline to wildlife was not identified; however, because of the predicted low concentrations of aniline in the environment, and the low accumulation and toxicity of aniline in aquatic organisms, adverse effects on aquatic-based wildlife from decreased availability of prey are considered unlikely.

Because of its low volatility and since it is likely to degrade rapidly in air, aniline is not expected to contribute to ozone depletion, global warming, or the formation of ground-level ozone.

Although it was possible to develop a tolerable daily intake (i.e., the intake to which it is believed that a person can be exposed daily over a lifetime without deleterious effects), available data were considered insufficient to assess exposure of the general population in Canada to aniline.

Based on these considerations, it has been concluded that aniline is not entering the environment in a quantity or concentration or under conditions that are having a harmful effect on the environment or that constitute a danger to the environment upon which human life depends. There are insufficient data to conclude whether aniline is entering the environment in a quantity or concentration or under conditions that constitute a danger to human life or health.

1.0 Introduction

The *Canadian Environmental Protection Act* (CEPA) requires the Minister of the Environment and the Minister of Health to prepare and publish a Priority Substances List that identifies substances, including chemicals, groups of chemicals, effluents, and wastes, that may be harmful to the environment or constitute a danger to human health. The Act also requires both Ministers to assess these substances and determine whether they are "toxic" as defined under Section 11 of the Act which states:

> "...a substance is toxic if it is entering or may enter the environment in a quantity or concentration or under conditions
>
> (a) having or that may have an immediate or long-term harmful effect on the environment;
>
> (b) constituting or that may constitute a danger to the environment on which human life depends; or
>
> (c) constituting or that may constitute a danger in Canada to human life or health."

Substances that are assessed as "toxic" as defined under Section 11 of the Act may be placed on the List of Toxic Substances (Schedule I of CEPA). Consideration can then be given to developing guidelines, codes of practice, or regulations necessary to control any aspect of these substances' life cycle, from the research and development stage through manufacture, use, storage, transport, and ultimate disposal.

The assessment of whether aniline is "toxic" as defined under CEPA, was based on the determination of whether it **enters** or is likely to enter the Canadian environment in a concentration or quantities or under conditions that could lead to **exposure** of humans or other biota to levels that could cause harmful **effects**.

Data relevant to the assessment of whether aniline is "toxic" under CEPA were identified through evaluation of existing review documents (U.S. EPA, 1985; 1991; IARC, 1974; 1982; 1987), as well as an unpublished review of the environmental behaviour and health effects of this substance prepared under contract by Cambridge Environmental Inc. (Croy and DeVoto, 1990), supplemented with information from published reference texts and literature identified through on-line searches (up to September 1992) of various databases [(CHEMICAL ABSTRACTS, BIOLOGICAL ABSTRACTS, ENVIROLINE, TOXLINE, TOXLIT, Registry of Toxic Effects of Chemical Substances (RTECS), Integrated Risk Information System (IRIS) (U.S. EPA, 1992a), Camford Information Services, Hazardous Substances Data Bank (HSDB), Chemical Carcinogenesis Research Information System (CCRIS), Directory of American Research Technology (DART), GENETOX, EMBASE, ENVIRONMENTAL BIBLIOGRAPHY, POLLUTION ABSTRACTS, FOOD SCIENCE AND TECHNOLOGY ABSTRACTS, CURRENT CONTENTS, United States Environmental Protection Agency Toxic Releases Inventory, Environment Canada Departmental Library

Catalogue (ELIAS), AQUAREF, Canadian Research Index (MICROLOG), Cooperative Documents Project (CODOC), and Canada Institute for Scientific and Technical Information (CISTIMON)]. In addition, officials of a number of provincial ministries were requested to provide any available information on the levels of aniline in the drinking water in those provinces. Additional information relevant to the assessment of the effects of aniline on the environment were obtained from the CEPA Domestic Substances List and Statistics Canada. Data relevant to the assessment of the effects of aniline on the environment and human health obtained after April 1992 and June 1993, respectively, were not considered for inclusion.

Review articles were consulted where appropriate. However, all original studies that form the basis for determining whether aniline is "toxic" under CEPA have been critically evaluated by the following Health Canada staff (human exposure and effects on human health) and Environment Canada staff (entry and environmental exposure and effects):

Health Canada	Environment Canada
R. Gomes	R.J. Maguire
R.G. Liteplo	
M.E. Meek	

In this report, a synopsis that will appear in the *Canada Gazette* is presented. A summary of the technical information that is critical to the assessment, which is presented in greater detail in unpublished supporting documentation, is presented in Section 2.0. The assessment of whether aniline is "toxic" as defined under CEPA is presented in Section 3.0.

As part of the review and approvals process adopted by Environment Canada for its contributions to assessments of priority substances, the environmental sections of this report were reviewed externally by Drs. C.M. Auer and W.H. Farland of the United States Environmental Protection Agency. Sections of the Assessment Report and the unpublished supporting documentation related to the effects on human health were reviewed by the British Industrial Biological Research Association Toxicology International (BIBRA) (Surrey, U.K.) and approved by the Standards and Guidelines Rulings Committee of the Bureau of Chemical Hazards of Health Canada. The final Assessment Report was reviewed and approved by the Environment Canada/Health Canada CEPA Management Committee.

Copies of this Assessment Report and the unpublished supporting documentation are available upon request from:

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2.0 Summary of Information Critical to Assessment of "Toxic"

2.1 Identity, Properties, Production, and Uses

Aniline (Chemical Abstracts Service Registry Number 62-53-3) is the simplest of the primary aromatic amines, having the molecular formula C_6H_7N. At room temperature, aniline is a clear, colourless, oily liquid (Sax, 1968). It has a vapour pressure of 89 Pa at 25°C (Sax, 1968), a melting point of -5.98°C (U.S. EPA, 1991), a solubility in water of 35 g/L at 20°C (Northcott, 1978), and a log n-octano1/water partition coefficient of 0.90 (Chiou *et al.*, 1982). Synonyms for aniline include benzeneamine, phenylamine, and aminobenzene.

The predominant method of commercial manufacture of aniline involves the catalytic reduction of nitrobenzene with iron filings, although it can also be produced by the catalytic reaction of chlorobenzene and aqueous ammonia, or by the ammonolysis of phenol (Northcott, 1978).

Aniline is not produced in Canada (Camford Information Services, 1990); however, aniline and aniline hydrochloride are imported. Based on available data, aniline hydrochloride contributes less than 5% to the total amount of aniline imported. The amounts imported since 1976 are: 332 to 1353 tonnes (1976 to 1989), 28 tonnes (1990), 107 tonnes (1991) (Statistics Canada, 1976 to 1990; Camford Information Services, 1990), and these levels may decline as aniline is replaced by other substances in the production of rubber. In 1990, approximately 1 million tonnes of aniline were produced in the United States (U.S. EPA, 1992b).

Approximately 93% of the aniline imported into Canada is used in the production of chemicals for the synthesis of rubber and polymers. In the rubber industry, aniline is used in the manufacture of antioxidants, antidegradants, and vulcanization accelerators such as mercaptobenzothiazoles, diphenylguanidine, diphenylthiourea, and condensation products of aniline with various aldehydes (Ontario Ministry of the Environment, 1980). In the polymer industry, aniline is used primarily for the manufacture of isocyanate intermediates in the synthesis of polyurethanes. Aniline is also used in the production of phenolic-based resins and unsaturated polyesters, and as a laboratory reagent.

In the United States, aniline is also used in the agricultural, dye, photographic chemical, and pharmaceutical industries. In the pharmaceutical industry, aniline is used in the manufacture of sulpha drugs, acetanilide, and sweetening agents. Aniline is also used in the manufacture of hydroquinone, optical whitening agents, resins, marking inks, perfumes, shoe polishes, and many organic chemicals. Derivatives of aniline are used as herbicides, fungicides, insecticides, animal repellents, and defoliants. Aniline and its N-alkyl derivatives have also been used as antiknock compounds in leaded gasolines (Northcott, 1978; Ontario Ministry of the Environment, 1980).

2.2 Entry into the Environment

No natural sources of aniline were identified. Aniline can enter the Canadian environment from anthropogenic sources during any stage in the production, storage, transport, use, and disposal of aniline itself or aniline-containing materials, or possibly by atmospheric and waterborne transport from other countries. Aniline can enter the environment in coal tar, as a result of coal gasification and shale oil retorting, and from the reduction of nitrobenzene; however, quantitative information was not identified.

Data on the release of aniline into the Canadian environment were not identified. Total industrial emissions of aniline to the environment in the United States in 1989 were estimated to be 3182 tonnes (U.S. EPA, 1992b). If it is assumed that the use of aniline in the United States amounted to 1 x 106 tonnes in 1989, losses would be 0.32% of total use. Based on the amount of aniline used in Canada in 1989 (354 tonnes), losses would be estimated as 1.1 tonnes.

Aniline is a degradation product of some chemically-related pesticides (Lyons *et al.*, 1985a; 1985b) that have been or are registered for use in Canada. Information was not identified, however, on the amount of aniline released into the Canadian environment (or elsewhere) from these sources.

2.3 Exposure-related Information

2.3.1 *Fate*

Owing to the relatively short half-life (i.e., up to a few weeks) of aniline in water, soil, and air, this substance is not expected to persist in the environment. Based on its relatively low vapour pressure and log n-octano1/water partition coefficient, and high solubility in water, it is anticipated that aniline would be present in the environment predominantly in water. Microbial degradation is the most significant process that governs the persistence of aniline in water (Sanders, 1979; Lyons *et al.*, 1984; Howard, 1989); however, photo-oxidation (in surface water) and biological degradation (in groundwater) may also be significant (Aelion *et al.*, 1987; 1989). The half-life for volatilization of aniline from surface water (1-metre deep, flowing at 1 in/s, with wind velocity of 3 m/s, at 200^{o}C) was estimated to be 359 hours, calculated according to a method described by Thomas (1982).

The fate of aniline in soil is governed by biological degradation, oxidation, and binding to soil constituents (Parris, 1980).

The half-life for the photodegradation of aniline in air is estimated to be 3.3 hours (Howard, 1989).

2.3.2 *Concentrations*

No information was identified on the levels of aniline in air, surface waters, biota, soil, or sediment in Canada.

The levels of aniline in samples (n = 1) of rural and urban ambient air in the United States were less than the detection limit (0.05 µg/m^3) (Hawthorne and Sievers, 1984). The concentration of aniline in a sample of suburban air in the United States was 45 ppb (171 µg/m^3) (Shah and Hyerdahl, 1988, cited in U.S. EPA, 1991).

The concentrations of aniline in samples of water collected from rivers in the Netherlands, Germany, and the United States ranged up to 13 µg/L (Meijers and van der Leer, 1976; Neurath *et al.,* 1977; Wegman and De Korte; 1981a; 198lb; U.S. EPA, 1988). Aniline was detected (but not quantitated) in samples of influent and effluent collected from a sewage treatment plant in Ontario (Ontario Ministry of the Environment, 1982). The concentrations of aniline in industrial effluent from chemical plants in the United States ranged up to 480 µg/L (Jungclaus *et al.,* 1978; Games and Hites, 1977).

Available data on the levels of aniline in groundwater in Canada (and the United States) are limited to studies in which samples were collected in the vicinity of known industrial sources. In surveys of groundwater conducted in Ontario, the concentration of aniline in samples collected near a landfill site (Reinhard *et al.,* 1984) and in the vicinity of a chemical company (Lesage *et al.,* 1990; Dames and Moore, Canada, 1992) was 0.01 mg/L and up to 300 mg/L, respectively. Levels of aniline ranged up to 20 000 mg/L in samples of dense non-aqueous phase liquid collected from an area located beneath former containment areas of a chemical plant in Ontario (CH2M HILL ENGINEERING LTD., 1991).

Available quantitative information on the levels of aniline in drinking water in Canada is restricted to the results of a survey conducted in Quebec in which this substance was not detected (i.e., levels were < 0.5 µg/L) in samples from 17 municipalities (Quebec Ministry of the Environment, 1992).

Identified information on the levels of aniline in soil or sediments was limited to one study conducted in the United States, in which the concentration of aniline in samples of soil collected near the disposal site of a dye manufacturing plant was 5 mg/kg (Nelson and Hites, 1980).

Aniline does not appear to bioaccumulate in aquatic biota. In a study in which the fate of aniline was assessed in a model aquatic ecosystem [including phytoplankton, zooplankton, green filamentous algae *(Oedogonium cardiacum),* snails *(Physa),* water flea *(Daphnia magna),* mosquito larvae (fourth instar) *(Culex quinquifasciatus),* and mosquito fish *(Gambusia affinis*)], aniline was retained in the mosquito fish with a bioconcentration factor of 6 (Lu and Metcalf, 1975). For *Daphnia magna,* bioconcentration factors range from 74 (uptake-phase data) to 590 (elimination-phase data) (Dauble *et al.,* 1986). Freitag *et al.* (1982) reported a 1-day bioconcentration factor of 4 for algae *(Chlorella fusca)* and a 3-day bioconcentration factor of less than 10 for fish (golden orfe, *Leuciscus idus melanotus).* Hardy *et al.* (1985) reported a bioconcentration factor of 91 for the alga *Scenedesmus quadricauda;* after 24 hours, 52% of the aniline remained unmetabolized. Data on the bioaccumulation of aniline in predator organisms were not identified.

Information on the levels of aniline in foodstuffs is limited to the results of a study conducted in Germany, in which concentrations were determined in only a small number of foods (i.e., fruits and vegetables). The concentration of aniline (detection limit not clearly specified) in samples (number not reported) of 15 individual foods ranged from < 0.1 mg/kg in "broken beans" to 30.9 mg/kg (wet weight) in fresh carrots (Neurath *et al.*, 1977).

Owing to the absence of data on fate and concentration of aniline in the Canadian environment, the likely distribution of this substance in the environment was predicted based on the level III fugacity model of Mackay and Paterson (1991) applied to southern Ontario using worst-case assumptions. It was assumed that all the aniline imported into Canada in 1989 was for use only in southern Ontario, and that it would be released into the water at a rate of 1.39 mol/h (based on a loss of 1.1 tonne [see Section 2.2]). The results indicate that under steady-state conditions, aniline would be distributed in air (0.002%), surface water (99.98%), sediment (0.015%), and soil (0.001%), resulting in concentrations of 2.15×10^{-9} µg/m^3 in air, 8.74×10^{-3} ng/L in water, 2.7×10^{-12} µg/g (dry weight) in soil, and 4.6×10^{-9} µg/g (dry weight) in sediment. Due to the possible formation of bound residues in sediment, however, predicted concentrations of aniline in sediment may be underestimated, while concentrations in water may be overestimated.

2.4 Toxicokinetics

In laboratory animals, aniline is metabolized (primarily in the liver) by three metabolic pathways, N-acetylation, aromatic hydroxylation, and N-hydroxylation (DECOS, 1989). The N-acetylation of aniline (to acetanilide) is catalyzed by the hepatic N-acetyltransferase, while the aromatic hydroxylation of aniline (to *o*- or *p*-aminophenol) involves the cytochrome P-450 (mixed function oxidase) enzyme system (aniline hydroxylase). The metabolic pathway in which aniline is N-hydroxylated by the cytochrome P-450 (mixed function oxidase) enzyme system, produces N-phenylhydroxylamine. It is believed that the N-acetylation pathway is an important route by which aniline is detoxified, while N-hydroxylation is the principal route by which aniline produces toxic effects in animals (and humans).

Based on the results of quantitative analyses of hepatic enzymes, radioactivity associated with macromolecules in various tissues, and aniline metabolites eliminated in the urine, McCarthy *et al.* (1985) concluded that in mice, aniline is metabolized (via N-acetylation) and detoxified to a greater extent than in rats, that its metabolism is not limited (in contrast to that of rats) at elevated levels of exposure, and that quantitatively fewer "reactive metabolites" are formed. The results of studies in rats have also indicated that there are quantitative differences in the metabolism of aniline in males and females (Pence and Schnell, 1979), which may be related to the greater sensitivity of male rats to the effects of aniline.

In humans, as in laboratory animals, aniline is metabolized (primarily in the liver) by three metabolic pathways, N-acetylation, aromatic hydroxylation, and N-hydroxylation (DECOS, 1989). The hepatic N-acetyl transferase appears to be present

in two genetically determined forms, one of which is more efficient than the other (NRC, 1981), with individuals displaying either a "slow acetylator" phenotype or a "rapid acetylator" phenotype (Lower, 1979). It is believed that "fast acetylators" metabolize aniline predominantly by N-acetylation (to acetanilide), followed by aromatic hydroxylation (to N-acetyl-p-aminophenol), and subsequent conjugation to glucuronide or sulphate (DECOS, 1989). Compared to "fast acetylators", individuals with a "slow acetylator" phenotype have a reduced capacity to metabolize aniline through N-acetylation. The predominant route of metabolism of aniline in these individuals is considered to be through aromatic hydroxylation (to *o*- or *p*-aminophenol), followed by conjugation to glucuronide or sulphate (DECOS, 1989).

2.5 Effects-related Information

2.5.1 Experimental Animals and In Vitro

The LD_{50}s for the oral administration of aniline to rats, either as the free base or as the hydrochloride salt, range from 440 to 1072 mg/[kg body weight (b.w.)·day] and 840 to 1070 mg/[kg (b.w.)·day], respectively (Hasegawa *et al.,* 1989; Sax and Feiner, 1984; Short *et al.,* 1983; Czajkowska *et al.,* 1977; Jacobson, 1972; Vernot *et al.,* 1977). The LC_{50} for the four-hour inhalation exposure of rats to aniline is 552 ppm (2100 mg/m^3) (Back *et al.,* 1972). An LC_{50} of 173 ppm (660 mg/m^3) was reported for the seven-hour inhalation exposure of mice to aniline (von Oettingen *et al,* 1947), while an LD_{50} of 195.5 mg/kg (b.w.) was reported by the same authors for the oral administration of aniline to dogs.

Information on the toxicological effects in laboratory animals following short-term exposure to aniline was limited to studies in which rats were administered a single dose level of aniline. In available short-term toxicity studies in which rats were exposed to aniline by ingestion for up to 20 days (Short *et al.,* 1983; Jenkins *et al.,* 1972), inhalation for up to two weeks (Kim and Carlson, 1986; du Pont, 1982, cited in U.S. EPA, 1991), or subcutaneous injection for up to two weeks (Toth *et al.,* 1971; Kovacs *et al.,* 1970), alterations in hematological parameters, and histopathological changes in the spleen, liver, kidney, adrenals, and bone marrow were observed. Based on these investigations, increased mortality, hematological effects, and histopathological effects in the spleen and bone marrow have been observed at doses of aniline greater than 106 mg/[kg (b.w.)·day].

Available studies on the toxicological effects in laboratory animals following subchronic exposure to aniline or aniline hydrochloride were limited to those in which rodents (rats and mice) were exposed via ingestion. Following the administration of 45 or 225 mg/[kg (b.w.)·day] of aniline (by gavage, vehicle not reported) to rats for six months, Czajkowska *et al.,* (1977) reported degeneration of the parenchyma of the liver and kidney, and an unspecified increase in the number of erythroblasts, reticuloendothelial cells, and hemosiderin deposits in the spleen of exposed animals; however, only a limited number of endpoints (growth, hematological, and histopathological effects) were examined {Lowest-Observed-Adverse-Effect-Level (LOAEL) = 45 mg/[kg (b.w.)·day] of aniline}. In Fischer 344 rats and $B6C3F_1$ mice administered a diet containing aniline hydrochloride (100, 300, 3000, or

10 000 ppm [mg/kg]) for eight weeks, gross alterations of the spleen [enlargement, discolouration, and irregular (granular) surface] were observed in animals administered 3000 or 10 000 ppm (mg/kg) of aniline hydrochloride in the diet, which were not observed in controls; however, only survival, body weight, and gross pathology were examined (NCI, 1978).

Several studies have been identified on the chronic toxicity and carcinogenicity of aniline. In a 103-week study in which the carcinogenicity of aniline was investigated in Fischer 344 rats and B6C3F_1 mice (NCI, 1978), a significant increase in the incidence of tumors was observed in rats, but not in mice, administered aniline hydrochloride in the diet. The incidence of splenic hemangiosarcoma in male rats administered diets containing 0, 3000, or 6000 ppm (mg/kg) of aniline hydrochloride {0, 174.4, or 350.5 mg/[kg (b.w.)·day] of aniline (U.S. EPA, 1991)} for 103 weeks was 0/25, 19/50 ($p < 0.001$), and 20/46 ($p < 0.001$), respectively. The combined incidence of splenic fibrosarcoma and sarcoma NOS ("not otherwise specified")[1] in male rats fed diets containing 0, 3000, or 6000 ppm (mg/kg) of aniline hydrochloride was 0/25,7/50, and 9/46 ($p = 0.015$), respectively. The combined incidence of fibrosarcoma and sarcoma NOS ("not otherwise specified") in other unspecified organs in the pleural and abdominal cavities in male rats fed diets containing 0, 3000, or 6000 ppm (mg/kg) of aniline hydrochloride was 0/25, 2/50, and 9/48 ($p = 0.017$), respectively. In male rats, the combined incidence of non-malignant and malignant adrenal pheochromocytomas occurred with a dose-related trend ($p = 0.022$); the incidence in males administered diets containing 0, 3000, or 6000 ppm (mg/kg) of aniline hydrochloride was 2/24, 6/50, and 12/44, respectively. In female Fischer 344 rats, the combined incidence of fibrosarcoma and sarcoma NOS ("not otherwise specified") of the spleen or other organs of the pleural or abdominal cavities occurred with a dose-related trend ($p = 0.009$); the combined incidence in female rats fed diets containing 0, 3000, or 6000 ppm (mg/kg) of aniline hydrochloride {0, 188.4, or 379.9 mg/[kg (b.w.)·day] of aniline (U.S. EPA, 1991)} for 103 weeks was 0/24, 1/50, and 7/50, respectively (NCI, 1978). {LOAEL (non-neoplastic effects) = 174.4 mg/[kg (b.w.)·day] of aniline (males); 188.4 mg/[kg b.w.)·day] of aniline (females); these were the lowest doses administered to each sex, and hematological parameters were not examined}.

In a review of the histopathological findings from the NCI (1978) study, Weinberger *et al.* (1985) reported that there was a significant increase in the incidence ($p \leq 0.001$) and severity of several splenic changes (including "fatty metamorphosis", fibrosis, capsule hyperplasia, and hemorrhage) in male rats administered diets containing 3000 or 6000 ppm (mg/kg) of aniline hydrochloride, compared to unexposed controls; females administered diets containing 3000 or 6000 ppm (mg/kg) of aniline hydrochloride had similar but less severe splenic alterations. In another review of the data from the NCI (1978) carcinogenicity bioassay, Goodman *et al.* (1984) reported that sarcomas appeared primarily in the splenic red pulp or splenic capsule, usually in association with areas of parenchymal and capsular fibrosis and pigmentation, with larger tumors metastasizing to the peritoneal cavity and abdominal organs.

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1 "Not otherwise specified" denotes a tumor that could not be classified further (Weinberger *et al.*, 1985).

In a second investigation concerning the carcinogenicity of aniline in rats (CIIT, 1982), the incidence of primary splenic sarcomas was increased in male CD-F rats receiving 100 mg/[kg (b.w.)·day] of aniline hydrochloride in the diet for 104 weeks.[2] The incidence of splenic stromal sarcoma and hemangiosarcoma in male rats receiving 0, 10, 30, or 100 mg/[kg (b.w.)·day] of aniline hydrochloride was 0/123, 0/129, 1/128, and 21/130, and 0/123, 0/129, 0/128, and 6/130, respectively; these increases were presumably significant, although statistical significance was not reported. A small increase (probably not significant) was also observed in the incidence of splenic fibrosarcoma, osteogenic sarcoma, and capsular sarcoma in male CD-F rats administered aniline hydrochloride, although statistical significance was not reported. The incidence of splenic fibrosarcoma and osteogenic sarcoma in male rats receiving 0, 10, 30, or 100 mg/[kg (b.w.)·day] of aniline hydrochloride was 0/123, 0/129, 0/128, and 3/130, and 0/123, 0/129, 0/128, and 3/130, respectively. The incidence of splenic capsular sarcoma in male rats receiving 0, 10, 30, or 100 mg/[kg (b.w.)·day] of aniline hydrochloride was 0/123, 0/129, 0/128, and 1/130, respectively. In female CD-F rats receiving 0, 10, 30, or 100 mg/[kg (b.w.)·day] of aniline hydrochloride in the diet for 104 weeks, the incidence of splenic hemangiosarcoma was 0/129, 0/129, 0/130, and 1/130, respectively (CIIT, 1982); there was no increase in the incidence of other splenic tumors in these animals.

Gross alterations of the spleen (including enlargement, dark red foci, and granular or irregular surface) were observed throughout the study period in male and female rats receiving 100 mg/[kg (b.w.)·day] of aniline hydrochloride in their diet. Evidence of hemolytic anemia [a reduction ($p \leq 0.05$) in the mean hematocrit, erythrocyte count, and concentration of hemoglobin] was observed in male and female rats administered diets containing 30 or 100 mg/[kg (b.w.)·day] of aniline hydrochloride (CIIT, 1982). The administration of 30 or 100 mg/[kg b.w.)·day] of aniline hydrochloride to rats produced a significant ($p \leq 0.05$) increase in the concentration of methemoglobin in the blood of males (130 to 160%) and females (43 to 83%), compared to unexposed controls. Animals receiving 100 mg/[kg b.w.)·day] of aniline hydrochloride had stromal hyperplasia and fibrosis of the splenic red pulp, chronic splenic capsulitis, splenic lymphoid atrophy, increased hematopoietic activity in the bone marrow, and increased hemosiderin deposits in the liver, compared to unexposed controls. Male rats receiving 100 mg/[kg (b.w.)·day] of aniline hydrochloride for 104 weeks had "fatty metamorphosis" of the spleen, and increased deposition of hemosiderin in the adrenals and pancreatic lymph nodes, compared to unexposed controls. Female rats receiving 100 mg/[kg (b.w.)·day] of aniline hydrochloride had increased splenic congestion, compared to unexposed controls. Male rats receiving 10, 30, or 100 mg/[kg (b.w.)·day] of aniline hydrochloride for 104 weeks had an increase in hemosiderin deposition, extramedullary hematopoiesis, and congestion in the spleen, compared to unexposed controls (CIIT, 1982). {LOAEL (non-neoplastic effects) = 7.2 mg/[kg (b.w.)·day] of aniline (male rats); No-Observed-Adverse-Effect-Level (NOAEL) = 7.2 mg/[kg (b.w.)·day] (female rats)}.

[2] Statistical significance not reported.

There were no increases in tumor incidence in male or female $B6C3F_1$ mice administered diets containing 6000 or 12 000 ppm (mg/kg) of aniline hydrochloride {736.8 or 1509.9 mg/[kg (b.w.)·day] of aniline for males; 733.0 or 1560.0 mg/kg (b.w.)·day] of aniline for females (U.S. EPA, 1991)} for 103 weeks, compared to unexposed controls; however, an increase in the incidence of chronic inflammatory biliary lesions at both levels of exposure was considered treatment-related (NCI, 1978). Compared to unexposed controls, rats administered 6000 ppm (mg/kg) of aniline hydrochloride in the diet had an increased incidence of hepatic Kupffer cell hemosiderosis (55% and 58% in males and females, respectively) (NCI, 1978). The administration of diets containing 3000 or 6000 ppm (mg/kg) of aniline hydrochloride produced an increase in the incidence of renal hemosiderosis in males (42% and 71%, respectively) and females (94% and 90%, respectively), compared to unexposed controls (NCI, 1978). {LOAEL (males) 736.8 mg/[kg (b.w.)·day] of aniline; NOAEL (females)= 1560.0 mg/[kg (b.w.)·day] of aniline; this was the lowest dose administered to male mice, and hematological effects were not examined}.

Other more limited chronic toxicity/carcinogenicity bioassays (in which no histopathologic or carcinogenic effects were observed) included a 20- to 26-week study in which several laboratory species (rats, mice, guinea pigs, and dogs) were exposed (6 hours/day, 5 days/week) to 5 ppm (19 mg/m^3) of aniline by inhalation (Oberst *et al.,* 1956), an 80-week study in which rats were administered 0, 300, 600, or 1200 ppm (mg/kg) of aniline hydrochloride {0, 21.8, 43.7, or 87.3 mg/[kg (b.w.)·day] of aniline (U.S. EPA, 1991)} in the diet (Hagiwara *et al.,* 1980), and a 52-week investigation of tumor incidence in hamsters following the weekly subcutaneous injection of 1.9 mmol/kg (b.w.)[177 mg/kg (b.w.)] of aniline (Hecht *et al.,* 1983). In the study reported by Hagiwara *et al.* (1980), the administration of aniline hydrochloride (in the diet) to rats for 80 weeks had no effect upon general growth, liver, or kidney weights, or blood clinical chemistry; however, dose-related changes in hematological parameters suggestive of hemolytic anemia were evident at all levels of exposure (U.S. EPA, 1991). {LOAEL= 21.8 mg/[kg (b.w.)·day] of aniline; this was the lowest dose administered, no statistical evaluation was presented, and the spleen was not examined histopathologically}.

The results of available studies on the genotoxic effects of aniline in various assays are mixed. In micro-organisms, aniline was generally not mutagenic (Jung *et al.,* 1992; Gentile *et al.,* 1987; von der Hude *et al.,* 1988; U.S. EPA, 1991; DECOS, 1989). In mammalian cell cultures, aniline had some mutagenic activity in mouse cells (McGregor *et al.,* 1991; Caspari *et al.,* 1988; Amacher *et al.,* 1980, cited in U.S. EPA, 1991 and DECOS, 1989), and produced an increase in the frequency of chromosomal aberrations in hamster cells, but only with metabolic activation (Ishidate *et al.,* 1988; Galloway *et al.,* 1987, cited in U.S. EPA, 1991 and DECOS, 1989). Aniline did not increase the frequency of unscheduled DNA synthesis in cultured rat hepatocytes (Yoshimi *et al.,* 1988; Butterworth *et al.,* 1989, cited in U.S. EPA, 1991) or cultured human hepatocytes (Butterworth *et al.,* 1989, cited in U.S. EPA, 1991). However, an increase in DNA damage was observed in cultured mouse lymphoma cells (Garberg *et al.,* 1988), but not in cultured rat hepatocytes (Williams, 1980, cited in DECOS, 1989) or hamster lung

fibroblasts (Swenberg *et al.*, 1976, cited in DECOS, 1989). Aniline increased the frequency of sister-chromatid exchange in cultured human cells (Wilmer *et al.*, 1981, cited in DECOS, 1989; Wilmer *et al*., 1984, cited in U.S. EPA, 1991 and DECOS, 1989) and in cultured hamster cells (Galloway *et al.*, 1987; Kawachi *et al.*, 1980; Abe and Sasaki, 1977, all cited in U.S. EPA, 1991 and DECOS, 1989; Takehisa *et al.*, 1988). Aniline also transformed mouse Balb/3T3 cells (Dunkel *et al.*, 1981, cited in U.S. EPA, 1991 and DECOS, 1989), but not other mouse or hamster cell lines (Dunkel *et al.*, 1981; Pienta, 1980; Purchase *et al.*, 1978, all cited in U.S. EPA, 1991 and DECOS, 1989; Dunkel *et al.*, 1988). In *in vivo* studies, aniline produced an increase in the number of micronuclei in bone marrow cells of rats (George *et al.*, 1990, cited in U.S. EPA, 1991) and mice (Westmoreland and Gatehouse, 1991), and an increase in the frequency of sister-chromatid exchange in bone marrow cells of mice (Parodi *et al.*, 1983, cited in U.S. EPA, 1991), but had no effect upon the frequency of chromosomal aberrations in the bone marrow cells of rats (Kawachi *et al.*, 1980, cited in U.S. EPA, 1991 and DECOS, 1989). Aniline produced DNA damage in the liver and kidney, but not in the spleen, of rats exposed to this substance, while no increase in DNA damage was observed in the liver, kidney, or bone marrow of aniline-exposed mice (Parodi *et al.*, 1982, cited in U.S. EPA, 1991 and DECOS, 1989).

In available studies in which the developmental and reproductive toxicity of aniline was investigated in rats and mice, the oral administration of aniline (or aniline hydrochloride) from day seven of gestation to parturition produced no pre- or postnatal effects on physical or behavioural development (Price *et al.*, 1985; Borriston Laboratories, 1983); however, compared to unexposed controls, signs of maternal toxicity (including a significant dose-related reduction in body weight gain, a significant dose-related increase in spleen weight, and a significant increase in methemoglobin) were evident in pregnant rats administered 10, 30, or 100 mg/[kg (b.w.)·day] of aniline hydrochloride {7.2, 21.6, or 71.9 mg/[kg (b.w.)·day] of aniline} during days 7 to 20 of gestation (Price *et al*, 1985). {LOAEL = 7.2 mg/[kg (b.w.)·day] of aniline (in dams); No-Observed-Effect-Level (NOEL) = 21.6 mg/[kg (b.w.)·day] of aniline (in offspring)}. Similarly, signs of maternal toxicity (including prostration, tremors, ataxia, lethargy, piloerection, and/or anal bleeding) were observed in pregnant mice administered 560 mg/[kg (b.w.)·day] of aniline during days 7 to 14 of gestation (Borriston Laboratories, 1983).

2.5.2 *Humans*

The acute exposure of humans to elevated concentrations of aniline produces cyanosis, headache, nausea, vomiting, tachycardia, ataxia, vertigo, tinnitus, weakness, confusion, drowsiness, convulsions, coma, and death, primarily from the development of anoxia caused by methemoglobinemia (Gosselin *et al.*, 1984). Hematotoxicity (manifested by intravascular haemolysis, anemia, and Heinz body formation), renal toxicity (renal failure), and hepatotoxicity (liver atrophy and cirrhosis) have also been observed in individuals acutely exposed to elevated concentrations of aniline (Donovan, 1983; Scott *et al.*, 1983; ACGIH, 1986; Gosselin *et al.*, 1984).

In the only clinical study identified in which the effects of orally administered aniline were examined in human volunteers, doses of 5, 15, or 25 mg of aniline were administered on three consecutive days to each of 20 volunteers. Higher doses of aniline (35, 45, 55, or 65 mg) were then administered to a small number (n = 1 to 5) of these individuals on successive days. No significant increase was observed in the level of methemoglobin in the blood of volunteers administered 5 or 15 mg of aniline; however, a significant ($p < 0.05$) increase in the level of methemoglobin was observed in individuals receiving 25 to 65 mg of aniline (Jenkins *et al.,* 1972).

Epidemiological investigations of the effects on human health produced by exposure to aniline are limited to studies of the incidence of "digestive" and "respiratory" cancer (Ott and Langner, 1983), bladder cancer (Ward *et al.*, 1991; Case *et al.,* 1954), or mortality due to bladder cancer (Case *et al.,* 1954) in occupationally-exposed workers. Generally, these individuals were exposed to other chemicals (including known human carcinogens) in addition to aniline, and little or no quantitative information was reported on the level or duration of exposure to aniline. In the most extensive epidemiological investigation to date, there was an increase in the incidence of bladder cancer in workers exposed to "aniline and *o*-toluidine"; however, the authors concluded that o-toluidine was more likely the responsible agent (Ward *et al.,* 1991).

Available information on the reproductive and developmental effects of exposure to aniline in humans was limited to one epidemiological study in which an increase in menstrual disturbances, ovarian dysfunction, and spontaneous abortion was reported in an incomplete account of a study of Russian women occupationally-exposed to aniline (in addition to other chemicals) (Podluzhnyi, 1979, cited in Barlow and Sullivan, 1982).

2.5.3 *Ecotoxicology*

The acute toxicity of aniline to aquatic biota has been examined in several species of invertebrates, bacteria, algae, fungi, fish, and amphibians. In fish, LC_5os range from 8.2 mg/L (168-hour) for the rainbow trout *Oncorhynchus mykiss* (Abram and Sims, 1982) to 187 mg/L (96-hour) for the goldfish *Carassius auratus* (Holcombe *et al.*, 1987). In other organisms, 48-hour LC_{50}^{s} range from 0.1 mg/L for *Daphnia pulex* to 800 mg/L for the mollusc *Lymnaea stagnalis* (Sloof *et al.*, 1983).

Among aquatic species, *Daphnia magna* appear to be the most sensitive to the effects of chronic exposure to aniline. Gersich and Milazzo (1988) reported a 21-day LC_{50} of 47 µg/L of aniline for *Daphnia magna*. The 14-day Lowest-Observed-Effect-Concentrations LOECs) were 22 µg/L for mortality and 43.2 µg/L for reproduction (mean total number of young per adult and mean brood size) and growth (mean dry weight) (Gersich and Milazzo, 1990). In *Daphnia magna*, the LOEC for immobilization was 98.8 µg/L of aniline (Tadokoro and Maeda, 1988). For zebra fish (*Brachydanio rerio*) exposed during the embryo larval life stages, the 28-day LC_{50} was 39 mg/L of aniline; the No-Observed-Effect-Concentration (NOEC) for hatching and growth was 1.8 mg/L (van Leeuwen *et al*., 1990)

Exposure to aniline of larvae from the mid-blastulae lifestage of the clawed toad *Xenopus laevis* produced teratogenic effects; the 96-hour EC_{50} was 370 mg/L (Davis *et al.,* 1981). In this species, embryonic development was inhibited following exposure to aniline; body size was reduced and pigmentation inhibited at concentrations of 1 mg/L and 20 to 40 mg/L, respectively (Dumpert, 1987).

Exposure of ova from bass *(Micropterus salmoides)* and goldfish *(Carassius auratus)* to concentrations of aniline as high as 100 mg/L produced teratogenic effects and reduced hatching and survival in the offspring (Birge *et al.,* 1979); the effects were less severe following exposure to 1 mg/L of aniline.

Baird *et al.* (1977) noted that aniline (20 mg/L) had some (unquantified) inhibitory effect on the respiration of organisms in activated sludge while this substance was being degraded, suggesting that a metabolite (or metabolites) may be responsible for the observed toxicity.

In terrestrial plants, aniline is taken up by the roots and appears to bind rapidly and irreversibly to plant constituents (Lyons *et al.,* 1985a*);* however, information was not identified on the bioavailability of such bound residues. The exposure of loblolly pines *(Pinus taeda* L.) to 0.4 to 10 g/m^3 of aniline for 21 to 35 days produced damage to the needles (Cheeseman *et al.,* 1980).

Data were not identified on the toxicity of aniline to wild mammals, birds, sediment, or soil biota.

3.0 Assessment of "Toxic" Under CEPA

3.1 CEPA 11(a) Environment

Aniline is not produced in Canada, but aniline and aniline hydrochloride are imported for use as intermediates in the production of chemicals for the synthesis of rubber and polymers. Approximately 1.1 tonnes of aniline may be released into the Canadian environment each year from various stages of its commercial life cycle; however, the aniline released is not expected to persist. Information was not identified on the concentrations of aniline in air, surface waters, biota, soil, or sediment within Canada.

The most sensitive aquatic species identified is *Daphnia magna*, with a 14-day LOEC (for mortality) of 22 µg/L of aniline. Dividing this value by a factor of 20 to convert to a chronic NOEC, to account for interspecies differences and to extrapolate laboratory results to the field, yields an estimated effects threshold of 1.1 µg/L. The concentration of aniline ($8.74 \times l0^{-3}$ ng/L) predicted in surface water in southern Ontario using worst-case assumptions of release is approximately 130 000 times less than the estimated effects threshold. Though the level of aniline in samples of groundwater collected in the vicinity of a chemical company in Ontario was considerably higher than the effects threshold, such contamination is not expected to be widespread.

The concentration of aniline (2.15×10^{-9} µg/m^3) predicted in air in southern Ontario using worst-case assumptions of release is approximately 2×10^{14} times less than the lowest concentration identified (0.4 g/m^3) that produced damage to needles of loblolly pine *(Pinus taeda* L.).

Information was not identified on the toxicity of aniline to wildlife. However, because of the extremely low concentrations of aniline predicted in the environment and the low accumulation and toxicity of aniline in aquatic organisms, adverse effects on aquatic-based wildlife due to decreased availability of prey are considered unlikely.

Therefore, based on available data, aniline is not considered to be entering the environment in a quantity or concentration or under conditions that are having a harmful effect on the environment.

3.2 CEPA 11(b) Environment on Which Human Life Depends

Aniline is expected to be slightly volatile and photolyze rapidly in air; therefore, it is not expected to contribute to ozone depletion, global warming, or the formation of ground-level ozone.

Therefore, based on available data, aniline is not considered to be entering the environment in a quantity or concentration or under conditions that constitute a danger to the environment upon which human life depends.

3.3 CEPA 11(c) Human Life or Health

Population Exposure. The estimated daily intakes of aniline by various age groups of the population of Canada were calculated using available limited quantitative data from other countries or the predicted values for the levels of aniline in air, water, and soil, and the amounts consumed by the population of Canada (Environmental Health Directorate, 1992). These estimated daily intakes differ by about seven orders of magnitude (see supporting documentation). Owing to the inconsistency of these estimates, it is not possible to assess the exposure of the general population of Canada to aniline.

Effects. Epidemiological studies on the carcinogenicity of aniline are limited to a few investigations of primarily small populations employed in chemical manufacturing plants who were exposed to aniline and other chemicals (including known human carcinogens). Although there was an increase in bladder cancer in workers exposed to "aniline and *o*-toluidine" in one study, the authors concluded that *o*-toluidine was more likely the responsible agent (Ward *et al.*, 1991). Due to the concomitant exposure of examined populations to other chemical substances, and the lack of analyses of outcome with duration or level of exposure to aniline, the available information is considered to be inadequate to assess the carcinogenicity of aniline in humans.

An increase in the incidence of splenic hemangiosarcomas in male CD-F rats receiving aniline hydrochloride in the diet (compared to controls) was observed and appeared to be significant at the highest dose {100 mg/[kg (b.w.)·day]}[2] (CIIT, 1982). In a carcinogenesis bioassay conducted by the National Cancer Institute (NCI, 1978), a statistically significant increase was observed in the incidence of splenic hemangiosarcoma in male Fischer 344 rats administered diets containing aniline hydrochloride. In the CIIT (1982) bioassay, there was an increase in the incidence of splenic stromal sarcoma in male CD-F rats administered aniline hydrochloride in their diet. The increase in the incidence of these sarcomas appeared to be significant at the highest dose {100 mg/[kg (b.w.)·day]}[2]. A small increase (probably not significant)[2] was also observed in the incidence of splenic fibrosarcoma, osteogenic sarcoma, and capsular sarcoma in male CD-F rats and of splenic hemangiosarcoma in female CD-F rats administered aniline hydrochloride (CIIT, 1982). There was a significant increase in the combined incidence of fibrosarcoma and sarcoma NOS ("not otherwise specified") in the spleen or other (unspecified) organs in the pleural and abdominal cavities in male Fischer 344 rats exposed to aniline hydrochloride; in female rats, the incidence of these tumors occurred with a dose-related trend (NCI, 1978). In the NCI (1978) study, there was a significant dose-response trend in the combined incidence of malignant and nonmalignant adrenal pheochromocytomas in male Fischer 344 rats administered aniline hydrochloride in their diet.

Other chronic toxicity/carcinogenicity bioassays (in which no histopathologic non-neoplastic or carcinogenic effects were observed) (Hecht *et al.*, 1983; Hagiwara

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2 Statistical significance not reported.

et al., 1980; Oberst *et al., 1956)* do not contribute to the assessment of the weight of evidence of the carcinogenicity of aniline due to limitations in the design of these studies (i.e., small number of animals, and short exposure and observation periods).

In the two most extensive carcinogenesis bioassays conducted to date (CIIT, 1982; NCI, 1978), there were considerable interspecies and sex-related variations in response. For example, the incidence of splenic hemangiosarcomas, and of fibrosarcomas and sarcomas NOS ("not otherwise specified") was increased significantly in male rats in the NCI (1978) bioassay. In female rats, however, there was a dose-related trend in fibrosarcomas and sarcomas NOS ("not otherwise specified") only and no increase in tumor incidence in male and female mice exposed to higher concentrations of aniline hydrochloride in their diets. In the CIIT bioassay, however, the incidence of splenic hemangiosarcomas and sarcomas was increased in male rats, and no increases in tumor incidence were observed in female rats. These observations are consistent with the greater metabolism of aniline by the hypothesized detoxification (N-acetylation) pathway in mice than in rats and the limitation of this pathway in rats at higher doses (i.e., 100 to 200 mg/[kg (b.w.)·day] } (McCarthy *et al.,* 1985) and with observed sex-related differences in the metabolism of aniline (Pence and Schnell, 1979). It is therefore likely that the increase in tumors predominantly in male rats is associated with the saturation of the N-acetylation detoxification pathway, and an increasing proportion of metabolism by the putatively toxic pathway (N-hydroxylation). However, McCarthy *et al.* (1985) reported similar levels of metabolism by the putatively toxic pathway in rats and mice administered doses of 50 and 100 mg/[kg (b.w.)·day] of aniline.

Since the increased incidence of splenic tumors in male rats administered aniline {at doses that may saturate the detoxification pathway, i.e., > 70 mg/[kg (b.w.)·day]} was associated with cellular damage, it is possible that the induction of these tumors results from enhanced cellular proliferation associated with cell damage resulting from the accumulation of damaged erythrocytes within this tissue (Weinberger *et al.,* 1985; Goodman *et al.,* 1984). Available data on the genotoxicity of aniline are mixed but are consistent with this hypothesis since, although based on limited data, aniline has not been genotoxic in the spleen. Aniline was either slightly or not mutagenic in bacterial and mammalian cells, and was genotoxic in some but not all assays in mammalian cells exposed *in vitro.* In *in vivo* studies, aniline increased the number of micronuclei and the frequency of sister-chromatid exchange in bone marrow cells of rats and mice, respectively (George *et al.,* 1990, cited in U.S. EPA, 1991; Parodi *et al.,* 1982; 1983, cited in U.S. EPA, 1991). In some assays, aniline produced DNA damage in the liver and kidney of rats administered this substance; however, no effect was observed in the spleen (the principal target organ in this species), or in the liver, bone marrow, or kidney of mice (Parodi *et al.,* 1982, cited in U.S. EPA, 1991 and DECOS, 1989).

In view of the inadequate information from epidemiological studies to assess the carcinogenicity of aniline in humans, and the limited evidence of carcinogenicity of aniline in laboratory animals exposed to high doses, aniline has been classified in Group III ("Possibly Carcinogenic to Humans") of the classification scheme developed for the determination of "toxic" under Paragraph 11(c) of the *Canadian Environmental*

Protection Act (Environmental Health Directorate, 1992). For compounds classified in Group III, generally a tolerable daily intake (TDI) is derived on the basis of a No-Observed-(Adverse)-Effect-Level [NO(A)EL] or Lowest-Observed-(Adverse)Effect-Level [LO(A)EL] in humans or animal species divided by an uncertainty factor, which when considered appropriate, takes into account the limited evidence of carcinogenicity.

The available epidemiological studies on human populations are considered to be inadequate for determining the TDI, owing to the absence of quantitative data on exposure, and possible confounding by concomitant exposure to other chemical substances. In the only clinical study identified in human volunteers, the level of methemoglobin and/or serum bilirubin increased following ingestion of 25 to 65 mg of aniline (Jenkins *et al.*, 1972). No increase in the level of methemoglobin was observed in individuals administered 15 mg of aniline [equivalent to a NOEL of 0.21 mg/kg (b.w.) in an adult weighing 70 kg]. However, this study is considered to be inadequate to serve as a basis for developing a TDI, since it was a short-term investigation of a limited range of biochemical effects in a very small number of subjects. Therefore, a TDI has been derived based on the lowest dose of aniline {LOAEL= 7.2 mg/[kg (b.w.)·day]} at which adverse effects (increased splenic hemosiderin, extramedullary hematopoiesis, and congestion in male CD-F rats) have been observed, in the only available long-term animal study in which an adequate range of endpoints has been examined (CIIT, 1982), and compared to that which could be derived on the basis of the limited data from clinical studies in humans. On the basis of a LOAEL of 7.2 mg/[kg (b.w.)·day] of aniline, a TDI has been derived as follows:

$$\text{TDI} = \frac{7.2 \text{ mg/kg (b.w.)}}{5000}$$

$$= 0.00144 \text{ mg/kg (b.w.)·day } \{1.44 \text{ µg/[kg (b.w.)·day]}\}$$

where:

- 7.2 mg/[kg (b.w.)·day] is the LOAEL in the longest term study of adequate design (CIIT, 1982);
- 5000 is the uncertainty factor (x 10 for intraspecies variation; x 10 for interspecies variation; x 10 for use of a LO(A)EL rather than a NO(A)EL; x5 for limited evidence of carcinogenicity).

This value for the TDI is similar to that which could be derived from the results of the limited clinical study reported by Jenkins *et al*. (1972) on formation of methemoglobin in volunteers administered aniline. In derivation of a TDI on the basis of this study in humans, the NOEL of 0.21 mg/kg (b.w.) could be divided by an uncertainty factor of 50 (which takes into account intraspecies variation and limitations of the study), yielding a value of 4.2 µg/[kg (b.w.)·day].

Generally, in the assessment of whether substances classified in Group III are "toxic" under Paragraph 11(c) of CEPA, the TDI is compared to the estimated daily intake by various age groups of the general population of Canada (Environmental Health Directorate, 1992). Estimates of the exposure of the population of Canada to aniline on the basis of predicted and measured concentrations (in the United States and Germany) differ by approximately seven orders of magnitude. Since one of these estimates is in the range of the TDI, the determination of whether aniline constitutes a danger in Canada to human life or health cannot be assessed with sufficient confidence.

Therefore, based on available information, there is insufficient information to conclude whether aniline is entering the environment in a quantity or concentration or under conditions that constitute a danger to human life or health.

3.4 Conclusions

Based on these considerations, it has been concluded that aniline is not entering the environment in a quantity or concentration or under conditions that are having a harmful effect on the environment or that constitute a danger to the environment upon which human life depends. There are insufficient data to conclude whether aniline is entering the environment in a quantity or concentration or under conditions that constitute a danger to human life or health.

4.0 Recommendations

1. To permit an assessment of the exposure of the general population of Canada to aniline, it is recommended that monitoring studies be conducted on the levels of aniline in air, drinking water, food, and soil. Owing to the relatively low value for the TDI of aniline, and limited evidence that aniline is released into the soil via the degradation of herbicides (Fishbein, 1980) and is taken up by plant roots (Lyons *et al.*, 1985a), such studies are considered to be of high priority.

2. Epidemiological studies of the health effects produced by exposure to aniline, in which there is account of potential confounding factors (such as other carcinogenic substances) and analysis of outcome with duration and extent of exposure to aniline, are recommended. Investigations of the metabolism of aniline in humans are also recommended, to permit an assessment of their sensitivity, relative to other species.

3. Data on the concentration of aniline in surface waters as well as information on the long-term toxicological effects on aquatic and terrestrial organisms should also be acquired. This research, however, is considered to be of low priority.

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