# CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

## 1.1 OVERVIEW AND U.S. EXPOSURES

ATSDR's *Toxicological Profile for N-Nitrosodi-n-Propylamine* was released in 1989. 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, 3, and 7 were revised to reflect the most current health effects and regulations/guidelines data. In some cases, other sections of the profile were updated as needed or for consistency or with the updated health effects data. However, the focus of the update to this profile is on health effects information.

N-Nitrosodi-n-propylamine ($C_6H_{14}N_2O$, CAS No. 621-64-7) belongs to a group of chemicals referred to as nitrosoamines, which share a common feature of the N-N=O structure. The general population can be exposed to N-nitrosodi-n-propylamine, and other nitrosoamines, in sodium nitrite-treated foods and certain alcoholic beverages or from the *in vivo* generation during digestion of nitrite- or secondary amine-containing foods or drugs (Magee et al. 1976; Roenen et al. 1980; Sakai et al. 1984). Tobacco products are also a source of N-nitrosodi-n-propylamine. Small quantities of N-nitrosodi-n-propylamine are produced for laboratory research. Typical N-nitrosodi-n-propylamine exposure levels have not been quantified and biomarkers of exposure have not been identified.

## 1.2 SUMMARY OF HEALTH EFFECTS

Information on the toxicity of N-nitrosodi-n-propylamine comes primarily from a small number of oral studies in laboratory animals. No epidemiology studies were identified. The 10 oral exposure studies only examined four possible health outcomes: death, liver toxicity, alterations in body weight gain, and carcinogenicity. Knowledge of the toxicity of N-nitrosodi-n-propylamine is supplemented with the results of intratracheal instillation and injection studies, which examined the hepatic, immune, developmental, and cancer endpoints.

The lowest-observed-adverse-effect levels (LOAELs) for liver, body weight, and cancer effect levels (CELs) identified in oral studies are presented in Figure 1-1.

***Hepatic Effects.*** Lethal single oral doses of N-nitrosodi-n-propylamine produced hepatic necrosis and hemorrhagic lesions in the liver (Druckrey et al. 1967). Similar effects were reported by Nishie et al. (1972), who observed that gavage doses of 40 mg/kg/day for 4 consecutive days produced swelling of

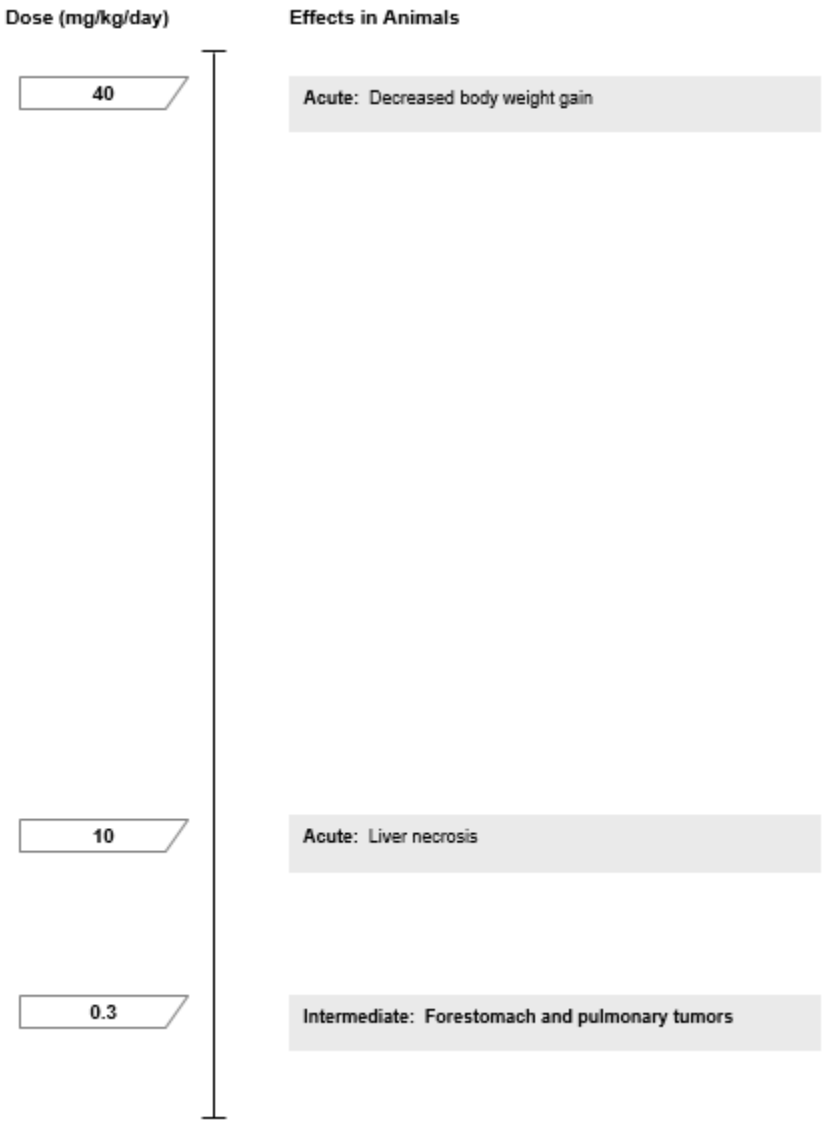
hepatocytes and possibly necrosis in the centrilobular area of the liver in mice. Hydropic degeneration, hepatitis, and increases in liver weight were also observed in mice administered intraperitoneal doses of N-nitrosodi-n-propylamine (Kaminiski et al. 1989). Hepatocellular necrosis was observed in rats administered 10 mg/kg/day for 14 days (Terashima et al. 2015). No liver effects were observed in mice administered 9.5 mg/kg/day for 1 week (Tyndall et al. 1978).

Hepatotoxicity and hemorrhagic lesions in the liver and other internal tissues are also the primary acute effects of other dialkylnitrosamine compounds (Magee et al. 1976). Based on data for other dialkylnitrosamines, it can be inferred that systemic effects of intermediate- or chronic-duration exposure to N-nitrosodi-n-propylamine are likely to include acute-type responses and preneoplastic alterations. Additionally, human fatalities due to intentional oral and accidental inhalation exposures to unknown levels of N-nitrosodimethylamine have been described in case reports in which hemorrhagic, necrotic, and cirrhotic alterations in the liver and diffuse internal bleeding were observed (Barnes and Magee 1954; Cooper and Kimbrough 1980; Freund 1937; Fussgaenger and Ditschuneits 1980; Pedal et al. 1982).

***Carcinogenic Effects.*** Information regarding the carcinogenicity of N-nitrosodi-n-propylamine in humans was not located. In animals, carcinogenicity of N-nitrosodi-n-propylamine has been demonstrated in several species in all studies that have been conducted. In rats observed for life, daily or partial weekly (administered 2 or 5 days/week) oral exposure produced tumors primarily in the liver, nasal cavity, and esophagus (Druckrey et al. 1967; Lijinsky and Reuber 1981, 1983; Lijinsky and Taylor 1978, 1979). In mice, increased incidences of forestomach tumors occurred as a result of twice weekly orally treatment for 50 weeks (Griciute et al. 1982). Respiratory tract, esophagus, and/or liver tumors have also been observed in monkeys, rats, mice, and hamster following chronic parenteral administration of N-nitrosodi-n-propylamine (Adamson and Sieber 1979, 1983; Althoff et al. 1973a, 1973b, 1977b; Dickhaus et al. 1977; Pour et al. 1973, 1974; Reznik et al. 1975).

The U.S. Department of Health and Human Services categorized N-nitrosodi-n-propylamine as reasonably anticipated to be a human carcinogen (NTP 2016), the U.S. Environmental Protection Agency (EPA) categorized it as a probable human carcinogen (Group B2) (IRIS 2002), and the International Agency for Research on Cancer categorized it as possibly carcinogenic to humans (group 2B) (IARC 1987).

## Figure 1-1. Health Effects Found in Animals Following Oral Exposure to N-Nitrosodi-n-Propylamine



## 1.3 MINIMAL RISK LEVELS (MRLs)

No inhalation studies were identified for N-nitrosodi-n-propylamine, thus precluding derivation of inhalation MRLs. The oral database was not considered adequate for derivation of an acute-duration oral MRL for N-nitrosodi-n-propylamine (Table 1-1). Liver and body weight were the only endpoints examined following acute-duration exposure. Cancer was the only adverse effect observed following intermediate-duration exposure, and no chronic oral studies were identified.

**Table 1-1. Minimal Risk Levels (MRLs) for N-Nitrosodi-n-Propylamine[a]**

| Exposure duration | MRL | Critical effect | Point of departure | Uncertainty factor | Reference |
|---|---|---|---|---|---|
| **Inhalation exposure** | | | | | |
| 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

NOAEL = no-observed-adverse-effect level