4,4'-Methylenebis(2-chlorobenzenamine) (MBOCA)

CAS No. 101-14-4

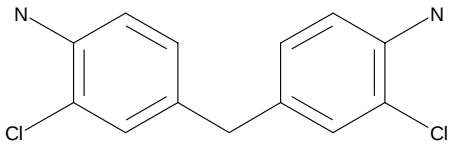

Figure 1: Structure of MBOCA

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 4,4'-Methylenebis(2-chlorobenzenamine) (MBOCA) (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This draft State of the Science Report for a screening assessment and associated unpublished supporting working documentation were prepared by evaluators within the Existing Substances Division of Health Canada; the content of these documents was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 October 2003 was considered for inclusion in this Report. The critical information and considerations upon which this Report is based are summarized below. Additional data identified between this date and the end of the external peer review period (April, 2004) were also scoped and determined not to impact upon the conclusions presented here.

Identity, Uses and Sources of Exposure

Based on submissions made under Section 71 of CEPA 1999, there were no manufacturers of MBOCA in Canada in the year 2000. The total quantity of MBOCA imported into Canada in 2000 ranged from 100 000 kg to 1 000 000 kg (Environment Canada, 2001). MBOCA is used principally as a curing agent for polyurethane prepolymers in the manufacturing of high-performance, specialized, castable urethane rubber products. Other potential uses in Canada include mouldings such as industrial tires and rollers, shock absorption pads and conveyor belting (IARC, 1993). MBOCA may also be used in the production of sport boots and shoes, roller skate wheels, cameras, computers, reproducing equipment, home appliances, electrical components and other wear-resistant industrial products (Rozinova et al., 1998; U.S. EPA, 1999). Curing agents, such as MBOCA, will be incorporated into the stable matrices of the cured polymers. Although trace amounts of unreacted MBOCA may be present in consumer products manufactured from polyurethane resins, no data have been identified on potential concentrations. Its high molecular weight and low volatility indicate that the rate of migration of any unreacted MBOCA to the surface of the polymer where consumer exposure would occur is expected to be very low. Potential exposure for the general population of Canada is expected to be as a result of industrial releases.

Exposure Assessment, Hazard Characterization and Risk Evaluation

Measured concentrations upon which to base upper-bounding estimates of intake of MBOCA were not available for any environmental media in Canada or elsewhere. Therefore, estimated concentrations were modelled for air, water and soil based upon the information provided in the Section 71 survey (Environment Canada, 2001). Based on these modelled concentrations, the formula fed 0-6 months age group of the general population is estimated to have the highest exposure to MBOCA in Canada, with the maximum upper bounding daily intake being 1.0×10^{-5} µg/kg-bw per day, and drinking water is estimated to be the most important source (see Table 1). Confidence in the exposure database is considered to be very low to low, as it is based solely on modelled concentrations of MBOCA in air, soil and water and there is no indication of the presence of MBOCA in food. MBOCA may also be present in residual amounts in consumer products, but no data were available to ascertain this.

Table 2 contains a summary of the available data on health effects information for MBOCA. The International Agency for Research on Cancer (IARC) has published an assessment of MBOCA (IARC, 1993). Long-term, oral exposure to MBOCA has induced an increased incidence of tumours in the urinary bladder and urethra of dogs, in the liver

of mice and in the lung, liver, and mammary gland of rats. In the study in which dose–response was best characterized, there was a significant increase in the incidence of lung tumours in male rats exposed to 125 ppm (6.25 mg/kg-bw per day) or more in the diet for 18 months. At the highest dose (50 mg/kg-bw per day), there was a significant increase in the incidence of mammary adenocarcinomas, Zymbal gland carcinomas and hepatocellular carcinomas. At 500 ppm (25 mg/kg-bw per day), significant increases in mortality were observed and body weights were markedly decreased. Non-neoplastic lesions, organ weights and clinical appearance were not reported (Kommineni et al., 1978). Based on a relatively extensive *in vivo* and *in vitro* database, MBOCA is considered "comprehensively genotoxic" (IARC, 1993); it also forms adducts with DNA in the same tissues in which tumours were induced in exposed rats (Cheever et al., 1988, 1990).

IARC (1993) has concluded that there is *inadequate evidence* in humans and *sufficient evidence* in experimental animals for the carcinogenicity of MBOCA and has classified the substance as *probably carcinogenic to humans* (Group 2A). Recent additional data confirm and add to the weight of evidence of the conclusions of IARC (1993). The weight of evidence of mutagenicity and carcinogenicity of MBOCA is also supported by rule-based structure–activity analysis (DEREK).

Confidence in the toxicological database for MBOCA is considered to be moderate to high. Repeated-dose toxicity studies and genotoxicity assays provided clear evidence of the carcinogenicity and genotoxicity of MBOCA; in view of the apparent high carcinogenic potency, any action taken to reduce cancer risks of this substance is likely to also be protective with respect to other endpoints (e.g., developmental and reproductive toxicity).

On the basis of available information, it is concluded that MBOCA induces tumours likely by direct interaction with genetic material. It is, therefore, considered to be a substance for which there may not be a level of exposure below which there is no probability of adverse health effects.

Table 1: Upper-bounding estimates of daily intake of MBOCA by the general population of Canada (estimated using ChemCAN 6.0)

Route of exposure	**Estimated intake (µg/kg-bw per day) of MBOCA 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]	5.0×10^{-9} - 5.0×10^{-8}		1.1×10^{-8} - 1.1×10^{-7}	8.3×10^{-9} - 8.3×10^{-8}	4.7×10^{-9} - 4.7×10^{-8}	4.1×10^{-9} - 4.1×10^{-8}	3.5×10^{-9} - 3.5×10^{-8}
Drinking water[10]	1.0×10^{-6} - 1.0×10^{-5}	3.8×10^{-7} - 3.8×10^{-6}	4.3×10^{-7} - 4.3×10^{-6}	3.4×10^{-7} - 3.4×10^{-6}	1.9×10^{-7} - 1.9×10^{-6}	2.0×10^{-7} - 2.0×10^{-6}	2.1×10^{-7} – 2.1×10^{-6}
Food and beverages[11]		NA[12]	NA	NA	NA	NA	NA
Soil[13]	1.9×10^{-8} - 1.9×10^{-7}		3.0×10^{-8} - 3.0×10^{-7}	9.8×10^{-9} - 9.8×10^{-8}	2.4×10^{-9} - 2.4×10^{-8}	2.0×10^{-9} - 2.0×10^{-8}	2.0×10^{-9} - 2.0×10^{-8}
Total intake	1.0×10^{-6} - 1.0×10^{-5}	4.1×10^{-7} - 4.1×10^{-6}	4.8×10^{-7} - 4.8×10^{-6}	3.6×10^{-7} - 3.6×10^{-6}	2.0×10^{-7} - 2.0×10^{-6}	2.1×10^{-7} - 2.1×10^{-6}	2.2×10^{-7} - 2.2×10^{-6}

1 No data were identified on concentrations of MBOCA 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 MBOCA in water used to reconstitute formula was based on modelling. No data on concentrations of MBOCA 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).

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 It was assumed that 0.005% of all MBOCA imported into Canada was released directly into the atmosphere (OECD, 2003). Modelling using ChemCAN 6.0 (CEMC, 2003) indicated that the concentration of MBOCA in ambient air ranged from 1.8×10^{-5} to 1.8×10^{-4} ng/m^3. Ambient air was assumed to be representative of exposure to indoor air since there is no indication of additional sources of MBOCA in indoor environments. *No measured data were identified.*

10 As there is no contact water used in the production of polyurethane (Polyurethane Manufacturers Association, 1999), it was assumed that there were no direct releases of MBOCA to water in Canada. Modelling using ChemCAN 6.0 (CEMC, 2003) indicated that the concentration of MBOCA in water ranged from 9.5×10^{-3} to 9.5×10^{-2} ng/L. For formula-fed infants, the concentration of MBOCA in the water used to reconstitute formula accounts for the intake of MBOCA from food. *No measured data were identified.*

11 No measured data were identified.

12 NA = not available.

[13] The solid waste generated during the use of MBOCA is sent to municipal landfill, therefore it was assumed that 0.01% of all MBOCA imported into Canada was released directly to soil. Modelling using ChemCAN 6.0 (CEMC, 2003) indicated that the concentration of MBOCA in soil ranged from 4.7×10^{-3} to 4.7×10^{-2} ng/g. *No measured data were identified.*

Table 2: Summary of health effects information for MBOCA

Endpoint	**Lowest effect levels[1]/Results**
Acute toxicity	Lowest **oral LD_{50}** (guinea pig) > 400 mg/kg-bw (NIOSH, 2002) [Additional studies: NIOSH, 2002]
Short-term repeated-dose toxicity	No data identified
Subchronic toxicity	No data identified
Chronic toxicity/ carcinogenicity	**Carcinogenicity bioassay in male rats**: *protein-adequate diet*: 0, 250, 500 or 1000 ppm (0, 12.5, 25 or 50 mg/kg-bw per day; Health Canada [1994] conversion); *protein-deficient diet*: 0, 125, 250 or 500 ppm (0, 6.25, 12.5 or 25 mg/kg-bw per day; Health Canada [1994] conversion) for 18 months (with 6-month observation period); significant increases in lung tumours were observed at all dose levels (protein-adequate diet: 1%, 23%, 37% and 70% for the control, low-, mid- and high-dose groups, respectively; protein-deficient diet: 0%, 6%, 15% and 26% for the control, low-, mid- and high-dose groups, respectively) (Kommineni et al., 1978). At the highest dose in both protein-adequate and protein-deficient rats, there was a significant increase in the incidence of mammary adenocarcinomas, Zymbal gland carcinomas and hepatocellular carcinomas. Increases in incidences of lung and liver tumours were also observed in other dietary studies in mice and rats (Grundmann and Steinhoff, 1970; Russfield et al., 1975; Stula et al., 1975) and in a subcutaneous exposure study in rats (Steinhoff and Grundmann, 1971). Increases in incidences of tumours of the urinary bladder and urethra were observed in dogs after dietary exposure to MBOCA (Stula et al., 1977). No increase in the incidence of skin papillomas was observed when MBOCA was tested as a dermal initiator or a promoter in female mice (Rozinova et al., 1998).
Developmental toxicity	No data identified
Reproductive toxicity	No data identified
Genotoxicity and related endpoints: *in vivo*	**Micronuclei assay** Positive: mouse, bone marrow (Salamone et al., 1981) Negative: rat, bone marrow; rat, peripheral blood (Wakata et al., 1998) **Mutagenicity, non-mammalian** Positive: *Drosophila melanogaster*, with activation (Kugler-Steigmeier et al., 1989) **Sister chromatid exchange** Positive: rat, lymphocytes (Edwards and Priestly, 1992)

Endpoint	Lowest effect levels[1]/Results
Genotoxicity and related endpoints: *in vitro*	**Comet assay** Positive: mouse, liver, urinary bladder and brain nuclei (Sasaki et al., 1999) **Micronuclei assay** Positive: MCL-5 and 5NA-1 cell lines (Schuler et al., 1997) **Mutagenicity** Positive: *Salmonella typhimurium*, with activation (McCann et al., 1975; Baker and Bonin, 1981; Bridges et al., 1981; Brooks and Dean, 1981; Garner et al., 1981; Hubbard et al., 1981; Ichinotsubo et al., 1981; MacDonald, 1981; Martire et al., 1981; Nagao and Takahashi, 1981; Rowland and Severn, 1981; Simmon and Shepherd, 1981; Trueman, 1981; Venitt and Crofton-Sleigh, 1981; Rao et al., 1982; Haworth et al., 1983; Cocker et al., 1985, 1986; Hesbert et al., 1985; Kugler-Steigmeier et al., 1989; Wu et al., 1989) *Escherichia coli* WP2 *uvr*A, with activation (Matsushima et al., 1981; Venitt and Crofton-Sleigh, 1981) *Mouse lymphoma L5178Y*, with activation (Mitchell et al., 1988; Myhr and Caspary, 1988) Negative: *S. typhimurium*, with activation (Baker and Bonin, 1981; Brooks and Dean, 1981; Hubbard et al., 1981; Ichinotsubo et al., 1981; Martire et al., 1981; Nagao and Takahashi, 1981; Richold and Jones, 1981; Rowland and Severn, 1981; Simmon and Shephard, 1981; Trueman, 1981; Haworth et al., 1983) *S. typhimurium*, without activation (Baker and Bonin, 1981; Brooks and Dean, 1981; Garner et al., 1981; Hubbard et al., 1981; Ichinotsubo et al., 1981; MacDonald, 1981; Martire et al., 1981; Nagao and Takahashi, 1981; Richold and Jones, 1981; Rowland and Severn, 1981; Simmon and Shepherd, 1981; Venitt and Crofton-Sleigh, 1981; Haworth et al., 1983; Cocker et al., 1985, 1986; Hesbert et al., 1985)
Salmonella typhimurium reverse mutation, without metabolic activation	Negative in strains TA98, TA100, TA1535, TA1537, TA1538 (Baker and Bonin, 1981; Brooks and Dean, 1981; Cocker et al., 1985, 1986; Garner et al., 1981; Haworth et al., 1983; Hesbert et al., 1985; Hubbard et al., 1981; Ichinotsubo et al., 1981; MacDonald, 1981; Martire et al., 1981; Nago and Takahashi, 1981; Richold and Jones, 1981; Rowland and Severn, 1981; Simmon and Shepherd, 1981; Venitt and Crofton-Sleigh, 1981)

Endpoint	Lowest effect levels[1]/Results
Salmonella typhimurium reverse mutation, with metabolic activation	Negative: Strain TA98 (Hubbard et al., 1981; Ichinotsubo et al., 1981; Richold and Jones, 1981; Rowland and Severn, 1981) Strain TA100 (Richold and Jones, 1981) Strain TA1535 (Baker and Bonin,1981; Brooks and Dean, 1981; Haworth et al., 1983; Richold and Jones, 1981; Rowland and Severn, 1981; Simmon and Shepherd, 1981) Strain TA1537 (Baker and Bonin,1981; Brooks and Dean, 1981; Haworth et al., 1983; Martire et al., 1981; Nagao and Takahashi, 1981; Richold and Jones, 1981; Rowland and Severn, 1981; Simmon and Shepherd, 1981; Trueman, 1981) Strain TA1538 (Baker and Bonin,1981; Brooks and Dean, 1981; Richold and Jones, 1981; Simmon and Shepherd, 1981; Trueman, 1981) Equivocal: TA100 (Trueman, 1981) Positive Strain TA98 (Baker and Bonin,1981; Brooks and Dean, 1981; Garner et al., 1981; MacDonald, 1981; Martire et al., 1981; Nagao and Takahashi, 1981; Simmon and Shepherd, 1981; Venitt and Crofton-Sleigh, 1981; Kugler-Steigmeier et al., 1989; Rao et al., 1982; Wu et al., 1989; Trueman, 1981) Strain TA100 (Baker and Bonin,1981; Brooks and Dean, 1981; Cocker et al., 1985, 1986; Garner et al., 1981; Haworth et al., 1983; Hesbert et al., 1985; Hubbard et al., 1981; Ichinotsubo et al., 1981; MacDonald, 1981; Martire et al., 1981; Nagao and Takahashi, 1981; Rowland and Severn, 1981; Simmon and Shepherd, 1981; Venitt and Crofton-Sleigh, 1981; Kugler-Steigmeier et al., 1989; Wu et al., 1989 Strain TA1535 (Trueman, 1981) Strain TA1538 (Garner et al., 1981) Unspecified strain (McCann et al., 1975)
	E. coli, without activation (Gatehouse, 1981; Matsushima et al., 1981; Venitt and Crofton-Sleigh, 1981) *E. coli*, with activation (Gatehouse, 1981; Matsushima et al., 1981) *Saccharomyces cerevisiae*, with and without activation (Mehta and von Borstel, 1981) *Mouse lymphoma L5178Y*, without activation (Mitchell et al., 1988; Myhr and Caspary, 1988) **Sister chromatid exchange** Positive: Chinese hamster ovary cells, with and without activation (Galloway et al., 1985) Negative: Chinese hamster ovary cells, with and without activation (Perry and Thomson, 1981) **Unscheduled DNA synthesis** Positive: Rat, mouse, hamster primary hepatocytes, without activation (McQueen et al., 1981; Williams et al., 1982; Mori et al., 1988)

[1] LD_{50} = median lethal dose.

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