CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

ATSDR's *Toxicological Profile for 4,4'-Methylenebis(2-chloroaniline) (MBOCA)* was released in 1994. In order to update the literature in this profile, ATSDR conducted a literature search focused on health effects information as described in Appendix B. Chapters 2 and 3 were revised to reflect the most current health effects data. In some cases, other sections of the profile were updated as needed or for consistency with the updated health effects data. However, the focus of the update to this profile is on health effects information.

4,4'-Methylenebis(2-chloroaniline) (MBOCA) is a synthetic chemical used in industry primarily to produce castable polyurethane parts. It also has a coating application in chemical reactions to "set" glues, plastics, and adhesives. Since plastics have many uses, MBOCA is used very widely. Pure MBOCA is a colorless solid, but MBOCA is usually made and used as yellow, tan, or brown pellets. If MBOCA is heated above 205°C, it may decompose. MBOCA has no odor or taste.

Most exposure to MBOCA occurs in the workplace. If you work with MBOCA, you may breathe small particles of it in the air or get it on your skin if you brush against a surface covered by MBOCA dust. There are several ways to be exposed to MBOCA outside of the workplace. For example, you may be exposed to MBOCA if you live in an area where the soil is contaminated with MBOCA. You may also be exposed if you eat foods grown in soils that contain MBOCA. However, you are unlikely to drink water contaminated with MBOCA because it does not dissolve in water.

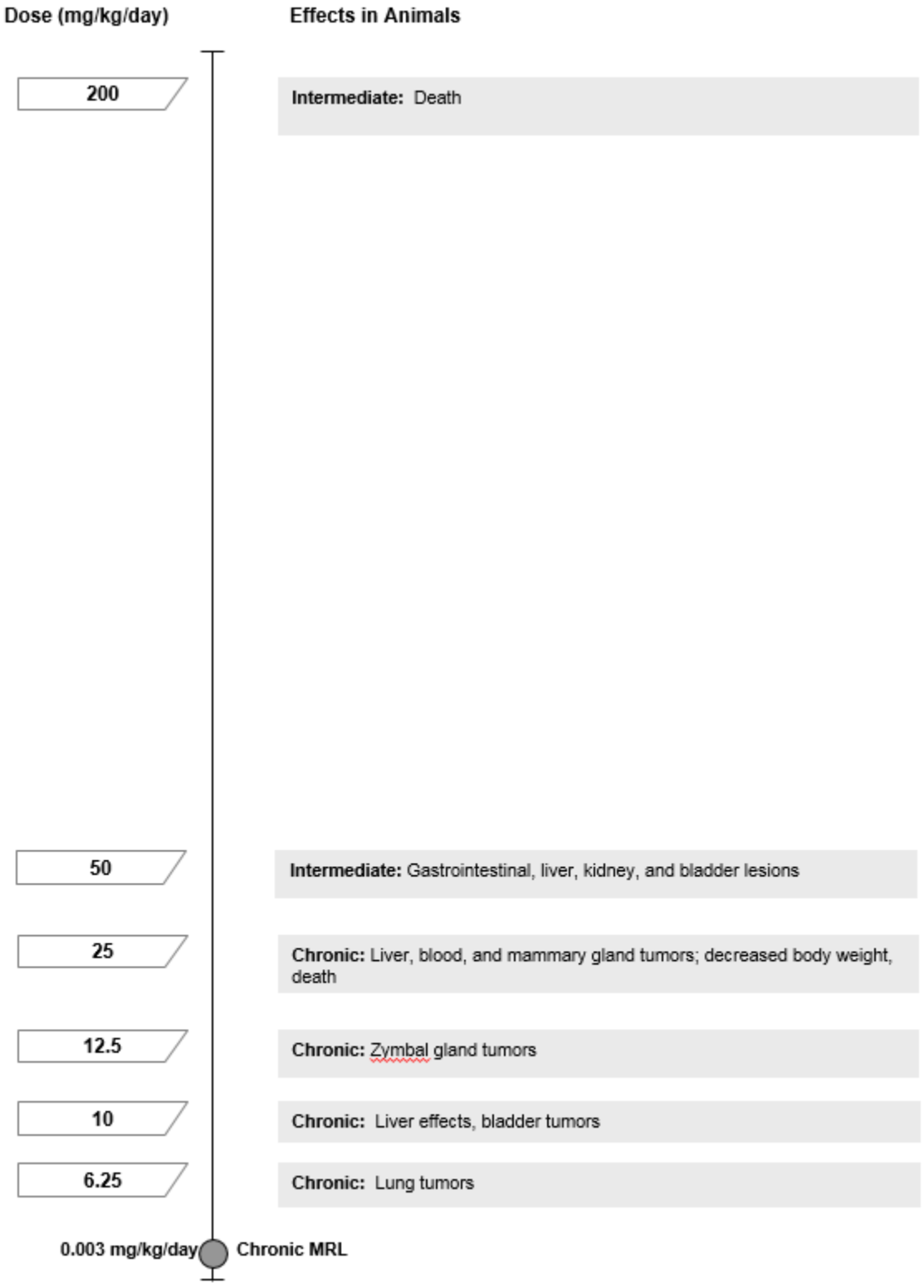
1.2 SUMMARY OF HEALTH EFFECTS

The health effects of MBOCA have been evaluated in two human occupational retrospective cohort studies of cancer, an occupational health survey, a limited number of case studies, a single intermediate-duration study evaluating oral and dermal exposure, a dermal initiation-promotion cancer study, and a limited number of chronic oral animal studies predominately focused on carcinogenicity. No animals studies evaluating potential health effects following inhalation exposure to MBOCA were identified.

As illustrated in Figure 1-1, cancer and the liver are the most sensitive targets of MBOCA toxicity in animals following oral exposure, followed by the gastrointestinal tract, kidney, and urinary bladder. Renal, dermal, ocular, and carcinogenic effects have also been described in a limited number of

occupational exposure studies with potential for exposure via multiple routes. Data regarding these effects are discussed briefly below. Available data following exposure to MBOCA in humans and animals are inadequate to determine the potential for adverse effects in the respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, endocrine, immune, nervous, or reproductive systems. It is unknown whether or not MBOCA can damage a developing fetus because no developmental exposure studies are available.

Figure 1-1. Health Effects Found in Animals Following Oral Exposure to MBOCA



Gastrointestinal Effects. Stomach upset was reported in a worker who was accidently sprayed in the face with molten MBOCA (some entered his mouth) (Hosein and Van Roosmalen 1978). In laboratory animals, stomach and intestinal degeneration and dysplasia were observed in mice following intermediate-duration oral exposure to doses ≥50 mg/kg/day or dermal exposure ≥100 mg/kg/day (Chen et al. 2014).

Hepatic Effects. No information was located regarding adverse hepatic effects in humans following exposure to MBOCA. Hepatic effects such as elevated liver enzyme levels, nodular hepatic hyperplasia, fatty changes, necrosis, fibrosis, and bile duct proliferation were observed in rats and dogs following chronic oral exposure to MBOCA to doses as low as 10 mg/kg/day (Stula et al. 1975, 1977). Hepatic degeneration and dysplasia were also observed in mice following intermediate-duration oral exposure to doses ≥50 mg/kg/day or dermal exposure ≥100 mg/kg/day (Chen et al. 2014). Neoplastic lesions associated with MBOCA exposure are discussed below in the ***Cancer*** section.

Renal and Urinary Bladder Effects. Information on the potential for renal effects following MBOCA exposure in humans is limited to evidence of altered urinalysis parameters in occupationally exposed workers, including heme and atypical cells in urine sediment in workers exposed to MBOCA for a median duration of 3.2 months (Ward et al. 1990) and urinalysis findings suggestive of transient renal tubule damage in a worker involved in a high-exposure occupational accident (Hosein and Van Roosmalen 1978). However, no atypical cells were found in another group of workers exposed for up to 16 years (Linch et al. 1971). Renal system effects in laboratory animals include renal and urinary bladder degeneration and dysplasia in mice following intermediate-duration oral exposure to doses ≥50 mg/kg/day or dermal exposure ≥100 mg/kg/day (Chen et al. 2014) and abnormal cytology in urine sediment in dogs following chronic exposure to 10 mg/kg/day (Stula et al. 1977). Abnormal cytology is considered a potential biomarker for urinary tract lesions and neoplasias; neoplastic lesions in the bladder associated with MBOCA exposure are discussed below in the ***Cancer*** section.

Cancer. A small number of retrospective cohort studies and case reports found increases in urinary bladder cancer following occupational exposure to MBOCA (Dost et al. 2009; Liu et al. 2005; Ward et al. 1988, 1990); however, these studies are limited by lack of control for confounding variables and concurrent exposures, lack of exposure levels and route information, small sample size, and/or low incidences. Chronic oral exposure studies in animals have found increases in neoplastic tumors in various organs in rodents and dogs, including the urinary bladder, lung, liver, mammary gland, Zymbal gland, and

vascular system (Grundmann and Steinhoff 1970; Kommineni et al. 1979; Russfield et al. 1975; Stula et al. 1975, 1977). Tumor type was affected by species, sex, and protein levels in the diet.

The U.S. Department of Health and Human Services (NTP 2016) has classified MBOCA as reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity in laboratory animals. The U.S. Environmental Protection Agency (EPA) has not categorized the carcinogenicity of MBOCA (IRIS 2017). The International Agency for Research on Cancer (IARC 2012) has categorized MBOCA as a Group 1 carcinogen (carcinogenic to humans) based on inadequate evidence in humans, sufficient evidence in laboratory animals, and strong mechanistic evidence indicating that carcinogenicity of MBOCA is mediated via a genotoxic mechanism of action (MOA) similar to other known cancer-causing aromatic amines.

1.3 MINIMAL RISK LEVELS (MRLs)

As presented in Figure 1-2, the limited available oral data for MBOCA suggest that the liver is the most sensitive target of toxicity. The inhalation database was considered inadequate for deriving MRLs (no animal inhalation studies identified). The MRL values are summarized in Table 1-1 and discussed in greater detail in Appendix A.

Figure 1-2. Summary of Sensitive Targets of MBOCA -- Oral

Cancer and the liver are the most sensitive targets of MBOCA.

Numbers in circles are the lowest LOAELs (mg/kg/day) for all health effects in animals; no reliable dose response data were available for humans.

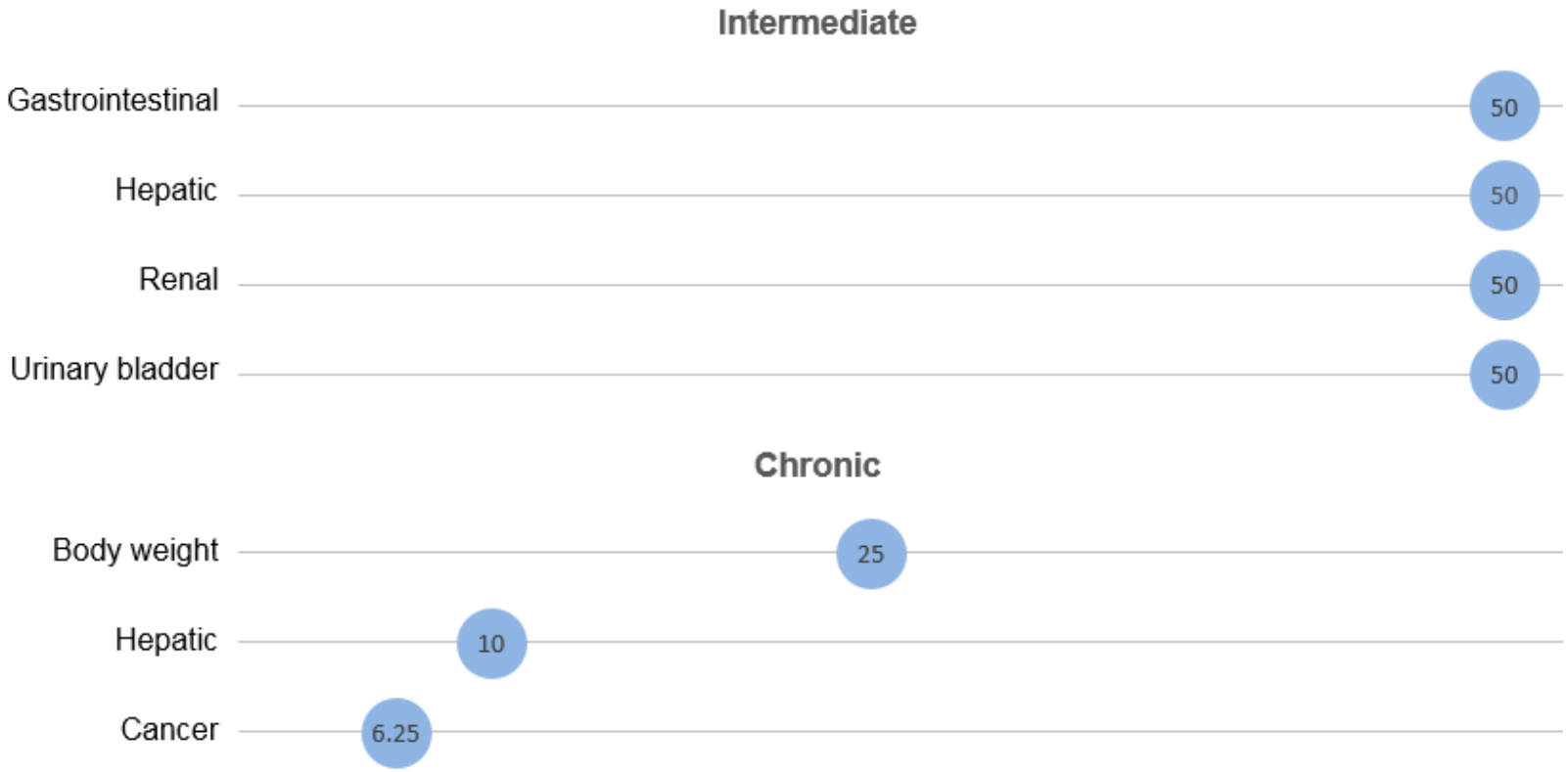


Table 1-1. Minimal Risk Levels (MRLs) for MBOCA[a]

Exposure duration	MRL	Critical effect	Point of departure	Uncertainty factor	Reference
Inhalation exposure (ppm)					
Acute	Insufficient data for MRL derivation				
Intermediate	Insufficient data for MRL derivation				
Chronic	Insufficient data for MRL derivation				
Oral exposure (mg/kg/day)					
Acute	Insufficient data for MRL derivation				
Intermediate	Insufficient data for MRL derivation				
Chronic	0.003	Increased ALT, nodular hepatic hyperplasia	10 (LOAEL)	3,000	Stula et al. 1977

[a]See Appendix A for additional information.

ALT = alanine transaminase; LOAEL = lowest-observed-adverse-effect level