# CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

## 1.1 OVERVIEW AND U.S. EXPOSURES

1,2-Diphenylhydrazine (Chemical Abstracts Service [CAS] number 122-66-7; hydrazobenzene is a common synonym) is a colorless, crystalline solid previously used as an intermediate in dye manufacturing (e.g., benzidine) and an intermediate in some pharmaceuticals. It rapidly oxidizes in water with a half-life of approximately 15 minutes. The general population is not likely to be exposed to 1,2-diphenylhydrazine in the environment; exposure may occur in workers involved in the manufacture or use of 1,2-diphenylhydrazine.

## 1.2 SUMMARY OF HEALTH EFFECTS

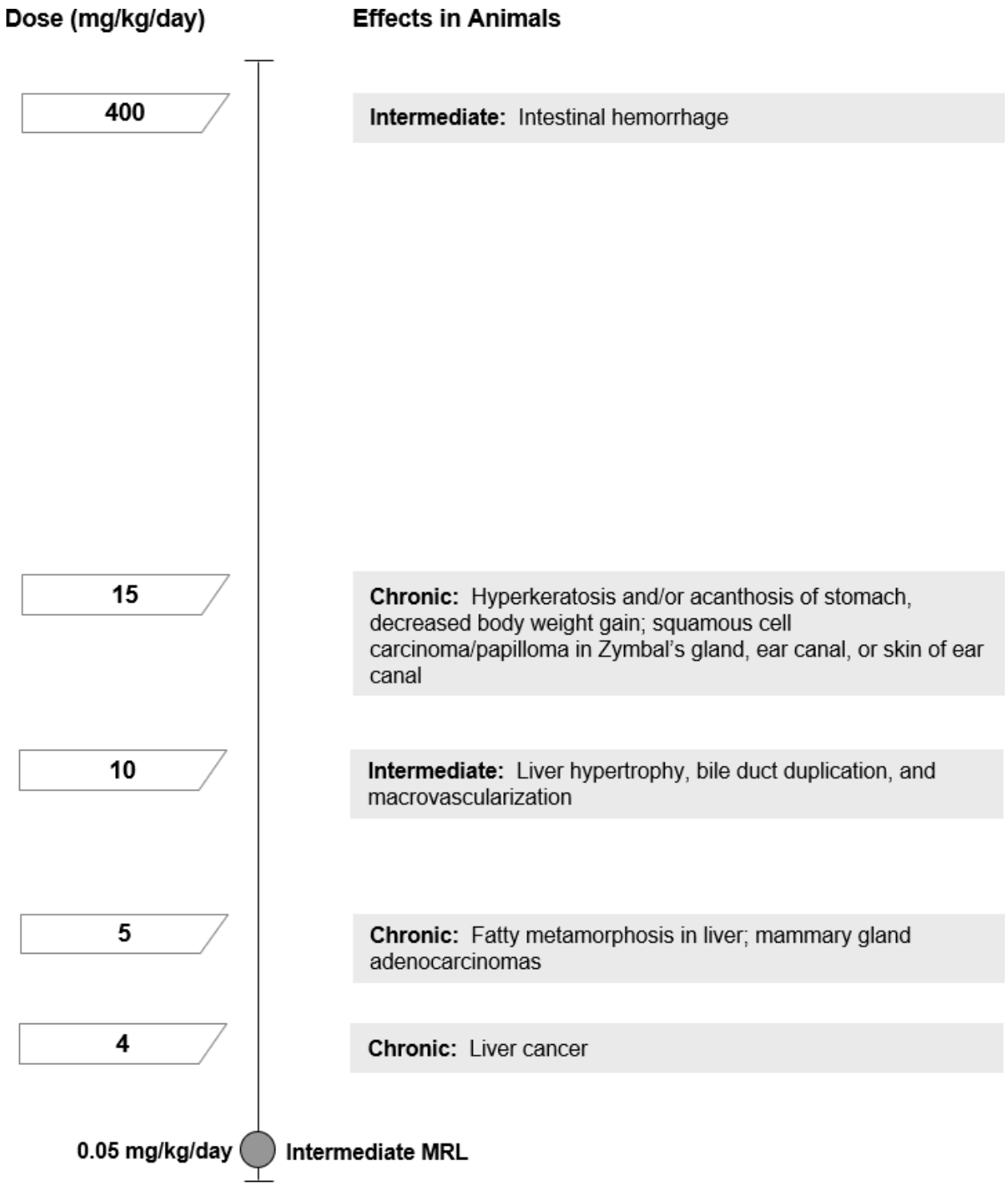
Information on the toxicity of 1,2-diphenylhydrazene is derived from a small number of health effect studies. No epidemiology or human exposure studies are available, and data are restricted to a few oral studies in laboratory animals. In addition to lethality and body weight changes, these studies evaluated primarily hepatic, non-neoplastic, and cancer endpoints. As illustrated in Figure 1-1, the most sensitive effects appear to be in the liver, lungs, and gastrointestinal tract, and cancer. A systematic review of the noncancer endpoints resulted in the following hazard identification conclusions:

- Hepatic effects are a presumed health effect for humans.
- The data are inadequate to conclude whether respiratory effects will occur in humans.
- The data are inadequate to conclude whether gastrointestinal effects will occur in humans.

***Hepatic Effects.*** Liver toxicity is considered a critical effect of 1,2-diphenylhydrazine exposure. Intermediate exposures in rats resulted in mild increases in liver weight, hypertrophy, multifocal macrovesiculation, and bile duct duplication (Dodd et al. 2012). Chronic oral administration of 1,2-diphenylhydrazine produced degenerative alterations in the liver of rats (fatty metamorphosis) and female mice (coagulative necrosis), as well as hepatocellular carcinomas in male rats and female mice and neoplastic nodules in female rats (NCI 1978).

***Other Nonneoplastic Effects.*** Interstitial inflammation of the lungs was observed in rats after chronic oral exposure to 1,2-diphenylhydrazine (NCI 1978), but not in similarly exposed mice. Gross pathological examinations conducted in a 4-week oral study (NCI 1978) reported intestinal hemorrhages

**Figure 1-1. Health Effects Found in Animals Following Oral Exposure to 1,2-Diphenylhydrazine**



in mice exposed to 390 mg/kg/day. In the chronic-duration study conducted by NCI (1978), histopathological analysis identified stomach hyperkeratosis and acanthosis in rats following dietary exposure. Potential respiratory and gastrointestinal effects were not examined in other studies.

***Cancer Effects.*** The carcinogenic potential of 1,2-diphenylhydrazine has been evaluated in rats and mice exposed to 1,2-diphenylhydrazine in the diet for 78 weeks (NCI, 1978). The tumor sites for 1,2-diphenylhydrazine include the liver (hepatocellular carcinoma and neoplastic nodules) in male and female rats and female mice, mammary gland (adenocarcinomas) in female rats, and Zymbal's gland/ear canal/skin of ear (squamous cell carcinoma or papilloma) in male rats (NCI 1978).

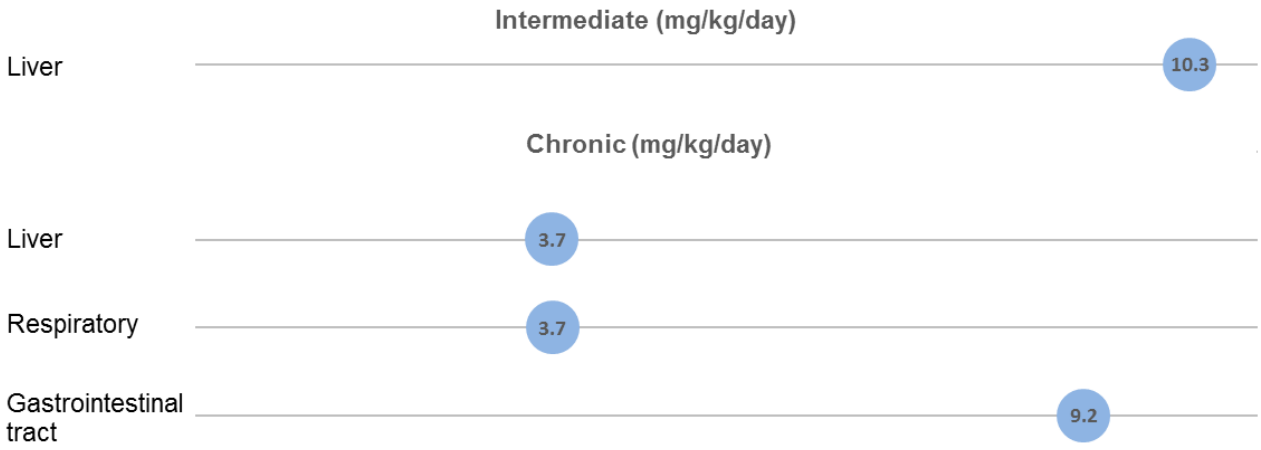
The Department of Health and Human Services (NTP 2016) has identified 1,2-diphenylhydrazine as reasonably anticipated to be a human carcinogen on the basis of sufficient evidence of carcinogenicity in experimental animals. EPA (IRIS 2006) classified it as a probable human carcinogen (Group B2).

## 1.3 MINIMAL RISK LEVELS (MRLs)

Due to absence of inhalation studies, derivation of inhalation MRLs was not feasible. As presented in Figure 1-2, the limited available data for 1,2-diphenylhydrazine have identified the liver, lungs, and gastrointestinal tract as sensitive targets. The oral database was considered adequate for derivation of an intermediate-duration MRL for 1,2-diphenyhydrazine. The MRL value is summarized in Table 1-1 and discussed in greater detail in Appendix A.

### Figure 1-2. Summary of Sensitive Targets of 1,2-Diphenylhydrazine – Oral

**The liver, lungs, and gastrointestinal tract are the most sensitive targets of 1,2-diphenylhydrazine.**
Numbers in circles are the lowest LOAELs for all health effects in animals; no human data were identified.



## Table 1-1. Minimal Risk Levels (MRLs) for 1,2-Diphenylhydrazine[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 | 0.05 | Liver hypertrophy, eosinophilic granular cytoplasm, and bile duct duplication | NOAEL = 4.80 | 100 | Dodd et al. 2012 |
| Chronic | Insufficient data for MRL derivation | | | | |

[a]See Appendix A for additional information.

NOAEL = no-observed-adverse-effect level