Phenol, 2,2'-methylenebis[6-(1,1-dimethylethyl)-4-methyl-

CAS No. 119-47-1

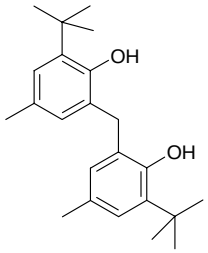

Figure 1: Structure of phenol, 2,2'-methylenebis[6-(1,1-dimethylethyl)-4-methyl-

Introduction

Under the *Canadian Environmental Protection Act, 1999* (CEPA 1999) the Minister of Health may gather information, conduct investigations and evaluations, including screening assessments, relevant for the purpose of assessing whether a substance is entering or may enter the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

Screening health assessments focus initially on conservative assessment of hazard or effect levels for critical endpoints and upper-bounding estimates of exposure, after consideration of all relevant identified information. Decisions based on the nature of the critical effects and margins between conservative effect levels and estimates of exposure take into account confidence in the completeness of the identified databases on both exposure and effects, within a screening context. Additional background information on screening health assessments conducted under this program is available at http://www.hc-sc.gc.ca/ewh-semt/contaminants/existsub/index_e.html.

A State of the Science Report for a screening assessment has been prepared on phenol, 2,2'-methylenebis[6-(1,1-dimethylethyl)-4-methyl- or 2,2’-methylenebis[6-(1,1-dimethylethyl)-4-methylphenol (MBMBP) (see Figure 1) on the basis that this compound was included in the Domestic Substances List pilot phase for screening as a substance likely to be prioritized on the basis for meeting the criteria for persistence and/or bioaccumulation and inherent toxicity to non-human organisms.

This draft State of the Science Report for a screening assessment and associated unpublished supporting working documentation were prepared by evaluators within the Existing Substances Division of Health Canada; the content of these documents was reviewed at several meetings of senior Divisional staff. The draft Report was

subsequently externally reviewed for adequacy of data coverage and defensibility of the conclusions. The supporting working documentation is available upon request by e-mail from ExSD@hc-sc.gc.ca

Information identified as of July 2003 was considered for inclusion in this Report. The critical information and considerations upon which this Report is based are summarized below.

Identity, Uses and Sources of Exposure

MBMBP is produced by the reaction of 2-*tert*-butyl-*p*-cresol with formaldehyde through a carbonyl condensation. It is used in industry as a stabilizer in styrenic and olefin polymers and polyoxymethylene homopolymers and copolymers and as an antioxidant in acrylonitrile-butadiene-styrene copolymer, polypropylene, polyacetal, rubber, latex and adhesives (NLM, 1998). A survey conducted pursuant to section 71 of the *Canadian Environmental Protection Act, 1999* (CEPA,1999) indicated that during the year 2000, between 10 and 100 tonnes of MBMBP at a concentration higher than 1% were imported into Canada. In addition, companies reported either importing or manufacturing MBMBP at a concentration lower than 1% and in a quantity meeting the reporting threshold of 100 kg. MBMBP was not reported as being manufactured at a concentration higher than 1% in Canada. Results of the Section 71 survey (Environment Canada, 2001) indicate that the pattern of use in Canada is similar to that reported elsewhere (OECD, 2003a): namely, as an adhesive and an antioxidant. No data have been identified to indicate the levels of MBMBP present in consumer products. However, given the physical and chemical properties of MBMBP, consumer products are not expected to contribute significantly to the exposure of the general Canadian population to this substance.

Exposure Assessment, Hazard Characterization and Risk Evaluation

Quantitative data upon which to base upper-bounding estimates of intake of MBMBP were not available for any environmental media in Canada or elsewhere. Estimated environmental concentrations were modelled for air, water and soil based upon the information provided in the Section 71 survey (Environment Canada, 2001). Children aged 0.5–4 years appear to be the subgroup (of the general population) most highly exposed to MBMBP in Canada, their maximum upper-bounding daily intake being 3.4×10^{-4} µg/kg-bw per day; this estimate is based on modelled environmental concentrations (see Table 1). Elevated exposure from drinking water may occur in populations close to point source releases of MBMBP to surface water. Due to the absence of monitoring data, upper-bounding estimates of daily intake associated with potential point source releases of MBMBP to surface water were estimated based on conservative modelled concentrations in drinking water.[1] Estimated intakes ranged from 7.1×10^{-3} µg/kg-bw per

[1] For the point source release scenario, it was assumed that 0.65% of the maximum estimated quantity of MBMBP imported into Canada was released into wastewater at one location (OECD, 2003b) and that the plant operated 300 days/year (European Communities, 2003). Removal of MBMBP during wastewater treatment was modelled (U.S. EPA, 2003) and subtracted from the amount released, and it was

day (12–19 years) to a maximum of 3.7×10^{-2} µg/kg-bw per day for the 0–6 months age group.

Confidence in the exposure database is considered to be very low to low, as it is based solely on modelled concentrations of MBMBP in air, soil and water and there is no indication of whether MBMBP is present in food. In view of MBMBP's high octanol/water partition coefficient, exposures through food and breast milk could occur. However, given the low concentrations predicted in water and soil and the fate of MBMBP in the environment, it is unlikely that exposures through foodstuffs and breast milk would exceed the conservative estimate presented here. MBMBP may also be present in residual amounts in consumer products, but no data were available as a basis to quantify this exposure, although it is expected to contribute minimally to total intake compared with soil.

Based on a screening-level evaluation of available toxicological data on MBMBP (see Table 2), the lowest Lowest-Observed-Effect Level (LOEL) identified was 6 mg/kg-bw per day in dogs exposed to MBMBP in the diet for 90 days (ACC, 1965b). At this dose, there was a significant difference in the change in plasma alkaline phosphatase activity from pre-exposure levels to those measured at weeks 12 and 17 in dogs exposed to MBMBP compared with controls, while histopathological changes in the liver were observed at the higher exposure levels (i.e., 10 mg/kg-bw per day or more). Results of the one limited chronic bioassay identified and the results of quantitative structure–activity relationship/structure–activity relationship modelling do not indicate that MBMBP is carcinogenic; similarly, the available limited data and model predictions do not suggest that the substance has a high potential for genotoxicity. The confidence in the database on health effects is considered to be moderate, based on the number of toxicity studies available addressing acute, repeated-dose, long-term genetic, reproductive and developmental toxicity endpoints.

Comparison of this conservative critical effect level with the upper-bounding modelled estimate of exposure for the highest exposed group (aged 0–6 months) living in the vicinity of a point source results in a margin of exposure of approximately 160 000.

Based on the level of confidence in the available database and the conservative nature of this evaluation, including the use of an upper-bounding exposure estimate based on modelled predictions and lowest reported effect level, the margin between estimated exposure levels of MBMBP and those causing health effects in experimental animals is considered adequate to account for the uncertainties in the database.

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assumed that there was no further biodegradation in the environment (i.e., half-lives were assumed to be negligible). Modelling indicated that water concentrations were estimated to be 0.35 µg/L. For formula-fed infants, the concentration of MBMBP in the water used to reconstitute formula accounts for the intake of MBMBP from food. No measured data were identified.

Table 1: Upper-bounding estimates of daily intake of MBMBP by the general population in Canada

Route of exposure	**Estimated intake (µg/kg-bw per day) of MBMBP by various age groups**						
	0–6 months[1, 2, 3]		**0.5–4 years[4]**	**5–11 years[5]**	**12–19 years[6]**	**20–59 years[7]**	**60+ years[8]**
	formula fed	**not formula fed**					
Air[9]	7.2×10^{-9}		1.5×10^{-8}	1.2×10^{-8}	6.8×10^{-9}	5.8×10^{-9}	5.1×10^{-9}
Drinking water[10]	6.4×10^{-6}	2.4×10^{-6}	2.7×10^{-6}	2.1×10^{-6}	1.2×10^{-6}	1.3×10^{-6}	1.3×10^{-6}
Food and beverages[11]		NA[12]	NA	NA	NA	NA	NA
Soil[13]	2.1×10^{-4}		3.4×10^{-4}	1.1×10^{-4}	2.6×10^{-5}	2.2×10^{-5}	2.2×10^{-5}
Total intake	2.2×10^{-4}	2.1×10^{-4}	3.4×10^{-4}	1.1×10^{-4}	2.8×10^{-5}	2.3×10^{-5}	2.3×10^{-5}

1 No data were identified on concentrations of MBMBP in breast milk.

2 Assumed to weigh 7.5 kg, to breathe 2.1 m^3 of air per day, to drink 0.8 L of water per day (formula fed) or 0.3 L/day (not formula fed), and to ingest 30 mg of soil per day (EHD, 1998).

3 For exclusively formula-fed infants, intake from water is synonymous with intake from food. The concentration of MBMBP in water used to reconstitute formula was based on modelling. No data on concentrations of MBMBP in formula were identified for Canada. For non-formula fed infants approximately 50% are introduced to solid foods by 4 months of age and 90% by 6 months of age (NHW, 1990 in EHD, 1998).

4 Assumed to weigh 15.5 kg, to breathe 9.3 m^3 of air per day, to drink 0.7 L of water per day and to ingest 100 mg of soil per day (EHD, 1998).

5 Assumed to weigh 31.0 kg, to breathe 14.5 m^3 of air per day, to drink 1.1 L of water per day and to ingest 65 mg of soil per day (EHD, 1998).

6 Assumed to weigh 59.4 kg, to breathe 15.8 m^3 of air per day, to drink 1.2 L of water per day and to ingest 30 mg of soil per day (EHD, 1998).

7 Assumed to weigh 70.9 kg, to breathe 16.2 m^3 of air per day, to drink 1.5 L of water per day and to ingest 30 mg of soil per day (EHD, 1998).

8 Assumed to weigh 72.0 kg, to breathe 14.3 m^3 of air per day, to drink 1.6 L of water per day and to ingest 30 mg of soil per day (EHD, 1998).

9 Modelling using ChemCAN 4.0 (Mackay et al., 1996) indicated that the highest concentration of MBMBP in ambient air was 2.56×10^{-8} µg/m^3. Ambient air was assumed to be representative of exposure to indoor air since there is no indication of additional sources of MBMBP in indoor environments. No measured data were identified.

10 It was assumed that 0.65% of the maximum estimated quantity of MBMBP imported into Canada was released via waste water (OECD, 2003) and that 92.97% of those emissions would be removed during waste water treatment prior to release into the environment (U.S. EPA, 2003). It was also assumed that there was no further biodegradation following the release of MBMBP to the environment (i.e., half lives were assumed to be negligible). Modelling using ChemCAN 4.0 (Mackay et al., 1996) indicated that the highest concentration of MBMBP in water was 6.0×10^{-5} µg/L. For formula-fed infants, the concentration of MBMBP in the water used to reconstitute formula accounts for the intake of MBMBP from food. No measured data were identified.

11 No measured data were identified.

12 NA = not available

13 It was assumed that 1.0% of the maximum estimated quantity of MBMBP imported into Canada was released via solid waste which would be sent to landfill and released to soil. It was also assumed that there was no biodegradation in the environment (i.e., half lives were assumed to be negligible). Modelling using ChemCAN 4.0 (Mackay et al., 1996) indicated that the highest concentration of MBMBP in soil was 52.2 µg/kg. No measured data were identified.

Table 2: Summary of health effects information for MBMBP

Endpoint	**Lowest effect levels[1]/Results**
Acute toxicity	Lowest **oral LD_{50}** (mouse) = 3200 mg/kg-bw (Ashland Oil Inc., 1992) [Additional studies: Hagan, 1952; Stasenkova et al., 1977; Sumitomo Chemical Co., 1977a; ACC, 1988; Bayer AG, 1988; Takagi et al., 1994; NLM, 1998] Lowest **dermal LD_{50}** (rabbit) >10 000 mg/kg-bw (ACC, 1988)
Short-term repeated-dose toxicity	Lowest **oral (gavage) LOEL** (rat) = 50 mg/kg-bw per day: prolongation of prothrombin time, increased liver weight, degeneration of spermatids and vacuolation of Sertoli cells (28- and 53-day studies) (MHW, 1996, 1999) [Additional studies: Hagan, 1952; Takahashi and Hiraga, 1981a, 1981b; Ashland Oil Inc., 1992]
Subchronic toxicity	Lowest **oral (diet) LOEL** (dog) = 6 mg/kg-bw per day: change in alkaline phosphatase activity (90-day study) (ACC, 1965b) [Additional studies: ACC, 1965a; Takagi et al., 1994]
Chronic toxicity/ carcinogenicity	Lowest **non-neoplastic oral (diet) LOEL** (rat) = 12.7 mg/kg-bw per day: increased relative liver weight (18-month study); no increases in tumour incidence observed in rats exposed to up to 42.3 mg/kg-bw per day for 18 months (Takagi et al., 1994)
Genotoxicity and related endpoints: *in vitro*	**Negative**: Mutagenicity in *Salmonella typhimurium* TA98, TA100, TA1535 and TA1537 and *Escherichia coli* (Sumitomo Chemical Co., 1977b; Yamaguchi et al., 1991; MHW, 1996), chromosomal aberrations in Chinese hamster lung cells (MHW, 1996), DNA damage in *Bacillus subtilis* (Sumitomo Chemical Co., 1977b) **Positive**: Cell transformation in BALB/c3T3 cells and promotion in Chinese hamster V79 lung fibroblasts (Tsuchiya et al., 1995)
Developmental toxicity	Lowest **oral (gavage) LOEL** (fetal rat) = 375 mg/kg-bw per day: increase in fetal deaths; **LOEL** (maternal) = 187 mg/kg-bw per day: decreased body weight gain (exposure during gestation days 7–17) (Tanaka et al., 1990) [Additional studies: Telford et al., 1962; MHW, 1999]
Reproductive toxicity	Lowest **oral (diet) LOEL** (male rat) = 42.3 mg/kg-bw per day: decreased absolute and relative testis weights, testis tubule atrophy and decreased spermatogenesis (18-month study) (Takagi et al., 1994) [Additional studies: MHW, 1996, 1999]

[1] LD_{50} = median lethal dose; LOEL = lowest-observed-effect level.

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