CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

ATSDR's *Toxicological Profile for N-Nitrosodiphenylamine* was released in 1993. 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.

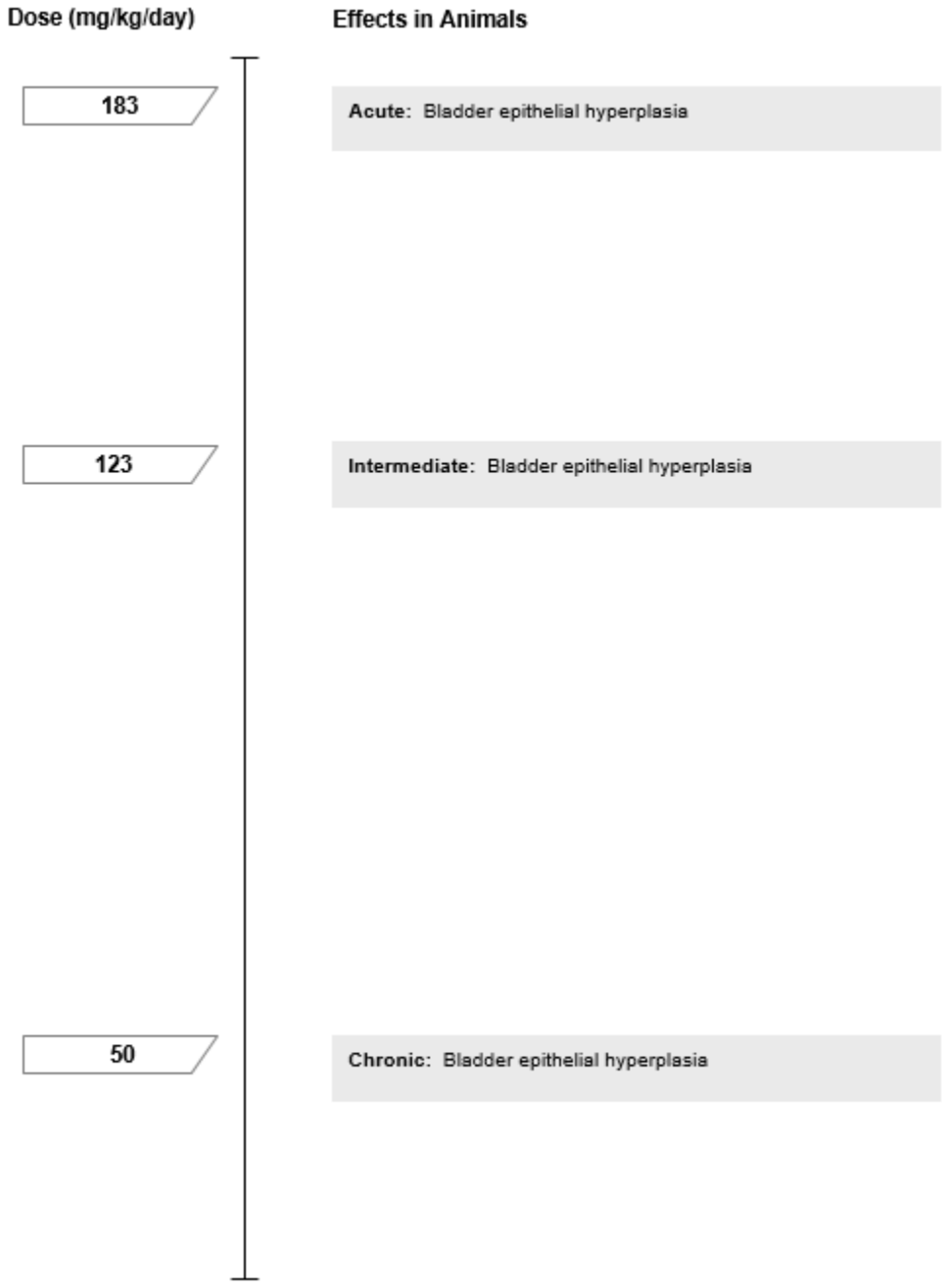
N-Nitrosodiphenylamine ($C_{12}H_{10}N_2O$, CAS No. 86-30-6) belongs to a group of chemicals referred to as nitrosamines, which share a common feature of the N-N=O structure. The general population of the United States does not appear to be exposed to any background levels of *N*-nitrosodiphenylamine. However, no studies investigating the concentrations of *N*-nitrosodiphenylamine in drinking water, foods, or ambient air were located. *N*-Nitrosodiphenylamine is not known to occur naturally in the environment (IARC 1982a). However, there is some evidence that microorganisms can produce *N*-nitrosodiphenyl-amine under laboratory conditions.

1.2 SUMMARY OF HEALTH EFFECTS

There is virtually no information regarding health effects in humans due to exposure to *N*-nitroso-diphenylamine. There is only limited information regarding effects in animals and it is almost exclusively from oral studies. Only one reliable chronic-duration oral study examined multiple organs and tissues of rats and mice and, other than the urinary bladder, no other organ or tissue showed compound-related gross or microscopic alterations. No studies were located regarding immunological, neurological, reproductive, or developmental effects of *N*-nitrosodiphenylamine in animals. There are multiple studies that examined the genotoxic effects of *N*-nitrosodiphenylamine using a variety of tests; the results have been mixed.

As illustrated in Figure 1-1, the most sensitive effect was urinary bladder lesions in rats, which developed into carcinoma as dose and exposure duration increased.

Figure 1-1. Health Effects Found in Animals Following Oral Exposure to *N*-Nitrosodiphenylamine



Cancer. The only neoplastic lesion shown to be significantly correlated with exposure to *N*-nitroso-diphenylamine was an increased incidence of bladder transitional cell carcinoma in rats exposed to 200 mg/kg/day *N*-nitrosodiphenylamine for 100 weeks; no significant increase occurred at 50 mg/kg/day (Cardy et al. 1979; NCI 1979). In a more recent shorter-duration oral study in male rats, preneoplastic urinary bladder lesions (transitional epithelium hyperplasia) were already observed in rats exposed to 183 mg/kg/day *N*-nitrosodiphenylamine for 2 weeks and in rats exposed to 123 mg/kg/day for 4 weeks (Dodd et al. 2013) indicating a concentration and exposure duration relationship of this effect. Other studies reported neoplastic lesions, including cancers of the integumentary system and liver in orally exposed rats and mice (Cardy et al. 1979; Innes et al. 1969; NCI 1968, 1979), but the increased incidences were not statistically significant. Some early studies reported no treatment-related tumors in orally exposed rats (Argus and Hoch-Ligeti 1961; Druckecy et al. 1967); however, the bladder was not routinely examined in these studies. The U.S. Environmental Protection Agency (EPA) classified *N*-nitrosodiphenylamine as a probable human carcinogen (Group B2) (IRIS 2002). The International Agency for Research on Cancer (IARC) determined that *N*-nitrosodiphenylamine is not classifiable as to its carcinogenicity to humans (Group 3) (IARC 2017). The Department of Health and Human Services (HHS) has not classified *N*-nitrosodiphenylamine as to its carcinogenicity (NTP 2016). A study of German workers exposed for years to various nitrosamines, including *N*-nitrosodiphenylamine, in the rubber industry found increases in mortality due to cancers of the prostate and oral cavity and pharynx, but there was no evidence of increased bladder cancer (Straif et al. 2000). Because there was exposure to multiple nitrosamines, the role of *N*-nitrosodiphenylamine in the cancers observed, if any, cannot be determined. The available evidence indicates that Fisher-344 rats, the strain used in studies by Cardy et al. (1979), NCI (1979), and Dodd et al. (2013), are susceptible to *N*-nitrosodiphenylamine-induced urinary bladder cancer, but the relevance of this outcome to human health is unknown.

1.3 MINIMAL RISK LEVELS (MRLs)

No inhalation MRLs were derived for *N*-nitrosodiphenylamine due to lack of adequate studies. In the single inhalation study available (from the Russian literature), rats exposed to 350–400 mg/m^3 *N*-nitrosodiphenylamine dusts for 2 hours/day for 20 days showed catarrhal bronchitis, reduced phagocytic activity of leukocytes, and decreased nerve excitability (Zhilova et al. 1966). This information is insufficient for MRL derivation.

No oral MRLs were derived for *N*-nitrosodiphenylamine due to lack of human studies and the fact that the effects observed at the lowest doses tested in an acute-duration study, an intermediate-duration study, and

a chronic-duration study in rats were considered precancerous lesions (epithelial hyperplasia and squamous metaplasia of the urinary bladder) (Dodd et al. 2013; NCI 1979). Only the urinary bladder was examined in the acute- and intermediate-duration studies (Dodd et al. 2013). In the chronic-duration study (NCI 1979), transitional cell carcinoma of the urinary bladder developed in male and female rats dosed with 200 mg/kg/day *N*-nitrosodiphenylamine (highest dose tested).