CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

3,3'-Dichlorobenzidine is a synthetic chlorinated primary aromatic amine structurally similar to benzidine, which is designated as a human carcinogen. It is used in the production of azo dyes and pigments in the textile, inks, plastics, rubber, and leather industries. In the United States, manufacturing use has significantly decreased since its classification as a possible human carcinogen, although its use in manufacturing processes abroad continues.

Among the general population, people living near production facilities or hazardous waste sites are at risk of 3,3'-dichlorobenzidine exposure through industrial wastewater effluents or groundwater contamination. 3,3'-Dichlorobenzidine has been detected over 6 km away from its source, and in wastewater effluent, can travel long distances when bound to sediment. In wastewater effluent, 3,3'-dichlorobenzidine has been measured at concentrations ranging from non-detectable to 654 μg/L with an estimated median concentration <10 μg/L. Trace amount of 3,3'-dichlorobenzidine has also been detected in cosmetics that use colorants containing azo dyes in concentrations of 0.16–1.70 mg/kg; the highest concentration was observed in cosmetic skin care facial masks. Laboratory studies have observed that the photodegradation of some yellow and orange pigments used in permanent skin tattoos can yield 3,3'-dichlorobenzidine. This suggests a possible dermal exposure route, although this process has yet to be observed in humans. Due to its use as a pigment in paint, exposure to 3,3'-dichlorobenzidine could occur through ingestion of paint chip debris; this is of particular concern for children. 3,3'-Dichlorobenzidine has also been found in trace amounts in some cosmetics, skin care, and personal hygiene products in China.

Manufacturing workers of processes using or producing 3,3'-dichlorobenzidine are most likely to be exposed by inhalation or dermal contact. In occupational settings, 3,3'-dichlorobenzidine has been reported at air concentrations ranging from ≤0.6 to 2.5 μg/m^3. Dermal exposure occurs when workers handle the chemical; however, exposures have not been quantified.

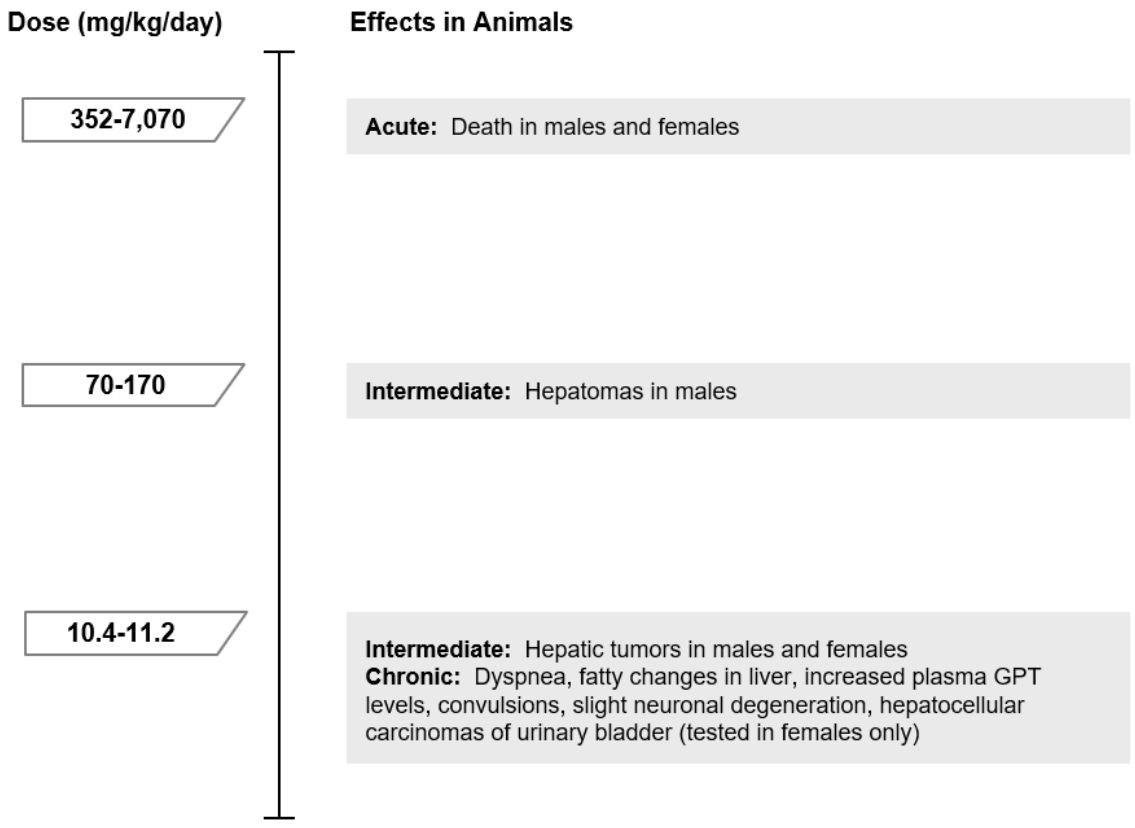
3,3’-Dichlorobenzidine and 3,3’-dichlorobenzidine metabolites are in excreted in urine; therefore, urinary levels of 3,3’-dichlorobenzidine and its metabolites are used as biomarkers of exposure. In addition, 3,3’-dichlorobenzidine metabolites can form adducts with hemoglobin and DNA, and the adducts are considered to be early biological effects of 3,3-dichlorobenzidine. Detection of these adducts can be used as both biomarkers of exposure and biomarkers of effect. Monitoring of hemoglobin and DNA adducts

combined with measuring urinary 3,3'-dichlorobenzidine and metabolite levels are effective tools for biological monitoring in humans. There are no baseline or "normal" human values for either urine or hemoglobin adduct levels for 3,3'-dichlorobenzidine. The lowest limit of detection for 3,3'-dichlorobenzidine in urine is 1.6 µg/L; and the lowest limit of detection for hemoglobin adducts is <0.1 ng/g (see Table 5-1).

1.2 SUMMARY OF HEALTH EFFECTS

The adverse health effects of 3,3'-dichlorobenzidine have been evaluated in a small number of epidemiology and animal studies. The available observational epidemiology studies primarily examined cancer as an endpoint. Most of the health effects data come from oral exposure studies in animals which evaluated the following endpoints: cancer, genotoxicity, neurological, endocrine, ocular, dermal, renal, hepatic, respiratory, body weight, and death. The lowest-observed-adverse-effect levels (LOAELs) seen in studies of animals orally exposed to 3,3'-dichlorobenzidine are presented in Figure 1-1. Exposure durations are defined as follows: acute (≤14 days), intermediate (15–364 days), and chronic (≥365 days).

Figure 1-1. Health Effects Found in Animals Following Oral Exposure to 3,3'-Dichlorobenzidine



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The most sensitive effects appear to be cancer and genotoxicity. Cancer studies were evaluated in both humans and animals. The U.S. Department of Health and Human Services classifies 3,3'-dichlorobenzidine as reasonably anticipated to be a human carcinogen (NTP 2016). The U.S. Environmental Protection Agency (EPA) classifies it as B2; probable human carcinogen (IRIS 2006). The International Agency for Research on Cancer (IARC) classifies 3,3'-dichlorobenzidine as possibly carcinogenic to humans (Group 2B) (IARC 1987).

Respiratory Effects. Limited animal findings include slight-to-moderate pulmonary congestion and pulmonary abscesses in rats following inhalation exposure, and dyspnea in one dog following oral exposure to 3,3'-dichlorobenzidine.

Hepatic Effects. Limited animal evidence suggests that chronic-duration oral exposure to 3,3'-dichlorobenzidine can result in mild-to-moderate liver injury.

***Dermal Effects*.** Dermatitis was cited as a health problem encountered by workers in contact with the free base of 3,3'-dichlorobenzidine in a manufacturing plant of the chemical (Gerarde and Gerarde 1974).

Neurological Effects. Convulsions and slight neuronal degeneration were seen in a single dog given an oral dose of 3,3'-dichlorobenzidine (Stula et al. 1978).

Cancer. The seven human studies identified involved occupationally exposed populations. The findings of the studies are mixed, and they are not of high quality. Three of the six studies found no association between exposure and bladder cancer incidence (Gadian 1975; Gerarde and Gerarde 1974; MacIntyre 1975). However, these three studies had limited power to detect an exposure-related effect due to small sample size, short follow-up time, no control group, or co-exposure to other chemicals. Two of the six studies reported an increase in bladder tumors in workers exposed to either benzidine-based azo dyes (Myslak et al. 1991) or arylamines (Ouellet-Hellstrom and Rench 1996). While the workers were exposed to 3,3'-dichlorobenzidine, they were exposed to other chemicals linked to bladder cancer. Rosenman and Reilly (2004), identified one case of bladder cancer among workers exposed only to 3,3'-dichlorobenzidine in a chemical manufacturing plant. Among these same workers, an increased risk for lymphohematopoietic cancer was identified (standardized mortality ratio [SMR] 6.62; 95% confidence interval [CI] 1.37–19.36). A limitation of this study is the lack of quantitative exposure data for the workers as only the number of years worked was provided. A follow-up to this study did not find associations between 3,3'-dichlorobenzidine and any cancer type (Millerick-May et al. 2021). The

evidence for carcinogenicity of 3,3'-dichlorobenzidine comes from studies on multiple animals and models. 3,3'-Dichlorobenzidine has been found to be carcinogenic in rats, mice, dogs, and equivocal in hamsters (Osanai 1976; Pliss 1959; Stula et al. 1975, 1978).

Genotoxic Effects. There is evidence of the genotoxicity of 3,3'-dichlorobenzidine, both *in vitro* and *in vivo* assays. Results of *in vitro* assays showed that 3,3'-dichlorobenzidine was mutagenic, increased the frequency of sister chromatid exchanges, damaged deoxyribonucleic acid (DNA), and demonstrated unscheduled DNA synthesis (Bratcher and Sikka 1982; Chen et al. 2003, 2014; Chung et al. 2000; Claxton et al. 2001; Hering et al. 2018;Imaoka et al. 1997; Lazear et al. 1979; Makena and Chung 2007; Savard and Josephy 1986; Shiraishi 1986; Vithayathil et al. 1983; Wang et al. 2005).

Results of *in vivo* assays in rats and mice showed micronuclei induction, unscheduled DNA synthesis, DNA damage, and DNA binding (Ashby and Mohammed 1988; Cihak and Vontorkova 1987; Ghosal and Iba 1990; Morita et al. 1997; Sasaki et al. 1999).

1.3 MINIMAL RISK LEVELS (MRLs)

The inhalation database was considered inadequate for the derivation of an MRL. The most sensitive targets following oral exposure to 3,3'-dichlorobenzidine are presented in Figure 1-2. The oral database was limited, and data were considered inadequate for the derivation of an MRL. MRL information for 3,3'-dichlorobenzidine is summarized in Table 1-1.

Figure 1-2. Summary of Sensitive Targets of 3,3'-Dichlorobenzidine – Oral

Hepatic, respiratory, and neurological effects are the most sensitive noncancer targets of 3,3'-dichlorobenzidine oral exposure. Cancer is the most sensitive effect.
Numbers in circles are the lowest LOAELs among health effects in animals.

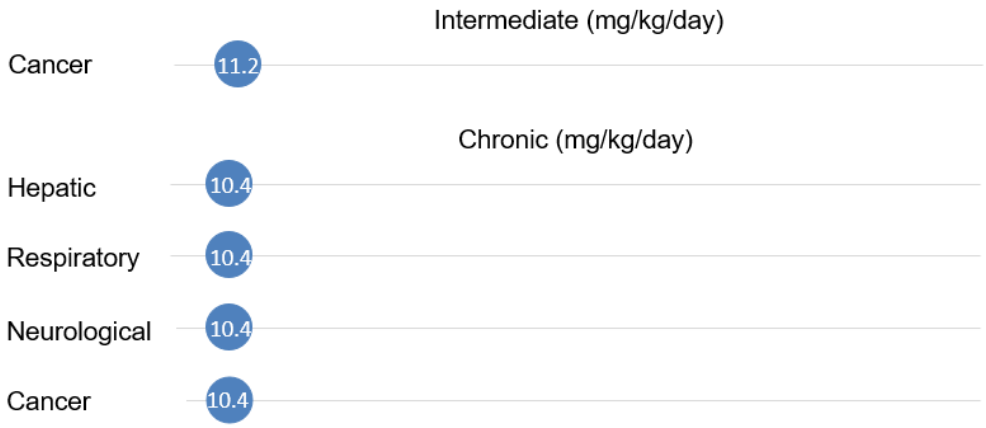

Table 1-1. Minimal Risk Levels (MRLs) for 3,3'-Dichlorobenzidine[a]

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		Insufficient data for MRL derivation			

[a]See Appendix A for additional information.