CHAPTER 6. ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of MBOCA is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the adverse health effects (and techniques for developing methods to determine such health effects) of MBOCA.

Data needs are defined as substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

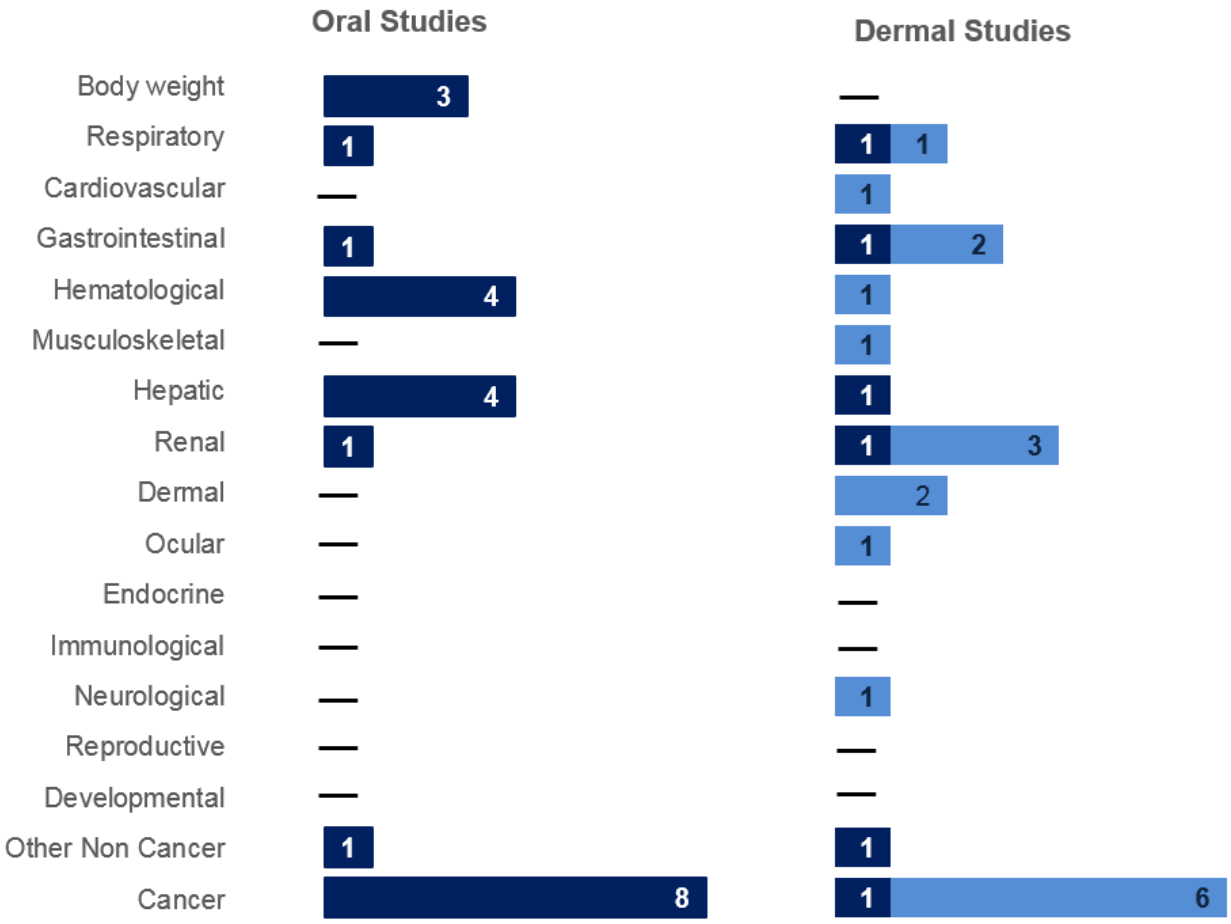
6.1 Information on Health Effects

Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to MBOCA that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of MBOCA. The number of human and animal studies examining each endpoint is indicated regardless of whether an effect was found and the quality of the study or studies.

With regard to human health effects of MBOCA, the few available studies were either case reports of acute occupational exposure or involved intermediate or chronic epidemiological studies. Acute exposures to MBOCA were by the inhalation, oral, and/or dermal routes, although in some studies, it was difficult to clearly define the exposure route. Intermediate exposures were by either inhalation and/or dermal contact; no intermediate oral exposure studies were located. Chronic exposure in humans occurred by inhalation and/or dermal contact; no chronic oral studies were located. These studies are included as dermal studies in Figure 6-1 to avoid double counting of the studies; however, it is acknowledged that exposure may have occurred via multiple routes. No information is available regarding body weight, hepatic, endocrine, immunological, reproductive, or developmental effects in humans by any route of exposure. Studies on cancer incidence in humans after inhalation and/or dermal exposure to MBOCA were located.

Figure 6-1. Summary of Existing Health Effects Studies on MBOCA By Route and Endpoint*

Potential carcinogenic, liver, and hematological effects were the most studied endpoints
The majority of the studies examined oral exposure in **animals** (versus **humans**)



*Includes studies discussed in Chapter 2; the number of studies include those finding no effect. No inhalation studies in animals were located. Human occupational exposure is expected to be predominately via dermal absorption and/or inhalation. For this figure, all human studies were counted only once under dermal exposure to avoid double counting the same study. However, it is acknowledged that exposure likely occurred via multiple routes.

Virtually all of the data regarding the health effects of MBOCA in animals were obtained from studies in which MBOCA was administered orally. No information is available regarding cardiovascular, musculoskeletal, dermal, ocular, endocrine, neurological, reproductive, or developmental effects in animals by any route of exposure. Extremely limited information is available regarding health effects in animals dermal exposure. No information is available regarding health effects in animals following inhalation exposure

6.2 Identification of Data Needs

Missing information in Figure 6-1 should not be interpreted as a "data need". A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Acute-Duration MRLs. Data were inadequate to derive acute-duration oral or inhalation MRLs. Acute data were limited to a single report of methemoglobinemia in dogs following a single oral dose (Barnes et al. 1964). Acute-duration studies are needed to identify sensitive targets of toxicity and establish dose-response relationships.

Intermediate-Duration MRLs. Data were inadequate to derive intermediate-duration oral or inhalation MRLs. Several limitations were identified in the only available intermediate-duration study (Chen et al. 2014), including examination of a limited number of endpoints, inadequate data reporting, and long recovery period (6 months) prior to examination. Additional intermediate-duration oral studies are needed; these studies should include examination of a wide range of potential targets. Intermediate-duration inhalation studies are needed to identify sensitive targets of toxicity and establish dose-response relationships.

Chronic-Duration MRLs. Data were inadequate to derive chronic-duration inhalation MRLs. Chronic-duration inhalation studies are needed to identify sensitive targets of toxicity and establish dose-response relationships. Data were considered adequate to derive a chronic-duration oral MRL; however, only a limited number of nonneoplastic endpoints have been evaluated following chronic oral exposure and a NOAEL for the critical effect (liver toxicity) has not been established. Additional chronic-duration

oral studies examining a comprehensive set of nonneoplastic endpoints over a range of doses would decrease the uncertainty in the MRL.

Health Effects. As discussed above, oral and inhalation studies of all durations would be helpful to identify the most sensitive nonneoplastic effects. Specifically, no studies were identified evaluating endocrine, reproductive, immunological, neurological, or developmental endpoints. Studies examining effects on these systems by any route of exposure would be useful.

Epidemiology and Human Dosimetry Studies. Human studies on MBOCA consist of either case reports of accidental exposure, occupational health surveys, or retrospective cohort analyses of workers previously exposed to MBOCA. Exposures are expected to be mainly inhalation and dermal. A common limitation in these studies is small sample size, lack of control for concurrent exposures, confounding factors (e.g., smoking), lack of exposure monitoring, and/or exposure via multiple routes. A well-designed prospective occupational study controlling for confounders would better evaluate the potential link between occupational MBOCA exposure and bladder cancer (and/or other health effects). In the absence of additional epidemiological studies, studies designed to evaluate potential MOAs, particularly cancer MOAs, would be useful to determine relevance of animal findings.

Biomarkers of Exposure and Effect.

Exposure. Sensitive methods for evaluation of MBOCA in urine are available. Since MBOCA can bind to body proteins and DNA, the presence of MBOCA adducts is an indication of exposure. Although information on some MBOCA metabolites and adducts is available, the development of sensitive methods for their determination is needed. Further identification of those two classes of biomarkers in humans would be helpful in assessing MBOCA exposure levels in high-risk populations.

Studies in rats showed that intraperitoneal injection of ring-labeled MBOCA, or ring-labeled n-acetylated MBOCA, resulted in the generation of three DNA adducts (Silk et al. 1989). These adducts were also produced by the *in vitro* reaction of the N-hydroxy derivative of MBOCA with rat liver slices. The major product of this reaction was also formed following incubation of DNA with N-hydroxy-6-amino-3-chlorobenzyl alcohol, the compound resulting from cleavage of the methylene bridge of N-hydroxy MBOCA. While the single ring species appears to be an intermediate in the formation of the DNA adduct, it is not known whether N-hydroxylation or bridge cleavage occurs first in the formation of the reactive species. The DNA adduct was analytically identified as N-(deoxyadenosin-8-yl)-4-amino-

3-chlorobenzyl alcohol. Since MBOCA adducts can be used as biomarkers of exposure, additional information regarding their characteristics such as half-life would be useful in estimating MBOCA exposures.

Effect. The urinary bladder is a potential target organ for MBOCA-induced carcinogenicity (Dost et al. 2009; Liu et al. 2005; Ward et al. 1988, 1990). Ward et al. (1990) demonstrated that evaluation of urine sediment cytology using the Papnicolaou technique (a current biological monitoring practice for occupational hygiene) is insensitive for detecting lesions in the urinary tract. Data from that study indicate that cystoscopy is a better biomarker of effect. Retrospective biological monitoring using cystoscopy would help identify new biomarkers necessary to characterize the preneoplastic state of the urinary bladder.

Absorption, Distribution, Metabolism, and Excretion. Quantitative data on the absorption of MBOCA in humans and animals following all routes of exposure are very limited. Human studies indicate that MBOCA is absorbed rapidly and that the amount absorbed is proportional to the dose for the inhalation (Cocker et al. 1988, 1990; Ichikawa et al. 1990; NIOSH 1986b) and/or dermal routes (Chin et al. 1983; NIOSH 1986b). Data on absorption rates for all three routes are needed. Additional quantitative absorption data in animals via all three routes would be useful because they could be used to estimate absorption in humans.

No studies were located regarding distribution in humans following inhalation, oral, or dermal exposures to MBOCA. Animal kinetic studies (following intraperitoneal or intravenous exposure) in rats and dogs indicate that MBOCA is distributed in the blood to liver, bile, kidney, lung, and fat (Cheever et al. 1991; Farmer et al. 1981; Manis et al. 1984; Morton et al. 1988; Sabbioni and Neumann 1990). It is not known if MBOCA reaches a steady state after repeated exposures. Additional inhalation and dermal exposure studies regarding distribution would be useful because of the potential for human exposure via those two routes.

Limited information is available regarding metabolism in humans (Cocker 1988, 1990; Ducos et al. 1985; Osorio et al. 1990) to MBOCA. Metabolism has been partially characterized in animals following oral exposure. *In vitro* studies investigating the capacity of MBOCA to form adducts characterized one of its metabolites, a product of cleavage between the methylene bridge and one of the aromatic nuclei, as a DNA adduct-forming metabolite, N-hydroxy-MBOCA (MBOCA-NHOH) (Silk et al. 1989). Several MBOCA metabolites were identified following N- and o-hydroxylation of MBOCA by the canine, guinea

pig, and rat liver mixed-function oxidase systems (Chen et al. 1989). Because differences in metabolism may occur with differences in the route of exposure, more data on metabolism following inhalation and dermal exposures would be useful. Also needed is information on MBOCA metabolites in terms of their potential carcinogenic capacities.

There is limited information on excretion in humans occupational exposure showing that the metabolites (N-acetyl MBOCA, β-N-glucuronide of MBOCA) and very limited amounts of parent MBOCA are excreted in the urine (Cocker et al. 1988; Ichikawa et al. 1990; NIOSH 1986b). Studies in rats show that after acute oral exposure to radioactive MBOCA, the majority of the label is in the feces (Farmer et al. 1981; Groth et al. 1984). More information is needed on the excretion rate in animals after exposure to MBOCA via all three routes in order to establish which is the major route of excretion.

Comparative Toxicokinetics. Studies using rats (Farmer et al. 1981; Groth et al. 1984; Morton et al. 1988; Tobes et al. 1983) and dogs (Manis et al. 1984b) indicate that the kinetics of MBOCA do not differ significantly across species and that the differences are primarily quantitative. Since the kinetic data alone do not allow for the identification of target organs common to humans and animals, additional studies on the distribution and toxicity may allow for identification of similar target organs. Additional studies in dogs would be helpful since they are similar to humans in that they develop bladder cancer following exposure to MBOCA. No animal data on toxicokinetics were located regarding interspecies differences or sex-related differences. The limited amount of animal data, as well as a relative lack of data across different routes of exposure, indicate that it may be difficult to compare the kinetics of MBOCA in animals with that in humans. Additional studies using several species and all three exposure routes are needed in order to determine similarities and differences between humans and animals.

Children's Susceptibility. No human or animal data are available regarding children's susceptibility. Children are not likely to be exposed to MBOCA; however, the potential for MBOCA to cause developmental effects in pregnant workers has not been evaluated. Developmental studies would be useful to address this data gap.

Physical and Chemical Properties. The physical and chemical properties of MBOCA are sufficiently defined (see Chapter 4) to allow assessments of the environmental fate of the compound to be made; no further information is needed.

Production, Import/Export, Use, Release, and Disposal. Presently, conflicting information exists on the number of people who have been or are being exposed to MBOCA in the workplace; the numbers range from 114 (NOES 1992) to 2,094 (Schulte et al. 1988). The general population is not likely to be exposed to MBOCA.

Information is unavailable on current or historical MBOCA production in the United States. MBOCA is only used in the workplace in 24 facilities in the United States (TR15 2017). Information on potential food contamination with MBOCA would also be useful in reducing risks associated with general population exposures. MBOCA may be released to the environment in waste waters or fugitive emissions from plants. Additional information is needed on atmospheric releases of MBOCA from manufacturing facilities to assess the potential for general population exposure.

At the present time, there is no information on the amounts of MBOCA disposed by different methods except for TRI data on the amounts released into different media (see Tables 5-1 and 5-2). Additional information on currently used disposal methods would allow the determination of their efficiency. Also needed is information on the availability of MBOCA residues from polyurethanes and other plastics.

Environmental Fate. The fate of MBOCA in soil has been described (EPA 1979; Voorman and Penner 1986a; Yoneyama and Matsumura 1984), and some information is available on the spread and transport of MBOCA in surface waters (Parris et al. 1980). Additional data on the aquatic fate of MBOCA, its residence time in the water column, and its absorption to sediment or organic matter in the water would assist in assessing drinking water contamination. Information on the fate of MBOCA adsorbed to sediment would be useful in assessing uptake by aquatic organisms and re-entry of MBOCA into the water column. Information on the half-life of MBOCA in the environment would also be useful for assessing the risk for human exposure.

Bioavailability from Environmental Media. Available pharmacokinetic data suggest that MBOCA is absorbed by humans following dermal and inhalation exposures (Chin et al. 1983; Cocker et al. 1988, 1990; Ichikawa et al. 1990; NIOSH 1986b). MBOCA has been measured in the urine of workers following dermal and/or inhalation exposures, suggesting rapid absorption and excretion. Information on the absorption of MBOCA by humans as a result of ingestion of contaminated water or food has not been found and would be useful in assessing the uptake of MBOCA from contaminated foods. Further information on the uptake of MBOCA by all three exposure routes, particularly the differentiation of

dermal and inhalation exposure in workers, would be helpful in determining potential uptake of MBOCA as a result of exposure to contaminated air, water, or foods, or contact with contaminated surfaces.

Food Chain Bioaccumulation. The bioconcentration factor of MBOCA has been estimated to be 5.75 in aquatic organisms (HSDB 1991). In addition, it has been shown that MBOCA binds to and penetrates the roots of plants grown in contaminated soil and is not easily removed by rinsing. However, MBOCA stays very close to the root surface and is not distributed throughout the plant, and the roots bioaccumulate the chemical (Voorman and Penner 1986b). This information suggests that there is a potential for food chain bioaccumulation both from aquatic organisms and the root systems of terrestrial plants. Actual data on the potential for aquatic organisms to bioaccumulate MBOCA would be useful in determining potential food chain concentrations.

Exposure Levels in Environmental Media. Some information exists on levels of MBOCA found in the workplace and the environment around facilities that manufacture or use MBOCA (Keeslar 1986; Parris et al. 1980). Further information on atmospheric levels of MBOCA in areas other than the workplace would be helpful for estimating general population exposure.

Reliable monitoring data for the levels of MBOCA at hazardous waste sites are also needed. The information collected on levels of MBOCA in the environment could be combined with the information on body burden to assess the potential risk of adverse health effects in populations living near hazardous waste sites.

Exposure Levels in Humans. Certain population groups are known to have a higher risk of exposure to MBOCA than others. The highest exposures are found in workers at manufacturing facilities that use MBOCA in the production of polyurethane plastics (Clapp et al. 1991; Ichikawa et al. 1990; Schulte et al. 1988; Ward et al. 1987). The next highest levels are found in populations that live near facilities where uncontrolled MBOCA releases occur (Keeslar 1986). Specific information on where such releases occur, on the populations living near such facilities, and on the levels to which they may be exposed was not found. This information is needed to assess whether health studies on these populations need to be conducted.

Exposures of Children. Children are not likely to be exposed to MBOCA unless they live near facilities where uncontrolled MBOCA releases occur (Keeslar 1986). Specific information on where such

releases occur and on the levels to which children may be exposed was not found. This information is needed to assess whether health studies on children need to be conducted.

Analytical Methods. Validated analytical methods exist for determination of MBOCA in urine and hemoglobin adducts (Robert et al. 1999a, 1999b; Vaughan and Kenyon 1996)

6.3 Ongoing Studies

No ongoing studies were identified for MBOCA.