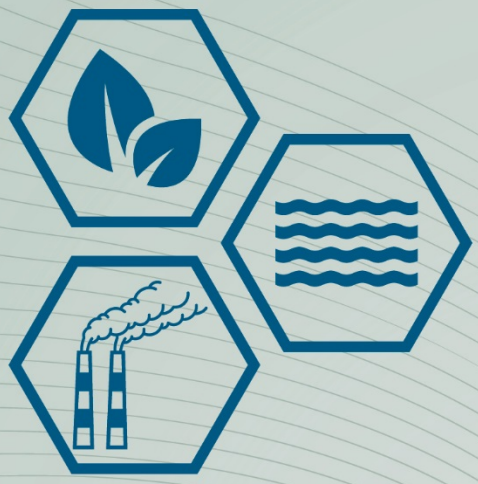


Toxicological Profile for 1,2-Diphenylhydrazine

Draft for Public Comment

May 2019

U.S. Department of Health and Human Services
Agency for Toxic Substances and Disease Registry

CS274127-A

DISCLAIMER

Use of trade names is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry, the Public Health Service, or the U.S. Department of Health and Human Services.

This information is distributed solely for the purpose of pre dissemination public comment under applicable information quality guidelines. It has not been formally disseminated by the Agency for Toxic Substances and Disease Registry. It does not represent and should not be construed to represent any agency determination or policy.

FOREWORD

This toxicological profile is prepared in accordance with guidelines developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for these toxic substances described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a relevance to public health discussion which would allow a public health professional to make a real-time determination of whether the presence of a particular substance in the environment poses a potential threat to human health. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to the protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a toxic substance to ascertain the levels of significant human exposure for the substance and the associated acute, intermediate, and chronic health effects;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine the levels of exposure that present a significant risk to human health due to acute, intermediate, and chronic duration exposures; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public. ATSDR plans to revise these documents in response to public comments and as additional data become available. Therefore, we encourage comments that will make the toxicological profile series of the greatest use.

Electronic comments may be submitted via: www.regulations.gov. Follow the on-line instructions for submitting comments.

Written comments may also be sent to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Human Health Sciences
Environmental Toxicology Branch
1600 Clifton Road, N.E.
Mail Stop S102-1
Atlanta, Georgia 30329-4027

The toxicological profiles are developed under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA or Superfund). CERCLA section 104(i)(1) directs the Administrator of ATSDR to "…effectuate and implement the health related authorities" of the statute. This includes the preparation of toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL) and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. In addition, ATSDR has the authority to prepare toxicological profiles for substances not found at sites on the NPL, in an effort to "…establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" under CERCLA Section 104(i)(1)(B), to respond to requests for consultation under section 104(i)(4), and as otherwise necessary to support the site-specific response actions conducted by ATSDR.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staffs of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

Patrick N. Breysse, Ph.D., CIH
Director, National Center for Environmental Health and
Agency for Toxic Substances and Disease Registry
Centers for Disease Control and Prevention

VERSION HISTORY

Date	Description
May 2019	Update of data in Chapters 2, 3, and 7
October 2009	Toxicological profile addendum
December 1990	Final toxicological profile released

CONTRIBUTORS & REVIEWERS

CHEMICAL MANAGER TEAM

Sam Keith, M.S., C.H.P.
ATSDR, Division of Toxicology and Human Health Sciences, Atlanta, GA

Lisa Ingerman, Ph.D., D.A.B.T.
Mario Citra, Ph.D.
Shelley Stevens, Ph.D.
SRC, Inc., North Syracuse, NY

REVIEWERS

Interagency Minimal Risk Level Workgroup:

Includes ATSDR; National Center for Environmental Health (NCEH); National Institute of Occupational Health and Safety (NIOSH); U.S. Environmental Protection Agency (EPA); National Toxicology Program (NTP).

Additional reviews for science and/or policy:

ATSDR, Division of Community Health Investigations; ATSDR, Office of Science; NCEH, Division of Laboratory Science; NCEH, Division of Environmental Health Science and Practice; EPA National Center for Environmental Assessment.

PEER REVIEWERS

1. Dr. Gisela de Aragão Umbuzeiro, Laboratório de Ecotoxicologia e Genotoxicidade LAEG, Faculdade de Tecnologia UNICAMP, Limeira Brazil

2. Cynthia Rider, Ph.D., General Toxicology and Cancer Group, Toxicologist, Durham, NC

3. Robert A. Michaels; PhD, CEP, RAM TRAC Corporation, Schenectady, NY

These experts collectively have knowledge of toxicology, chemistry, and/or health effects. All reviewers were selected in conformity with Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

ATSDR scientists review peer reviewers' comments and determine whether changes will be made to the profile based on comments. The peer reviewers' comments and responses to these comments are part of the administrative record for this compound.

The listing of peer reviewers should not be understood to imply their approval of the profile's final content. The responsibility for the content of this profile lies with ATSDR.

CONTENTS

LIST OF FIGURES

LIST OF TABLES

CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

ATSDR's *Toxicological Profile for 1,2-Diphenylhydrazine* was released in 1990. 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 with the updated health effects data. However, the focus of the update to this profile is on health effects information.

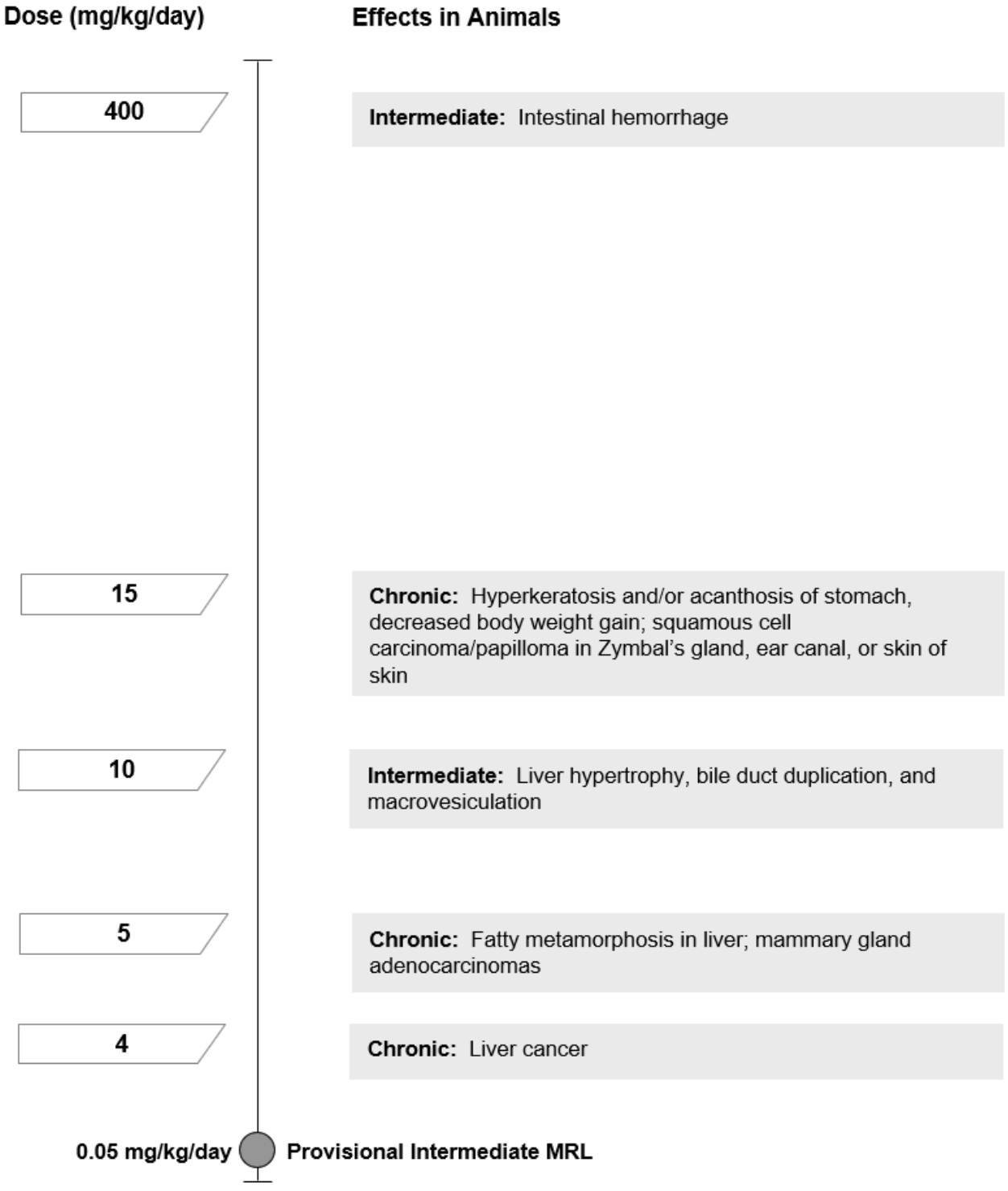
1,2-Diphenylhydrazine (Chemical Abstracts Service [CAS] number 122-66-7; hydrazobenzene is a common synonym) is a colorless, crystalline solid previously used as an intermediate in dye manufacturing (e.g., benzidine) and an intermediate in some pharmaceuticals. It rapidly oxidizes in water with a half-life 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.

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



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 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 a provisional 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 target of 1,2-diphenylhydrazine.
Numbers in circles are the lowest LOAELs for all health effects in animals; no human data were identified.

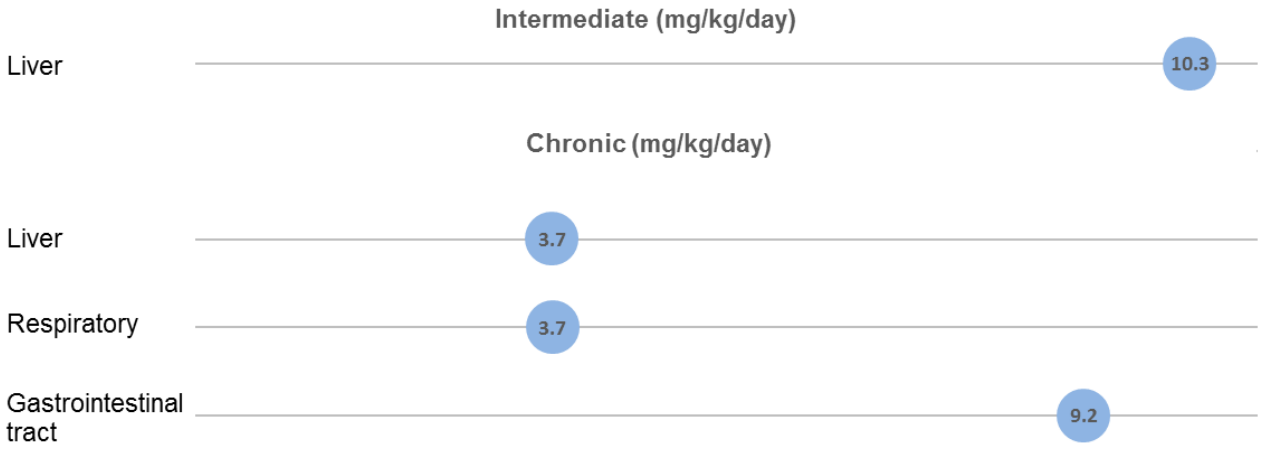


Table 1-1. Minimal Risk Levels (MRLs) for 1,2-Diphenylhydrazine[a]

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[b]	Liver hypertrophy, eosinophilic granular cytoplasm, and bile duct duplication	4.80 (NOAEL)	100	Dodd et al. 2012
Chronic	Insufficient data for MRL derivation				

[a]See Appendix A for additional information.
[b]Provisional MRL.

NOAEL = no-observed-adverse-effect level

CHAPTER 2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of 1,2-diphenylhydrazine. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health. When available, mechanisms of action are discussed along with the health effects data; toxicokinetic mechanistic data are discussed in Section 3.1.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized by health effect. These data are discussed in terms of route of exposure (inhalation, oral, and dermal) and three exposure periods: acute (≤14 days), intermediate (15–364 days), and chronic (≥365 days).

As discussed in Appendix B, a literature search was conducted to identify relevant studies examining health effect endpoints. Figure 2-1 provides an overview of the database of studies in humans or experimental animals included in this chapter of the profile. These studies evaluate the potential health effects associated with inhalation, oral, or dermal exposure to 1,2-diphenylhydrazine, but may not be inclusive of the entire body of literature. A systematic review of the scientific evidence of the health effects associated with exposure to 1,2-diphenylhydrazine was also conducted; the results of this review are presented in Appendix C.

Levels of significant exposure (LSEs) for each route and duration are presented in tables and illustrated in figures. Animal oral studies are presented in Table 2-1 and Figure 2-2; no reliable inhalation or dermal data were identified for 1,2-diphenylhydrazine.

The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those

whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an endpoint should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these endpoints. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health. Levels of exposure associated with cancer (Cancer Effect Levels, CELs) of 1,2-diphenyl-hydrazine are indicated in Table 2-1 and Figure 2-2.

A User's Guide has been provided at the end of this profile (see Appendix D). This guide should aid in the interpretation of the tables and figures for LSEs and MRLs.

As illustrated in Figure 2-1, there are limited data on the toxicity of 1,2-diphenylhydrazine. No human studies were identified, and data from laboratory animal studies primarily come from a small number of oral studies. Nine studies published in three papers have examined the toxicity and carcinogenicity following oral exposure. Two additional oral studies only examined lethality and one study assessed carcinogenicity following dermal exposure. A chronic study in rats and mice was the only study examining a wide range of potential endpoints; other studies have focused on liver or body weight effects. No studies were located that evaluated possible effects on immunological, reproductive, or developmental function. Based on these data, the available studies suggest the following targets of toxicity:

- **Hepatic Endpoint:** Hepatic effects are a presumed health effect for humans based on evidence from intermediate and chronic oral studies in rats and mice. Liver hypertrophy, bile duct duplication, and macrovesiculation was observed in rats after 13 weeks of dietary exposure; no alterations were observed after shorter exposure durations. After chronic exposure, fatty metamorphosis and coagulative necrosis were observed in rats and mice, respectively.

- **Cancer Endpoint:** Increases in the incidences of neoplastic lesions in the liver, mammary gland, and Zymbal’s gland/ear canal/skin of ear were observed in chronically exposed rats. In mice, liver tumors were observed in females only.

- **Gastrointestinal Endpoint:** Data are inadequate to conclude whether gastrointestinal effects will occur in humans. Inconsistent results have been observed in oral exposure animal studies. Intestinal hemorrhage was noted in mice exposed to 1,2-diphenylhydrazine in the diet for 4 weeks

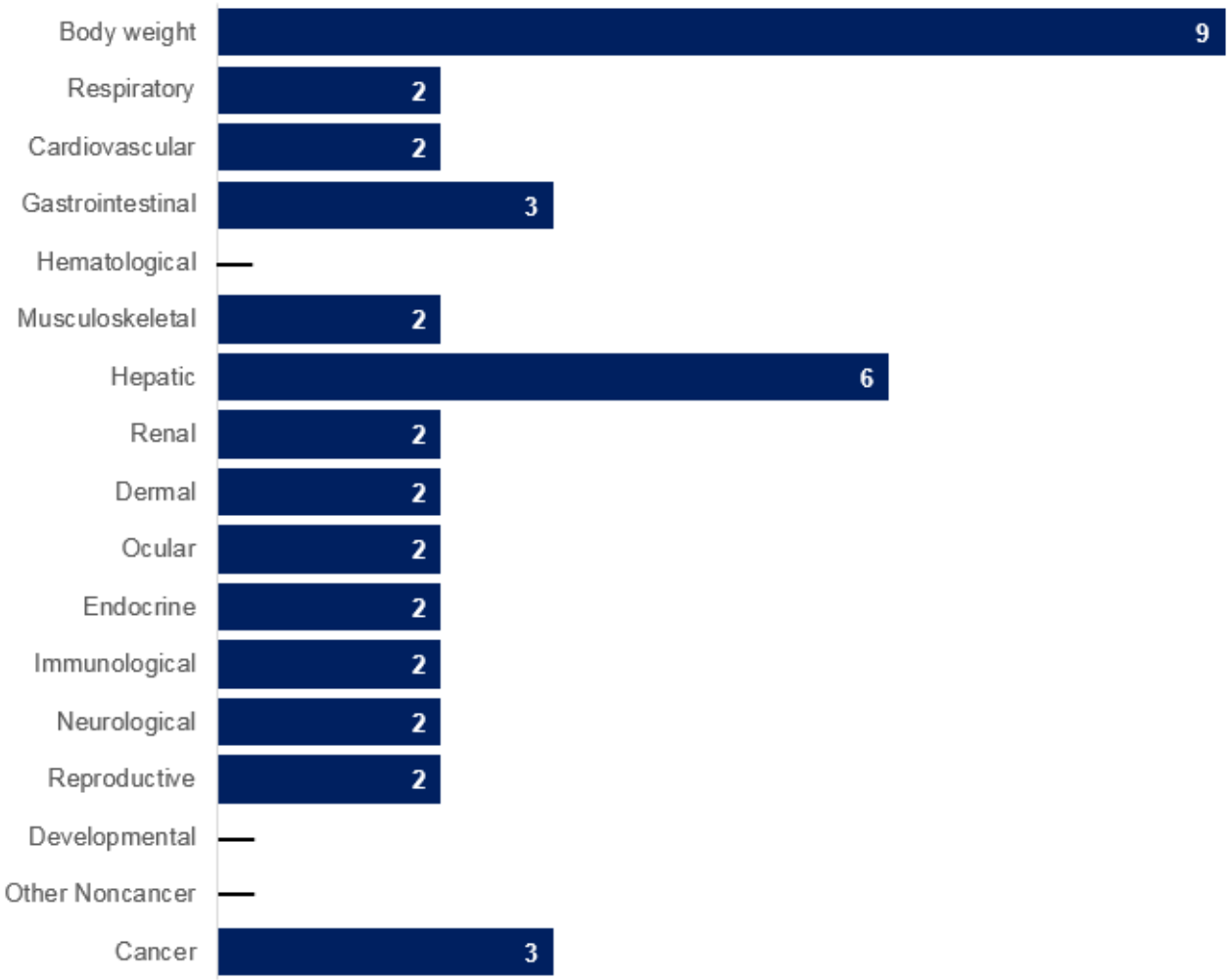
and stomach hyperkeratosis and/or acanthosis were observed in rats chronically exposed to 1,2-diphenylhydrazine in the diet.

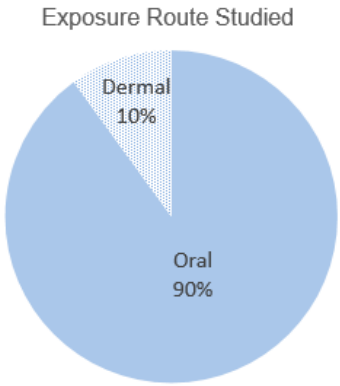
- **Respiratory Endpoint:** Data are inadequate to conclude whether respiratory effects will occur in humans. Inconsistent results have been observed in oral exposure animal studies. Interstitial inflammation of the lungs was noted in rats chronically exposed to 1,2-diphenylhydrazine in the diet.

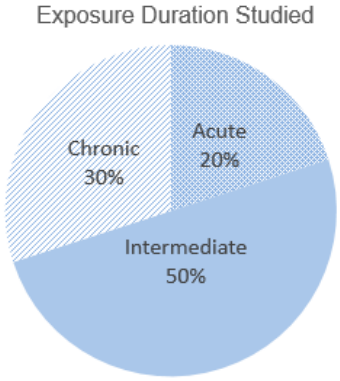
Figure 2-1. Overview of the Number of Studies Examining 1,2-Diphenylhydrazine Health Effects

Body weight, hepatic, gastrointestinal, and cancer effects of 1,2-diphenylhydrazine were the most widely examined potential toxicity outcomes

The majority of the studies examined oral exposure in **animals**; no data were identified for **humans** (counts represent studies examining endpoint)







*Includes studies discussed in Chapter 2. A total of 10 studies (including those finding no effect) have examined toxicity; most animal studies examined multiple endpoints.

Table 2-1. Levels of Significant Exposure to 1,2-Diphenylhydrazine – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
ACUTE EXPOSURE									
1	Rat (Fischer 344) 10M	5 days (F)	0, 0.32, 1.26, 4.80, 10.3, 15.5	CS, BC, BW, HP, OW, FI, GN	Bd wt	15.5			
					Hepatic	15.5			Slight decrease (13%) in alkaline phosphatase at 15.5 mg/kg/day was not considered biologically relevant; no alterations in hepatic serum enzymes or liver histopathology
Dodd et al. 2012									
2	Rat (Fischer 344) 10M	2 weeks (F)	0, 0.32, 1.26, 4.80, 10.3, 15.5	CS, BC, BW, HP, OW, FI, GN	Bd wt	15.5			
					Hepatic	15.5			Slight decrease (12%) in alkaline phosphatase at 15.5 mg/kg/day was not considered biologically relevant; no other alterations in hepatic serum enzymes or liver histopathology
Dodd et al. 2012									
3	Rat (Sprague-Dawley) 6–10F	2 exposures 21 and 4 hours prior to sacrifice (G)	0, 60, 180	LE, BC, EA	Death				No increases in mortality
Kitchin et al. 1992									
4	Rat	Once (GW)	959	LE	Death			959	LD_{50}
Marhold et al. 1968									

Table 2-1. Levels of Significant Exposure to 1,2-Diphenylhydrazine – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
INTERMEDIATE EXPOSURE									
5	Rat (Fischer 344) 10M	4 weeks (F)	0, 0.32, 1.26, 4.80, 10.3, 15.5	CS, BC, BW, HP, OW, FI, GN	Bd wt	15.5			
					Hepatic	15.5			13% and 26% reductions in serum alkaline phosphatase and aspartate aminotransferase, respectively, at 15.5 mg/kg/day were not considered biologically relevant; no alterations in liver histopathology
Dodd et al. 2012									
6	Rat (Fischer 344) 10M	13 weeks (F)	0, 0.32, 1.26, 4.80, 10.3, 15.5	CS, BC, BW, HP, OW, FI, GN	Bd wt	15.5			
					Hepatic	4.80[b]	10.3		Slight to mild hypertrophy, minimal eosinophilic granular cytoplasm, minimal to slight multifocal bile duct duplication and slight to mild multifocal macrovesiculation at ≥10.3 mg/kg/day. Reduction in serum alkaline phosphatase (19.7%) and aspartate aminotransferase (26%) at 15.5 mg/kg/day; no other alterations in hepatic serum enzymes.
Dodd et al. 2012									
7	Rat	288 days (F)	0, 19	BW	Bd wt	19			
Marhold et al. 1968									
8	Rat (Fischer 344) 5M, 5F	4 weeks (F)	M: 0, 3.5, 7, 14, 27, 54, 107, 150, 211 F: 0, 0.04, 0.15, 0.55, 1, 2, 7.5, 52, 365, 2,600	CS, BW, GN	Death			54M 365F	2/5 males died at 54 mg/kg/day; 100% mortality at higher doses
					Bd wt	211M 2,600F			
NCI 1978									

Table 2-1. Levels of Significant Exposure to 1,2-Diphenylhydrazine – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
9	Mouse (B6C3F1) 5M, 5F	4 weeks (F)	M: 0, 9.1, 18, 36, 71, 140, 280, 391, 550; F: 0, 0.39, 1.04, 1.4, 2.6, 5.2, 19, 135, 950, 6,700	CS, BW, GN	Death			391M 950F	1/5 males and 4/5 females died
					Bd wt	550M 6,700F			
					Gastro			391M 950F	Intestinal hemorrhage
NCI 1978									
CHRONIC EXPOSURE									
10	Rat (Fischer 344 50M, 50F	78 weeks followed by 28–30-week recovery (F)	M: 0, 6.3, 24 F: 0, 3.7, 9.2	BW, GN, HP, CS	Death			9.2F	Increased mortality
					Bd wt	6.3M 3.7F	24M 9.2F		Decreased body weight gain
					Resp		6.3M		Interstitial inflammation of the lung in males at ≥6.3 mg/kg/day and females at 3.7 mg/kg/day but not at 9.2 mg/kg/day
					Cardio	9.2F 24M			
					Gastro	6.3M	24M 3.7F		Hyperkeratosis and acanthosis of stomach in males at 24 mg/kg/day and acanthosis of the stomach in females at 3.7 mg/kg/day, but not at 9.2 mg/kg/day
					Musc/skel	9.2F 24M			
					Hepatic	6.3M 3.7F	24M 9.2F		Fatty metamorphosis in females at 9.2 mg/kg/day and males at 24 mg/kg/day
					Renal	9.2F 24M			
					Dermal	9.2F 24M			

Table 2-1. Levels of Significant Exposure to 1,2-Diphenylhydrazine – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
					Ocular	9.2F 24M			
					Endocr	9.2F 24M			
					Immuno	9.2F 24M			No histological alterations in immunological organs
					Neuro	9.2F 24M			No histological alterations in the brain
					Repro	9.2F 24M			No histological alterations in reproductive organs
					Cancer			6.3M 9.2F	CEL: hepatocellular carcinoma at ≥6.3 mg/kg/day in males only. Adrenal pheochromocytoma; squamous cell carcinoma in Zymbal's gland; and ear canal, Zymbal's gland, and skin of the ear squamous cell carcinoma or squamous cell papilloma were observed in males at 24 mg/kg/day. In females, increases in liver neoplastic nodules and mammary gland adenocarcinomas were observed at 9.2 mg/kg/day.
NCI 1978									
11	Mouse (B6C3F1) 50M, 50F	78 weeks followed by 28–30-week recovery (F)	M: 0, 14, 69 F: 0, 6.9, 69	LE, HP	Death			69	Increased mortality
					Bd wt	14M 6.9F		69M,F	Decreased body weight gain (36%)
					Resp	69			
					Cardio	69			
					Gastro	69			
					Musc/skel	69			
					Hepatic	6.9F	69F		Coagulative necrosis
					Renal	69			
					Dermal	69			

Table 2-1. Levels of Significant Exposure to 1,2-Diphenylhydrazine – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
					Ocular	69			
					Endocr	69			
					Immuno	69			No histological alterations in immunological organs
					Neuro	69			No histological alterations in the brain
					Repro	69			No histological alterations in reproductive organs
					Cancer			69F	CEL: hepatocellular carcinoma in females
NCI 1978									

[a]The number corresponds to entries in Figure 2-2; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-2. Where such differences exist, only the levels of effect for the most sensitive gender are presented.
[b]Used to derive a provisional intermediate-duration oral MRL of 0.05 mg/kg/day based on a NOAEL of 4.80 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability)

BC = biochemistry; Bd wt or BW = body weight; Cardio = cardiovascular; CEL = cancer effect level; CS = clinical signs; EA = enzyme activity; Endocr = endocrine; (F) = feed; F = female(s); FI = food intake; (G) = gavage; Gastro = gastrointestinal; GN = gross necropsy; HP = histopathology; immuno = immunological; LD_{50} = lethal dose, 50% mortality; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); Musculo/skel = musculoskeletal; Neuro = neurological; NOAEL = no-observed-adverse-effect level; OW = organ weight; Repro = reproductive; Resp = respiratory

Figure 2-2. Levels of Significant Exposure to 1,2-Diphenylhydrazine – Oral
Acute (≤14 days)

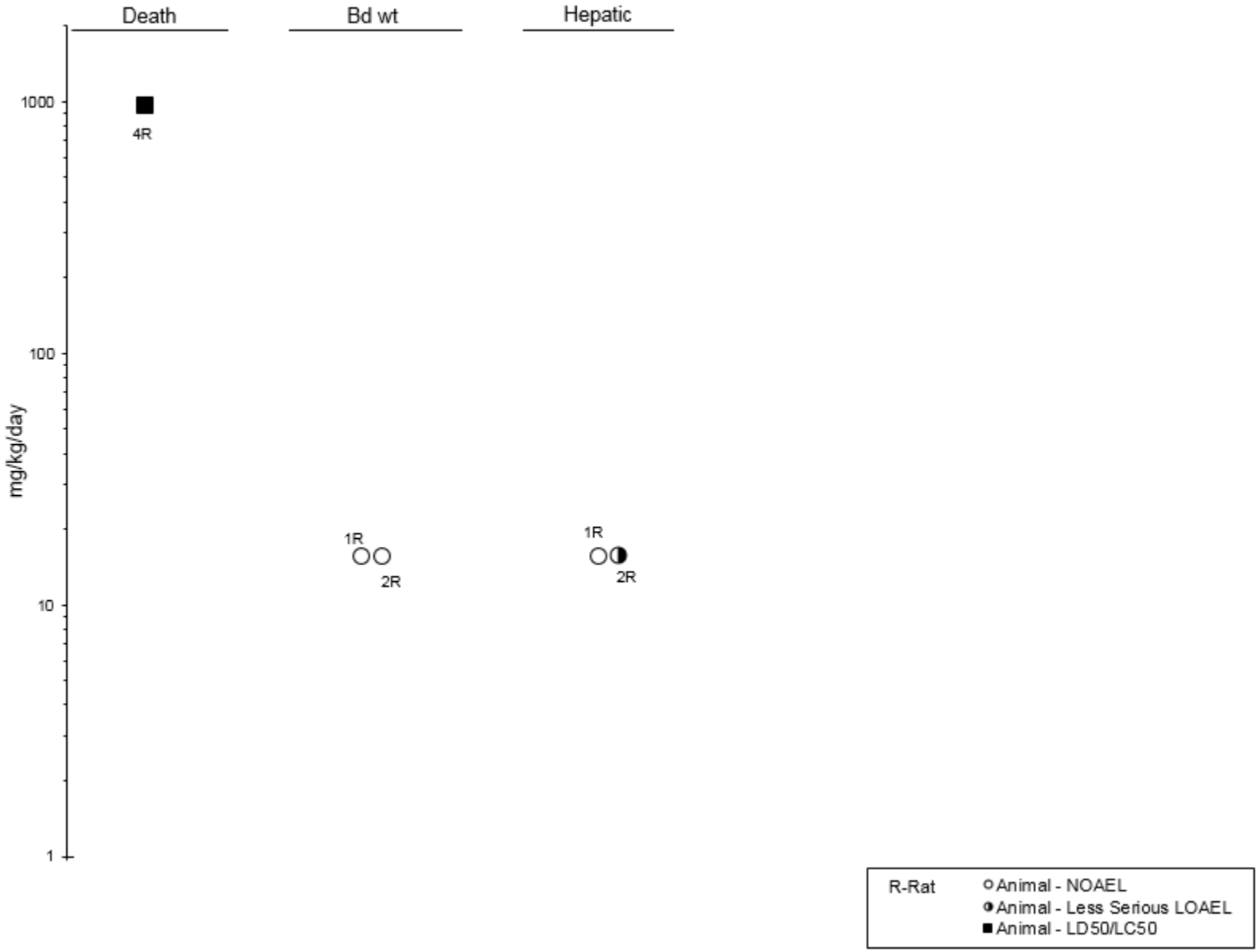


Figure 2-2. Levels of Significant Exposure to 1,2-Diphenylhydrazine – Oral
Intermediate (15-364 days)

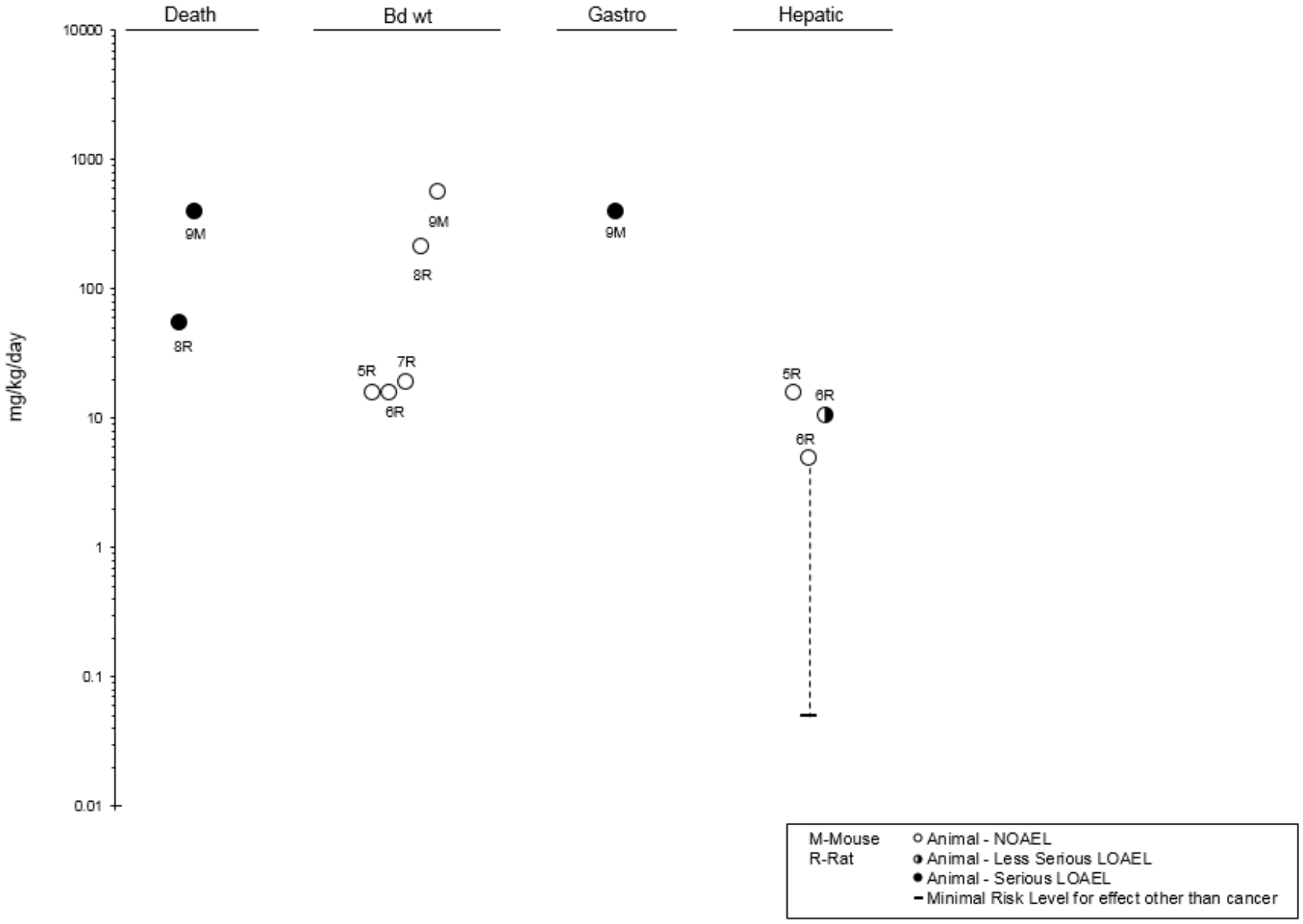


Figure 2-2. Levels of Significant Exposure to 1,2-Diphenylhydrazine – Oral

Chronic (≥365 days)

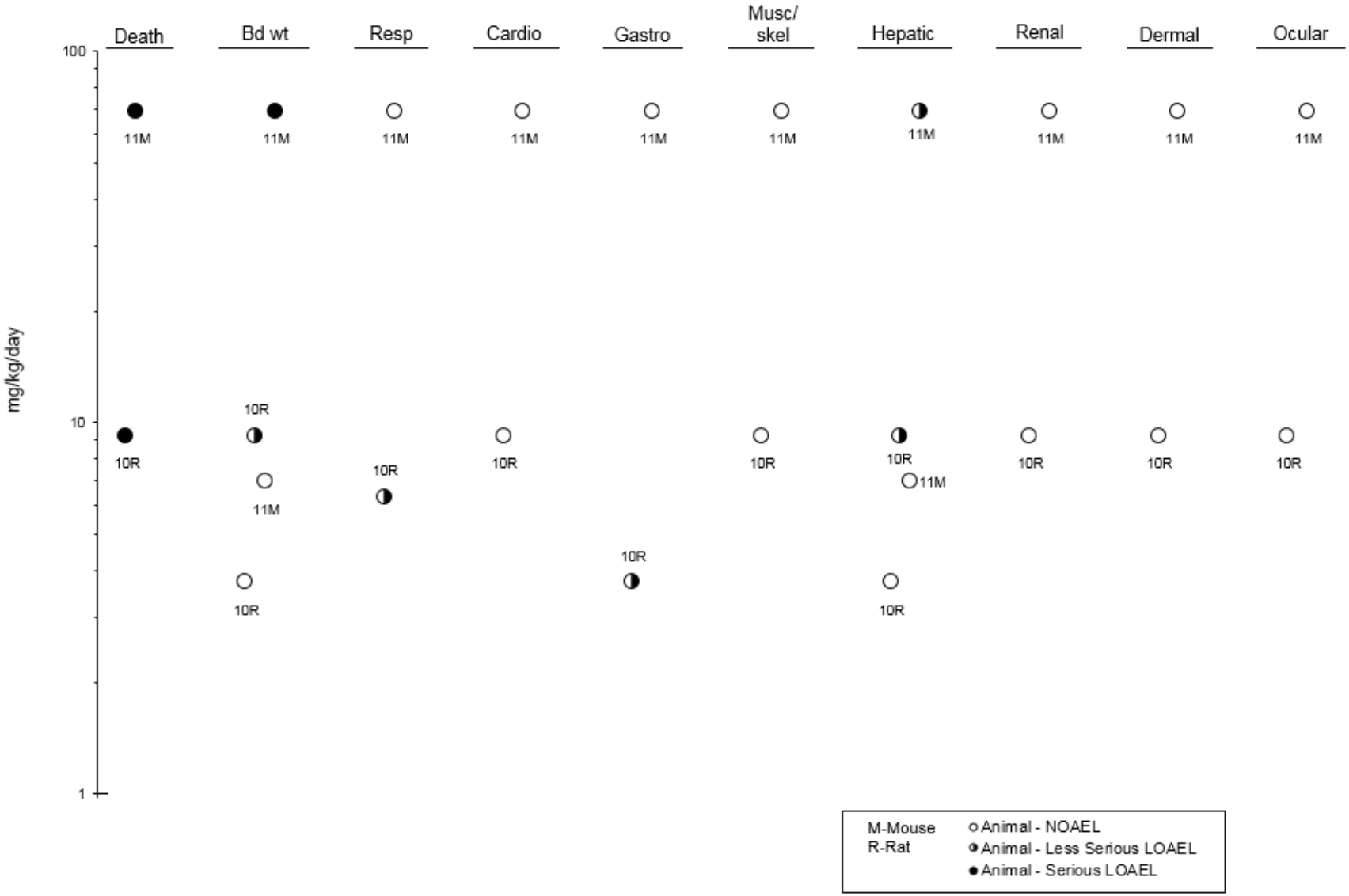
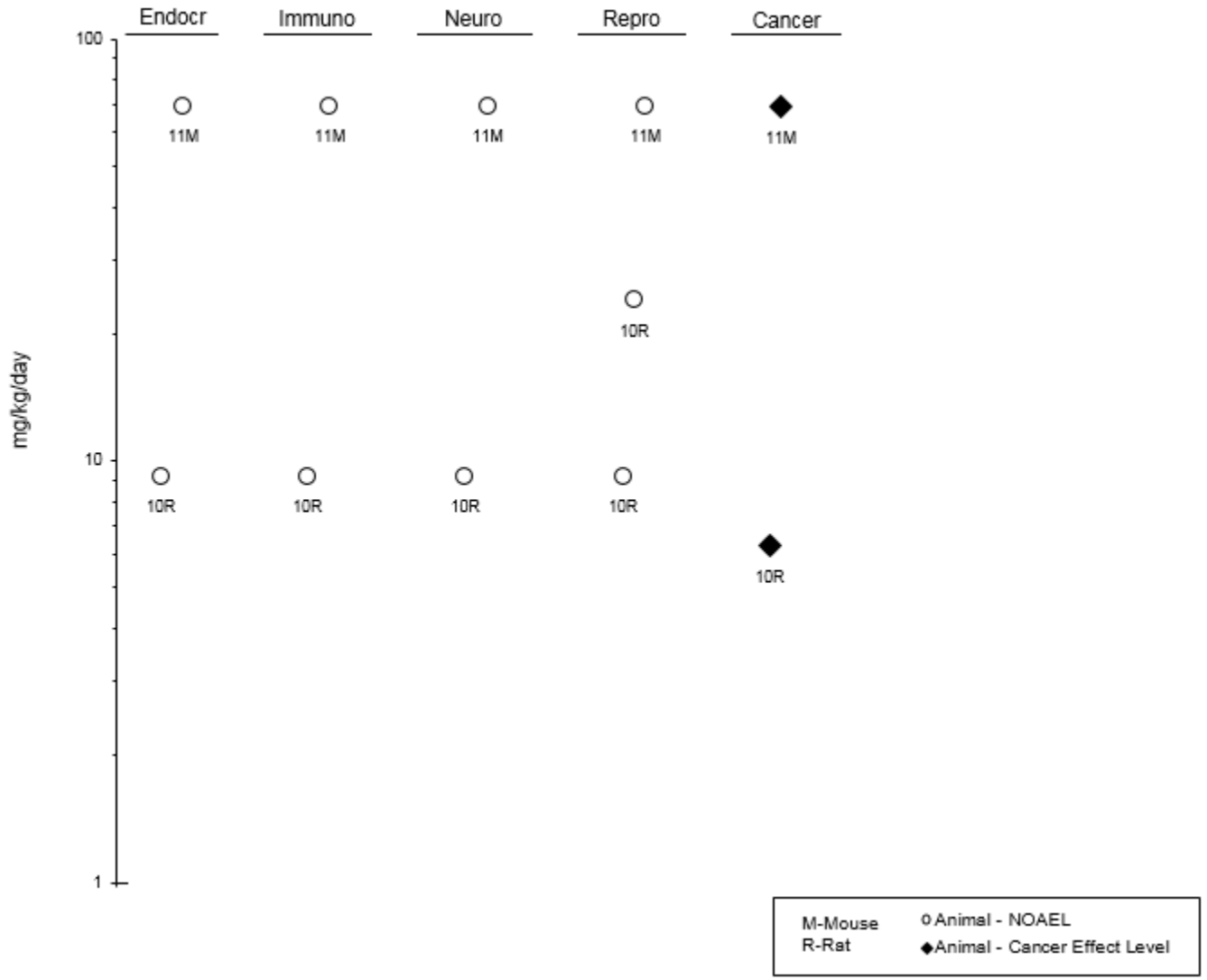


Figure 2-2. Levels of Significant Exposure to 1,2-Diphenylhydrazine – Oral
Chronic (≥365 days)



2.2 DEATH

Limited information is available regarding the lethality of orally administered 1,2-diphenylhydrazine in animals. An incompletely documented acute LD_{50} of 959 mg/kg in rats (Marhold et al. 1968) and an unreliable acute lethal dose 1,213 mg/kg/day in wild deer mice (Schafer and Bowles 1985) have been reported. Interpretation of the results of the Schafer and Bowles (1985) study is limited by the method used to measure dose (estimated from the number of 1,2-diphenylhydrazine-treated seeds consumed) and the lack of information on the actual number of deaths was not reported. No deaths were observed in rats administered two gavage doses of 180 mg/kg (sacrificed within 21 hours of last dose) (Kitchin et al. 1992) or rats exposed to 15.5 mg/kg/day in the diet for 5 days or 2 weeks (Dodd et al. 2012).

In repeated exposure studies, deaths were observed in rats and mice exposed to 54 or 390 mg/kg/day, respectively, for 4 weeks (NCI 1978). In another study, no deaths were observed in rats fed up to 15.5 mg/kg/day 1,2-diphenylhydrazine for 4 weeks or 13 weeks (Dodd et al. 2012). In a chronic dietary study, increases in mortality were observed in female rats exposed to 9.2 mg/kg/day and male and female mice exposed to 69 mg/kg/day (NCI 1978).

2.3 BODY WEIGHT

Chronic (NCI 1978), but not acute (Dodd et al. 2012) or intermediate (Dodd et al. 2012; Marhold et al. 1968; NCI 1978) oral exposure to 1,2-diphenylhydrazine led to significant alterations in body weight in laboratory animals. Male rats treated with 1,2-diphenylhydrazine in the diet at a dose of 24 mg/kg/day for 78 weeks had approximately l0–15% decreased body weight gain (NCI 1978); food consumption data were not reported. Decreased weight gain (approximately 36% at termination of the study) was observed in male and female mice exposed to 69 mg/kg/day in the diet for 78 weeks (NCI 1978).

2.4 RESPIRATORY

Respiratory effects occurred in rats after chronic exposure to 1,2-diphenylhydrazine in the diet for 78 weeks (NCI 1978); the incidences of interstitial inflammation of the lungs were significantly increased in male rats exposed to 6.3 or 24 mg/kg/day and in females at 3.7 mg/kg/day, but not at 9.2 mg/kg/day (NCI 1978).

2.5 CARDIOVASCULAR

No histological alterations were observed in rats or mice chronically exposed to doses as high as 24/9.2 (males/females) or 69 mg/kg/day, respectively (NCI 1978).

2.6 GASTROINTESTINAL

Intestinal hemorrhages were noted in mice exposed to lethal doses (≥390 mg/kg/day) for 4 weeks (NCI 1978). The severity and incidences of the hemorrhage were not described. Statistically increased incidences of hyperkeratosis and acanthosis in the stomach occurred in male rats at 24 mg/kg/day and acanthosis was observed in female rats at 3.7 mg/kg/day 1,2-diphenylhydrazine in the diet for 78 weeks (NCI 1978); the incidence in female rats administered 9.2 mg/kg/day (11%) was not significantly different from concurrent controls (4%). No gastrointestinal lesions were observed in mice treated with doses up to 69 mg/kg/day (NCI 1978).

2.7 HEMATOLOGICAL

No studies were located that evaluate hematological effects in animals following exposure to 1,2-diphenylhydrazine by inhalation, oral, or dermal routes. In a single study, intravenous injection of an 18.4 mg/kg dose of 1,2-diphenylhydrazine did not cause methemoglobinemia in rats, although methemoglobin was formed by an equimolar dose of aniline (Pfordte 1973).

2.8 MUSCULOSKELETAL

No histopathological alterations were observed in the musculoskeletal system of rats or mice exposed to 9.2/24 or 69 mg/kg/day, respectively, in the diet for 78 weeks (NCI 1978).

2.9 HEPATIC

Male rats exposed in the diet to up to 15.5 mg 1,2-diphenyldydrazine/kg/day for 5 days or 2 weeks had significant, but mild, increases in relative liver weights (4.7 and 4.4%, respectively) (Dodd et al. 2012). Serum concentrations of alkaline phosphatase decreased by approximately 13 and 12% at 5 days and 2 weeks, respectively, but no changes in serum alanine aminotransferase, aspartate aminotransferase, total bilirubin or lactate dehydrogenase, as compared to controls, were reported (Dodd et al. 2012); the toxicological significance of the decreased alkaline phosphatase levels is not known. No histopathological changes were observed following acute exposure (Dodd et al. 2012). Rats treated by

gavage at 21 and 4 hours prior to sacrifice with 60 or 180 mg/kg had no alterations in alanine aminotransferase (Kitchin et al. 1992).

Exposure via the diet to 10.3 or 15.5 mg/kg/day for 13 weeks resulted in increases in the incidences of slight/mild hypertrophy, eosinophilic granular cytoplasm, and multifocal bile duct duplication; multifocal macrovesiculation was also observed at 15.5 mg/kg/day (Dodd et al. 2012). However, no histological alterations were observed in rats exposed to up to 15.5 mg/kg/day for 4 weeks (Dodd et al. 2012). Decreases in alkaline phosphatase (7–13%) and aspartate aminotransferase (17–26%) were also noted at 15.5 mg/kg/day in rats exposed for 4 or 13 weeks.

Chronic exposure resulted in histological alterations in rats and mice exposed to 1,2-diphenylhydrazine in the diet for 78 weeks (NCI 1978). In rats, the lesions included increased fatty metamorphosis of the liver in male and female rats at 24 and 9.2 mg/kg/day, respectively. However, the increased incidence in 9.2 mg/kg/day female rats was only statistically significantly when compared to the low-dose control group due to the high incidence observed in the high-dose control group (12% in the high dose controls compared to 4% in the low-dose controls). Coagulative necrosis was observed in female mice at 69 mg/kg/day, but was not observed in male mice. Other liver alterations were noted in the NCI (1978) chronic rat and mouse study, but the incidences were not dose-related.

Current hypotheses relating to the hepatic effects of 1,2-diphenylhydrazine exposure in animals include possible contributions of cytochrome P450 induction to the development of hepatic hypertrophy; the involvement of peroxisome proliferation in developing eosinophilic granular cytoplasm; aberrant lipid metabolism or transport contributing to hepatocyte cytoplasm macrovesiculation; and epithelial cell injury or hepatic necrosis that could have induced biliary duct duplication (Dodd et al. 2012).

2.10 RENAL

No significant histological alterations in the kidney were observed in animals chronically treated for 78 weeks with up to 24/9.2 mg/kg/day (rats) or 69 mg/kg/day (mice) (NCI 1978).

2.11 DERMAL

No significant histological alterations in the skin were observed in rats or mice chronically exposed to 24/9.2 or 69 mg/kg/day, respectively (NCI 1978).

2.12 OCULAR

No significant histological alterations in ocular tissues were observed in rats exposed to 24/9.2 mg/kg/day or mice exposed to 69 mg/kg/day 1,2-diphenylhydrazine in the diet for 78 weeks (NCI 1978).

2.13 ENDOCRINE

No histological alterations were observed in the adrenal or thyroid glands of rats or mice chronically exposed to doses as high as 24/9.2 or 69 mg/kg/day 1,2-diphenylhydrazine, respectively, in the diet for 78 weeks (NCI 1978).

2.13 IMMUNOLOGICAL

No studies examined immune function following exposure to 1,2-diphenylhydrazine. Chronic exposure in the diet of rats or mice to 24/9.2 or 69 mg/kg/day, respectively, did not result in histological alterations in the bone marrow, spleen, or lymph nodes (NCI 1978).

2.15 NEUROLOGICAL

Rats and mice chronically treated with 1,2-diphenylhydrazine in the diet did not show symptoms of toxicity or histological alterations in the brain (NCI 1978), but no behavioral or neurological evaluations were conducted.

2.16 REPRODUCTIVE

Reproductive function has not been evaluated in laboratory animals. The NCI (1978) chronic study of rats exposed to 24 mg/kg/day (males) or 9.2 mg/kg/day (females) and of mice exposed to 69 mg/kg/day (males and females) did not find histological alterations in the reproductive tissues.

2.17 DEVELOPMENTAL

No studies were located regarding developmental effects of 1,2-diphenylhydrazine in humans or animals by any route of exposure.

2.18 OTHER NONCANCER

No studies examining other noncancer effects were identified.

2.19 CANCER

The carcinogenicity of 1,2-diphenylhydrazine has been investigated in oral, dermal, and parenteral studies in laboratory animals. Treatment-related neoplasms occurred in rats and mice that were treated with low or high doses of 1,2-diphenylhydrazine in the diet for 78 weeks, followed by untreated observation periods of 28 or 30 weeks (rats) and 17 or 18 weeks (mice) (NCI 1978); tumor incidences were calculated as combined incidences for animals dying early, sacrificed at 78 weeks, or at the end of the observation period. Male rats had statistically significant increased incidences of hepatocellular carcinomas and/or neoplastic nodules in the liver at 6.3 and 24 mg/kg/day. At 24 mg/kg/day, squamous-cell carcinomas of the Zymbal's gland; squamous cell carcinomas or papillomas of the ear canal, Zymbal’s gland, and skin of the ear (combined incidences). The incidence of adrenal pheochromocytomas or malignant pheochromocytomas was significantly higher in the 24 mg/kg/day male rats ($p=0.042$ for the Fisher exact test), as compared to controls; however, the result was not significant under the Bonferroni criteria. Incidences of liver neoplastic nodules and mammary gland adenocarcinomas were increased significantly in female rats treated with 6.3 mg/kg/day, but not 3.7 mg/kg/day. A significantly increased incidence of hepatocellular carcinoma occurred in female mice treated with 69 mg/kg/day, but not 6.9 mg/kg/day. Doses of 14 or 69 mg/kg/day were not neoplastic for male mice. ATSDR notes that the nomenclature for classifying proliferative hepatocellular lesions was revised and the term “neoplastic nodule” is no longer recommended by the National Toxicology Program (NTP) to describe lesions that would now be termed hepatocellular hyperplasia or hepatocellular adenoma (Maronpot et al. 1986a).

In other studies, tumors were not observed in male rats treated with 19 mg/kg/day doses of 1,2-diphenyl-hydrazine in the diet for life (mean survival time=288 days) (Marhold et al. 1968). The significance of this finding is uncertain because the type and scope of pathological examination were not reported. Pliss (1974) reported increased numbers of tumors of the liver, Zymbal's gland, mammary gland, and other sites in rats that were treated with 1,2-diphenylhydrazine in the diet at an estimated dose of 85 mg/kg/day, 5 days/week for 588 days (Pliss 1974). These findings are inconclusive, however, because of lack of control data and other report inadequacies.

Inconclusive data for carcinogenicity of dermally applied 1,2-diphenylhydrazine in mice are available. Dermal application of an estimated 1,2-diphenylhydrazine dose of 63 mg/kg/day 3 times/week for

442 days caused a 22.2% incidence of tumors in mice (Pliss 1974). Tumors occurred in the lung, liver, and other tissues, and the tumor incidence in control mice was 17%. The significance of these findings cannot be determined, as incidences of specific tumors in the control group were not reported.

Intraperitoneal administration of 200 mg/kg 1,2-diphenylhydrazine 3 times/week for 8 weeks resulted in increases in the incidence of lung tumors in male mice; evidence in female mice was considered equivocal (Maronpot et al. 1986b). Increases in tumors have also been observed in other studies involving subcutaneous injection in rats and mice (Genin et al. 1975; Kurlyandskiy et al. 1976; Pliss 1974; Shabad and Genin 1975; Spitz et al. 1950); however, the results are inconclusive due to inadequate reporting and other limitations.

Based on sufficient evidence of carcinogenicity in laboratory animal studies, the Department of Health and Human Services concluded that 1,2-diphenylhydrazine is reasonably anticipated to be a human carcinogen (NTP 2016) and EPA concluded that it is a probable human carcinogen (Group B2) (IRIS 2006).

2.20 GENOTOXICITY

The genotoxicity of 1,2-diphenylhydrazine has been evaluated in a limited number of *in vitro* and *in vivo* studies. No studies were located regarding the genotoxicity of 1,2-diphenylhydrazine in humans by any route of exposure. A limited number of assays have been conducted using bacteria, or mammalian cells. As indicated in Table 2-2, 1,2-diphenylhydrazine was mutagenic in *Salmonella typhimurium* (Dunkel et al. 1985; Haworth et al. 1983), but not in *Escherichia coli* (Dunkel et al. 1985). Exogenous metabolic activation systems were necessary for expression of the aforementioned effects. In mammalian cell culture, 1,2-diphenylhydrazine produced chromosome aberrations and sister chromatid exchanges in Chinese hamster cells (Galloway et al. 1987). Ohnishi et al. (2000) reported DNA damage in calf thymus DNA fragments incubated with a 10% (v/v) ethanol solution of 1,2-diphenylhydrazine. The addition of 20 µM copper(II) chloride increased the DNA damage.

Table 2-2. Genotoxicity of 1,2-Diphenylhydrazine *In Vitro*

Species (test system)	Endpoint	Results: Activation With	Results: Activation Without	Reference
Prokaryotic organisms				
Salmonella typhimurium (plate incorporation)	Gene mutation	(+)	–	Dunkel et al. 1985
S. typhimurium (plate incorporation)	Gene mutation	+	–	Haworth et al. 1983
Escherichia coli WP2uvrA	Gene mutation	–	–	Dunkel et al. 1985
Mammalian cells				
Chinese hamster ovary cells	Chromosome aberrations	+	+/–	Galloway et al. 1987
Chinese hamster ovary cells	Sister chromatid exchange	+	–	Galloway et al. 1987

+ = positive results; (+) = weakly positive results; +/– = inconclusive; – = negative results

In *in vivo* studies (Table 2-3), 1,2-diphenylhydrazine inhibited testicular DNA synthesis in mice when administered as a single 100 mg/kg intraperitoneal injection (Seiler et al. 1977), but did not cause hepatic DNA damage in rats administered two oral doses of 180 mg/kg, at 21 and 4 hours before sacrifice (Kitchin et al. 1994). Exposure by feed or injection did not cause sex-linked recessive lethal mutations in *Drosophila* (Yoon et al. 1985).

Table 2-3. Genotoxicity of 1,2-Diphenylhydrazine *In Vivo*

Species (exposure route)	Endpoint	Results	Reference
Invertebrate systems			
Drosophila melanogaster (feeding)	Sex-linked recessive lethal mutation	–	Yoon et al. 1985
D. melanogaster (injection)	Sex-linked recessive lethal mutation	–	Yoon et al. 1985
Laboratory animal evidence			
Mouse (strain not reported) (intraperitoneal injection)	DNA damage; inhibition of testicular DNA synthesis.	+	Seiler et al. 1977
Sprague-Dawley rat (gavage)	DNA damage (Hepatic DNA alkaline elution)	–	Kitchin et al. 1994

– = negative result; + = positive result

CHAPTER 3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

3.1 TOXICOKINETICS

No studies were located regarding the toxicokinetics of 1,2-diphenylhydrazine in humans; limited laboratory animal data, summarized below, are available.

- 1,2-Diphenylhydrazine is presumed to be absorbed following oral exposure based on the appearance of urinary metabolites and adverse health effects.
- No information on the distribution of 1,2-diphenylhydrazine was identified.
- The available data suggest that 1,2-diphenylhydrazine is metabolized to aniline in the gut and that it readily forms benzidine in the acidic stomach.
- No information is available on the excretion of 1,2-diphenylhydrazine; one study reported the presence of unidentified urinary metabolites.

3.1.1 Absorption

No studies were located containing specific information regarding absorption after inhalation, oral, or dermal exposure to 1,2-diphenylhydrazine in humans or animals. Pulmonary absorption of 1,2-diphenylhydrazine by rats is suggested by detection of an unidentified metabolite in the urine following intratracheal administration of 1,2-diphenylhydrazine in water suspension and dimethyl sulfoxide (DMSO) (Dutkiewicz and Szymanska 1973). It is not known, however, if any of the dose was ingested.

Gastrointestinal absorption of 1,2-diphenylhydrazine by rodents is indicated by the occurrence of parent compound and metabolites in the urine following oral treatment (Section 3.1.4) and adverse health effects observed following oral exposure (Chapter 2).

3.1.2 Distribution

No studies were located regarding distribution in humans or animals after inhalation, oral, or dermal exposure to 1,2-diphenylhydrazine.

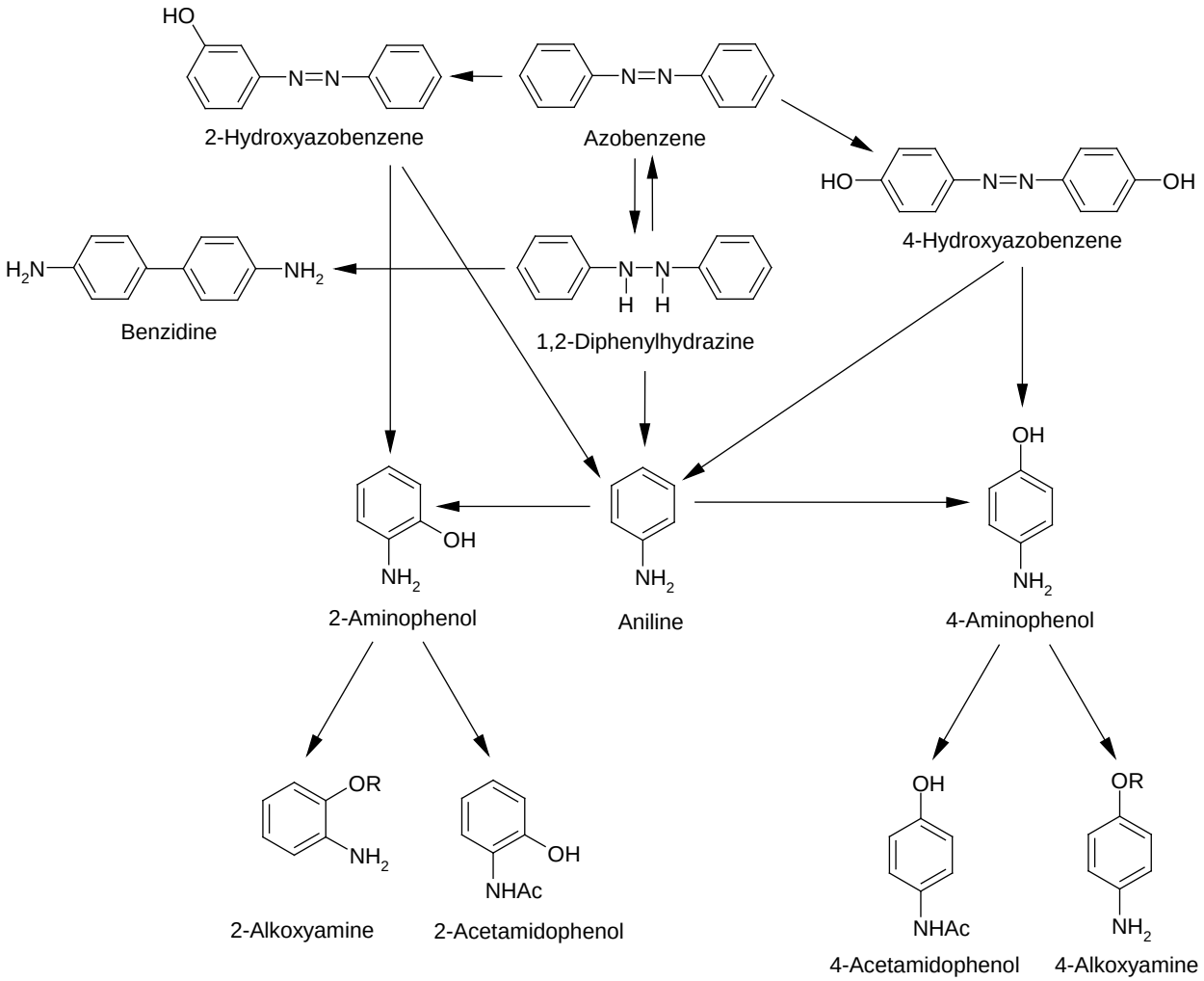
3.1.3 Metabolism

Limited information is available on the metabolism of 1,2-diphenylhydrazine. In the only study involving 1,2-diphenylhydrazine as the parent compound, rat urine was analyzed for metabolites following single oral (200 or 400 mg/kg), intraperitoneal (100 or 200 mg/kg), intravenous (4 or 8 mg/kg), and intratracheal (5 or 10 mg/kg) doses of 1,2-diphenylhydrazine (Dutkiewicz and Szymanska 1973). Unchanged 1,2-diphenylhydrazine was detected following treatment by all routes, and aniline and benzidine were identified following the oral and intraperitoneal treatments. Other metabolites included two unspecified hydroxy derivatives of benzidine (oral route), 2- and 4-aminophenol (intraperitoneal route), and unidentified compounds (oral, intravenous, and intratracheal routes). Amounts of compounds excreted were not quantitated. The validity of the findings of this study is uncertain, however, as the analytical methodology (thin-layer chromatography) may have produced degradation products that were identified as unchanged 1,2-diphenylhydrazine or metabolites. The metabolites identified by Dutkiewicz and Szymanska (1973) are consistent with a metabolic scheme proposed by Williams (1959) (Figure 3-1), which is based on data for azobenzene and aniline. As summarized by NRC (1981), aniline is oxidized by hydroxylation of a ring carbon to form 2- or 4-aminophenol or of the nitrogen to form phenylhydroxylamine, and then is conjugated to glucuronic or sulfuric acid. An oral study of azobenzene with conventional and germ-free rats (Macholz et al. 1985) showed that metabolism of 1,2-diphenyl-hydrazine to aniline resulted from the reductional and hydrolytic capability of gut flora. *In vitro* metabolism of 1,2-diphenylhydrazine to aniline by rat intestinal microorganisms has been demonstrated (Bolton and Griffiths 1978). Benzidine is formed readily from 1,2-diphenylhydrazine by acid rearrangement. It has been suggested that benzidine may be produced from 1,2-diphenylhydrazine by acidity in the stomach (IARC 1972).

3.1.4 Excretion

No studies were located regarding excretion in humans or animals after inhalation, oral, or dermal exposure to 1,2-diphenylhydrazine. The presence of an unidentified metabolite in the urine of rats following intratracheal and oral administration of 1,2-diphenylhydrazine in water and DMSO suspensions (Dutkiewicz and Szymanska 1973) suggests that some urinary excretion occurs.

Figure 3-1. Metabolic Scheme of 1,2-Diphenylhydrazine



Source: Williams 1959

3.1.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

PBPK models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic endpoints.

No PBPK models were identified for 1,2-diphenylhydrazine.

3.1.6 Animal-to-Human Extrapolations

There are insufficient data in which to evaluate possible species differences in the toxicokinetic properties of 1,2-diphenylhydrazaine.

3.2 CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Children may be more or less susceptible than adults to health effects from exposure to hazardous substances and the relationship may change with developmental age.

This section also discusses unusually susceptible populations. A susceptible population may exhibit different or enhanced responses to certain chemicals than most persons exposed to the same level of these chemicals in the environment. Factors involved with increased susceptibility may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters can reduce detoxification or excretion or compromise organ function.

Populations at greater exposure risk to unusually high exposure levels to 1,2-diphenylhydrazine are discussed in Section 5.7, Populations with Potentially High Exposures.

No data are available in on the toxicity of 1,2-diphenylhydrazine in children and it is assumed to be similar to adults. No developmental toxicity studies have been identified for this compound. No populations with unusual susceptibility to health effects of 1,2-diphenylhydrazine have been identified. It is possible that people with chronic liver disease or possibly compromised hepatic function (e.g., very young or very old people, alcoholics) might be unusually susceptible to 1,2-diphenylhydrazine, because the liver is a target organ of 1,2-diphenylhydrazine in animals.

3.3 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as biomarkers of exposure, biomarkers of effect, and biomarkers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. Biomarkers of exposure to 1,2-diphenylhydrazine are discussed in Section 3.3.1. The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of the exposure of a generalizable sample of the U.S. population to environmental chemicals using biomonitoring (see http://www.cdc.gov/exposurereport/). If available, biomonitoring data for 1,2-diphenylhydrazine from this report are discussed in Section 5.6, General Population Exposure.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that (depending on magnitude) can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effect caused by 1,2-diphenylhydrazine are discussed in Section 3.3.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the

biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.2, Children and Other Populations that are Unusually Susceptible.

3.3.1 Biomarkers of Exposure

No studies were located regarding biomarkers of exposure to 1,2-diphenylhydrazine. The metabolites of 1,2-diphenylhydrazine were identified in one study (Dutkiewicz and Szymanska 1973); however, the validity of the findings is uncertain because of the analytical methodology used (see Section 3.1.3). No enzymatic changes that could be used as biomarkers of 1,2-diphenylhydrazine exposure are known.

3.3.2 Biomarkers of Effect

No biomarkers of effects were identified for 1,2-diphenylhydrazine exposure. No specific alterations in the organism that could be recognized as biomarkers were found, and the most susceptible organs or tissues were not identified.

3.4 INTERACTIONS WITH OTHER CHEMICALS

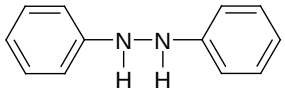
A carcinogenicity study was reported in which groups of rats were given weekly subcutaneous injections of 1,2-diphenylhydrazine (20 mg) alone or concurrently with benzidine sulfate (15 mg) for life (Genin et al. 1975). Combined incidences of tumors (injection site, liver, and other sites) were increased and the mean tumor latent period was decreased in the group with combined 1,2-diphenylhydrazine and benzidine sulfate exposure. It is unclear whether these findings provide evidence for an interaction between 1,2-diphenylhydrazine and benzidine or additive effects of two carcinogens. The results of this study were also reported by Shabad and Genin (1975) and Kurlyandskiy et al. (1976).

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Data pertaining to the chemical identity of 1,2-diphenylhydrazine listed in Table 4-1.

Table 4-1. Chemical Identity of 1,2-Diphenylhydrazine

Characteristic	Information	Reference
Chemical name	1,2-Diphenylhydrazine	CAS 1988
Synonym(s) and registered trade name(s)	Hydrazobenzene; N,N'-diphenylhydrazine; sym-diphenylhydrazine	CAS 1988; SANSS 1988
Chemical formula	$C_{12}H_{12}N_2$	CAS 1988
Chemical structure		SANSS 1988
Identification numbers:		
CAS Registry	122-66-7	CAS 1988

CAS = Chemical Abstracts Services

4.2 PHYSICAL AND CHEMICAL PROPERTIES

The physical and chemical properties of 1,2-diphenylhydrazine are presented in Table 4-2. 1,2-Diphenyl-hydrazine can rapidly oxidize to azobenzene under some environmental conditions; therefore, accurate experimental determination of properties such as the water solubility and Henry's Law constant may not be possible.

Table 4-2. Physical and Chemical Properties of 1,2-Diphenylhydrazine

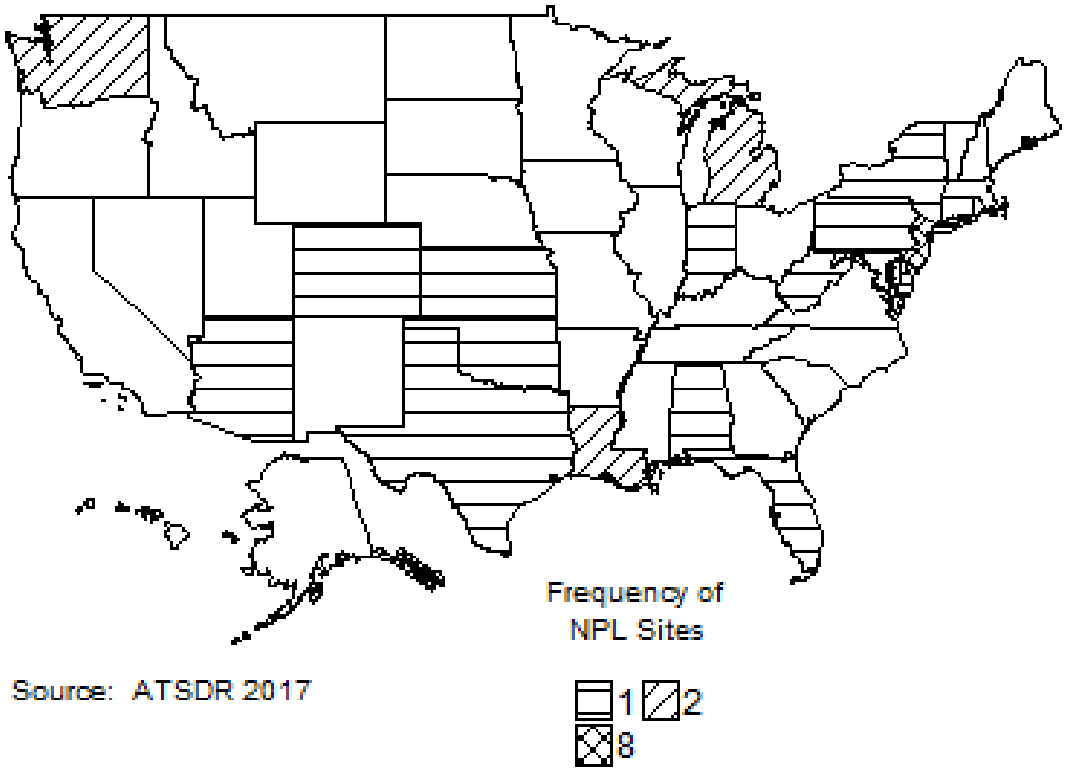
Property	Information	Reference
Molecular weight	184.24	
Color	White	Ahuja et al. 1988
Physical state	Crystalline solid	Dean 1985
Melting point	123–126°C	Aldrich Catalog 1988
Boiling point	309°C	PCGEMS Estimation
Density at 20°C		
Odor	No data	
Odor threshold:		
Water	No data	
Air	No data	
Solubility:		
Water at 20°C[a]	66.9 mg/L (estimated)	Neely and Blau 1985
Organic solvents	Very soluble in alcohol; slightly soluble in benzene	Dean 1985
Partition coefficients:		
Log K_{ow}	2.94 (experimental)	Hansch and Leo 1985
Log K_{oc}	2.73 (calculated using equation 4–10)	Lyman et al. 1982
Vapor pressure at 25°C	2.6×10^{-5} mmHg	Mabey et al. 1981
Henry's law constant at 25°C[a]	9.42×10^{-8} atm-m^3/mol (estimated)	
Autoignition temperature	No data	
Flashpoint	No data	
Flammability limits	No data	
Conversion factors	No data	

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

1,2-Diphenylhydrazine has been identified in at least 26 of the 1,832 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2017). However, the number of sites in which 1,2-diphenylhydrazine has been evaluated is not known. The number of sites in each state is shown in Figure 5-1.

Figure 5-1. Number of NPL Sites with 1,2-Diphenylhydrazine Contamination



- The general population is not likely to be exposed to 1,2-diphenylhydrazine because dye manufacturers in the United States no longer produce benzidine based dyes, which was the former principle use of 1,2-diphenylhydrazine.
- The only current use of 1,2-diphenylhydrazine in the United States is in the production of anti-inflammatory pharmaceutical agents.
- 1,2-Diphenylhydrazine is reversibly oxidized in the environment under aerobic conditions, with a half-life in water as short as 15 minutes. This oxidation also occurs in air and soil.
- The fate, transport, and distribution of 1,2-diphenylhydrazine in the environment are influenced by its rapid oxidation to azobenzene.

5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.2.1 Production

1,2-Diphenylhydrazine is produced in the stepwise reduction of nitrobenzene by the action of iron or zinc powder in caustic solution (e.g., caustic soda, alcoholic alkaline) first to azoxybenzene, then azobenzene, and finally 1,2-diphenylhydrazine (Sandridge and Staley 1978). A batch process is used in which a caustic soda solution is added to a heated vessel charged with nitrobenzene and iron borings. Additions of iron in caustic soda solution are made to continue the reaction. When the reaction is complete, separation of the 1,2-diphenylhydrazine from the iron sludge is accomplished by solvent extraction or by alternative methods, such as stopping the reaction at the azobenzene step and performing the final reduction in a zinc-alcoholic alkali solution followed by filtration and washing of the sodium zincate mass.

Table 5-1 summarizes information on U.S. companies that reported the manufacture or use of 1,2-diphenylhydrazine in 2016 (TRI16 2017). Toxics Release Inventory (TRI) data should be used with caution since only certain types of industrial facilities are required to report. This is not an exhaustive list.

Table 5-1. Facilities that Produce, Process, or Use 1,2-Diphenylhydrazine

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
OH	1	100	999	12
TX	1	1,000	9,999	12

[a]Post office state abbreviations used.
[b]Amounts on site reported by facilities in each state.
[c]Activities/uses:

1. Produce
2. Import
3. Onsite use/processing
4. Sale/Distribution
5. Byproduct
6. Impurity
7. Reactant
8. Formulation Component
9. Article Component
10. Repackaging
11. Chemical Processing Aid
12. Manufacturing Aid
13. Ancillary/Other Uses
14. Process Impurity

Source: TRI16 2017 (Data are from 2016)

5.2.2 Import/Export

No information concerning the importation or exportation of 1,2-diphenylhydrazine in the United States was located in the literature.

5.2.3 Use

One of the major former uses of 1,2-diphenylhydrazine was as a starting material in the production of benzidine-based dyes; however, these are no longer produced or used in the United States. 1,2-Diphenylhydrazine rearranges to benzidine upon treatment with strong acid; benzidine was used by the dye industry for the production of benzidine-based dyes including many of the Direct dyes (e.g., Direct Red 28, Direct Black 4, Direct Blue 2) (Ferber 1978; Lurie 1964). Fabricolor, the last producer of benzidine-based dyes, discontinued production in 1988 (Personal communication, Alvarez 1989).

1,2-Diphenylhydrazine is used by the pharmaceutical industry for the production of the drugs phenylbutazone (trade name Butazolidin, an anti-inflammatory agent) and sulfinpyrazone (trade name Anturane, a uricosuric agent for the treatment of gouty arthritis) (Barnhart 1988; Hughes 1981; Kornis 1982). Phenylbutazone is no longer marketed for human use in the United States, but is still listed for veterinary use (FDA 2016). Sulfinpyrazone has been withdrawn for sale in the United States (FDA 2009). These drugs are made by the condensation of 1,2-diphenylhydrazine with malonic acid derivatives to form pyrazolidinedione structures. It is not clear from the literature if the 1,2-diphenylhydrazine used in the condensation reaction is produced by the manufacturers or if it is purchased by them as an isolated product.

5.2.4 Disposal

Very little information was located in the literature concerning the disposal of 1,2-diphenylhydrazine. Dietrich et al. (1985) reported that wet air oxidation (heating waste water under pressure with the addition of an oxygen-containing gas such as air) would remove 99.88% of the 1,2-diphenylhydrazine in the water (initial concentration, 5,000 mg/L). Results of treatment by wet air oxidation are in keeping with the observation that 1,2-diphenylhydrazine oxidizes to azobenzene (Riggin and Howard 1979). Information regarding the amount of 1,2-diphenylhydrazine disposed of in the United States was not located in the literature.

5.3 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data, presented in Table 5-2, should be used with caution because only certain types of facilities are required to report (EPA 2005). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ

≥10 full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes ≥25,000 pounds of any TRI chemical or otherwise uses >10,000 pounds of a TRI chemical in a calendar year (EPA 2005).

Table 5-2. Releases to the Environment from Facilities that Produce, Process, or Use 1,2-Diphenylhydrazine[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
OH	1	No data	No data	No data	No data	No data	No data	No data	No data
TX	1	14	0	0	0	0	14	0	14
Total	2	14	0	0	0	0	14	0	14

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, waste water treatment (metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI16 2017 (Data are for 2016)

5.3.1 Air

Estimated releases of 14 pounds (~0.0063 metric tons) of 1,2-diphenylhydrazine to the atmosphere from two domestic manufacturing and processing facilities in 2016, accounted for 100% of the estimated total environmental releases from facilities required to report to the TRI (TRI16 2017). These releases are summarized in Table 5-2.

No information concerning the release of 1,2-diphenylhydrazine to air was located in the literature. Since there are very limited uses of 1,2-diphenylhydrazine, emissions to the atmosphere are expected to be low.

5.3.2 Water

There were no releases of 1,2-diphenylhydrazine to water from manufacturing and processing facilities required to report to the TRI (TRI16 2017) (Table 5-2).

No other information concerning the release of 1,2-diphenylhydrazine to water was located in the literature. If discharged to water, detectable concentrations will probably persist for only a short time, since the half-life of (100 µg/L) 1,2-diphenylhydrazine in waste water is about 15 minutes (Riggin and Howard 1979 1982).

5.3.3 Soil

There were no releases of 1,2-diphenylhydrazine to soil from manufacturing and processing facilities required to report to the TRI (TRI16 2017) (Table 5-2).

No other information concerning the release of 1,2-diphenylhydrazine to soil was located in the literature. The manufacturing process for 1,2-diphenylhydrazine generates a sludge containing iron and/or zinc compounds, probably along with small amounts of unextracted 1,2-diphenylhydrazine. Some of this material may be disposed of in landfills, but no information is available concerning the 1,2-diphenyl-hydrazine disposal practices.

5.4 ENVIRONMENTAL FATE

5.4.1 Transport and Partitioning

No information concerning the transport and partitioning of 1,2-diphenylhydrazine in the environment was located in the literature. Based upon its short persistence time and its physical-chemical properties, volatilization from water or soil surfaces, bioconcentration in aquatic organisms, and leaching from soils to underlying groundwater are not expected to be important environmental fate processes for 1,2-diphenylhydrazine.

5.4.2 Transformation and Degradation

Air. No studies were located regarding the rates or products of reaction of 1,2-diphenylhydrazine in the atmosphere. Based on its rapid degradation in aerated water, 1,2-diphenylhydrazine will oxidize in air to form azobenzene as well as other products resulting from the abstraction of a hydrogen from a nitrogen by hydroxyl radicals. The reaction rate constant of 1,2-diphenylhydrazine with photochemically generated hydroxyl radicals was estimated as $211x10^{-12}$ cm^3 $molecule^{-1}$ $second^{-1}$ using a structure estimation method discussed in Atkinson (1987). This corresponds to an atmospheric half-life of <2 hours, assuming a hydroxyl radical concentration of $0.5xl0^6$ molecules cm^{-3}. 1,2-Diphenylhydrazine also absorbs light above 290 nm (Sadtler Index, no date) and may be susceptible to photolysis. No information was found concerning the characteristics of this potential reaction.

Water. Riggin and Howard (1979, 1982) reported the results of a study on the stability of 1,2-diphenylhydrazine in a number of solvents including distilled water and waste water. In distilled water at pH values of 2, 4.7, 7, and 10 and at 4°C or at room temperature, <10% of the initial 10 µg/L of 1,2-diphenylhydrazine remained in the water after 1 day. At pH 2, 1,2-diphenylhydrazine degraded to benzidine, while at pH 7, it degraded to an unidentifiable oxidizable product. At pH 10, 1,2-diphenyl-hydrazine degraded to azobenzene, and at pH 4.7, it degraded into two unidentifiable products, which were not azobenzene or benzidine. In secondary municipal sewage effluent, Riggin and Howard (1979, 1982) reported that 100 µg/L of 1,2-diphenylhydrazine had a half-life of about 15 minutes in the presence of oxygen, and about 60 minutes when no oxygen was present. These results suggest that 1,2-diphenyl-hydrazine is unlikely to persist in the environment, particularly under aerobic conditions.

Tabak et al. (1981a, 1981b) and Patterson and Kodukala (1981) stated that 5 or 10 mg/L of 1,2-diphenyl-hydrazine was degraded up to 80% when initially cultured with settled domestic wastewater. This

degradation rate, however, was reduced to 40% in the case of the 10 mg/L concentration, after the third subculture. The authors suggested that a de-adaptive and toxification process was occurring with 1,2-diphenylhydrazine. It is unclear if the analytical methods used by these authors would have been able to detect 1,2-diphenylhydrazine if present. Both dissolved organic carbon and gas chromatography (GC) analyses were performed on the samples. Considering the sample preparation procedures, however, the compound detected might not have been 1,2-diphenylhydrazine, but a decomposition product such as azobenzene.

Sediment and Soil. No information concerning the fate of 1,2-diphenylhydrazine in soil was located in the literature. Based on the fate of 1,2-diphenylhydrazine in water and sediment, detectable concentrations probably will not persist for long periods, but this may depend on the initial concentration.

5.5 LEVELS IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to 1,2-diphenylhydrazine depends, in part, on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of 1,2-diphenylhydrazine in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on 1,2-diphenylhydrazine levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable.

The rapid oxidation of 1,2-diphenylhydrazine in water to form azobenzene and other compounds makes its sampling and analysis difficult. Storing a sample containing 1,2-diphenylhydrazine for even short periods can result in complete oxidation; in GC, 1,2-diphenylhydrazine is oxidized to azobenzene upon injection onto the chromatographic column (Riggin and Howard 1982). Therefore, unless sampling and analysis are performed under conditions that will prevent oxidation or unless concentrations of 1,2-diphenylhydrazine in the sample are very high, analyses of environmental samples for 1,2-diphenylhydrazine are inaccurate (Ahuja et al. 1988; Riggin and Howard 1979). It is doubtful that the concentrations measured reflect on the concentrations present in the sample at the time of collection (i.e., measured concentrations would underestimate actual concentrations) (Riggin and Howard 1982).

Detections of 1,2-diphenylhydrazine in air, water, and soil at NPL sites are summarized in Table 5-3.

Table 5-3. 1,2-Diphenylhydrazine Levels in Water, Soil, and Air of National Priorities List (NPL) Sites

Medium	Median[a]	Geometric mean[a]	Geometric standard deviation[a]	Number of quantitative measurements	NPL sites
Water (ppb)			No data		
Soil (ppb)	1,000	1,000	1,710	4	3
Air (ppbv)			No data		

[a]Concentrations found in ATSDR site documents from 1981 to 2015 for 1,854 NPL sites (ATSDR 2017). Maximum concentrations were abstracted for types of environmental media for which exposure is likely. Pathways do not necessarily involve exposure or levels of concern.

5.5.1 Air

No ambient air monitoring for 1,2-diphenylhydrazine was located in the literature. This may be due to both the rapid oxidation of 1,2-diphenylhydrazine and its low vapor pressure, which limit the amount of 1,2-diphenylhydrazine entering the atmosphere. In addition, no information was located suggesting that any studies have sought but not found 1,2-diphenylhydrazine.

5.5.2 Water

Two reported identifications of 1,2-diphenylhydrazine in water samples were located in the literature. Melton et al. (1981) reported that 1,2-diphenylhydrazine was present in drinking water in Cincinnati, Ohio (river water treated by coagulation, sand filtration, and chlorination). 1,2-Diphenylhydrazine was reported at a concentration of 1 ng/L. Since the sample preparation involved aeration and the original sample was chlorinated, it is unclear if the detected material was 1,2-diphenylhydrazine or azobenzene. Riggin and Howard (1982) found that, in addition to injection onto a GC column, either chlorination or aeration of a sample resulted in total disappearance of 1,2-diphenylhydrazine. Tang et al. (1983) reported 1,2-diphenylhydrazine in coal gasification waste water at concentrations of 0.149 and 1.786 µg/L. Sample preparation in this case involved separation into classes by pH, liquid-liquid extraction, concentration, and GC/mass spectroscopy (MS) analysis. No precautions were taken to reduce the aeration of the sample. Also, the analytical procedure indicates that no 1,2-diphenylhydrazine would have been able to survive the conditions of the sample preparation and the detection may be of azobenzene or of 1,2-diphenylhydrazine from another source (e.g., decomposition of another compound to 1,2-diphenylhydrazine).

Hall et al. (1985) reported that no 1,2-diphenylhydrazine (<1 µg/L) was detected in the Nanticoke River near the Chesapeake Bay. The analytical method involved liquid-liquid extraction, concentration, and analysis by GC/MS.

5.5.3 Sediment and Soil

1,2-Diphenylhydrazine has been identified in soil only at hazardous waste sites (see Table 5-3); however, it is not clear if the measurements were for 1,2-diphenylhydrazine or its degradation product.

5.5.4 Other Media

1,2-Diphenylhydrazine has been assayed but not detected in fish samples from the Great Lakes area. Camanzo et al. (1987) reported that no 1,2-diphenylhydrazine was detected in fish samples from 13 Lake Michigan tributaries and Grand Traverse Bay fish. Analyses were made by GC/MS and no detection limits were given. Similarly, DeVault (1985) reported that a GC/MS did not identify any of the peaks present in fish samples from Great Lakes harbors and tributaries as 1,2-diphenylhydrazine.

Phenylbutazone and sulfinpyrazone can hydrolyze to yield 1,2-diphenylhydrazine, and these drugs may contain some 1,2-diphenylhydrazine (Ahuja et al. 1988; Fabre et al. 1984; Matsui et al. 1983). Phenylbutazone is a drug used for the treatment of inflammatory conditions (e.g., arthritis) in animals and sulfinpyrazone is used to treat gouty arthritis. Although potential exists for exposure to 1,2-diphenyl-hydrazine from using these drugs, no information regarding body burden was located in the literature.

5.6 GENERAL POPULATION EXPOSURE

Virtually no information concerning occupational exposure or general population was located in the literature. In the past, general population exposure could come from use of anti-inflammatory medication made synthesized with 1,2-diphenylhydrazine, since these drugs may contain small residual amounts (Fabre et al. 1984; Matsui et al. 1983). However, phenylbutazone and sulfinpyrazone are not currently used as human medications (FDA 2009, 2016). The National Institute for Occupational Safety and Health (NIOSH), National Occupational Exposure Survey (NOES) reported as of May 1988 that 977 total employees and 154 female employees are potentially exposed to 1,2-diphenylhydrazine (100% from actual observations) (NIOSH 1988).

The available database limits analysis of exposures in two ways. First, very little information is available concerning the manufacturing processes used in the production of phenylbutazone and sulfinpyrazone, the two drugs that use 1,2-diphenylhydrazine as a starting material. A better understanding of these processes would allow the estimation of worker exposure potentials. Second, dye manufacturers in the United States no longer produce benzidine-based dyes (the last manufacturer stopped production in 1988) and the number of workers potentially exposed to 1,2-diphenylhydrazine is now less than at the time of the NOES survey cited above. Thus, the survey may no longer accurately reflect the number of workers potentially exposed to 1,2-diphenylhydrazine.

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

The only populations with potentially high exposure appear to be persons those living near hazardous waste sites where 1,2-diphenylhydrazine is present and those in occupations that manufacture or use 1,2-diphenylhydrazine. Very little information concerning these populations, however, is available to clearly understand the extent of these potential exposures.

CHAPTER 6. ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of 1,2-diphenylhydrazine is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the adverse health effects (and techniques for developing methods to determine such health effects) of 1,2-diphenylhydrazine.

Data needs are defined as substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.1 INFORMATION ON HEALTH EFFECTS

Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to 1,2-diphenylhydrazine that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of 1,2-diphenylhydrazine. The number of human and animal studies examining each endpoint is indicated regardless of whether an effect was found and the quality of the study or studies.

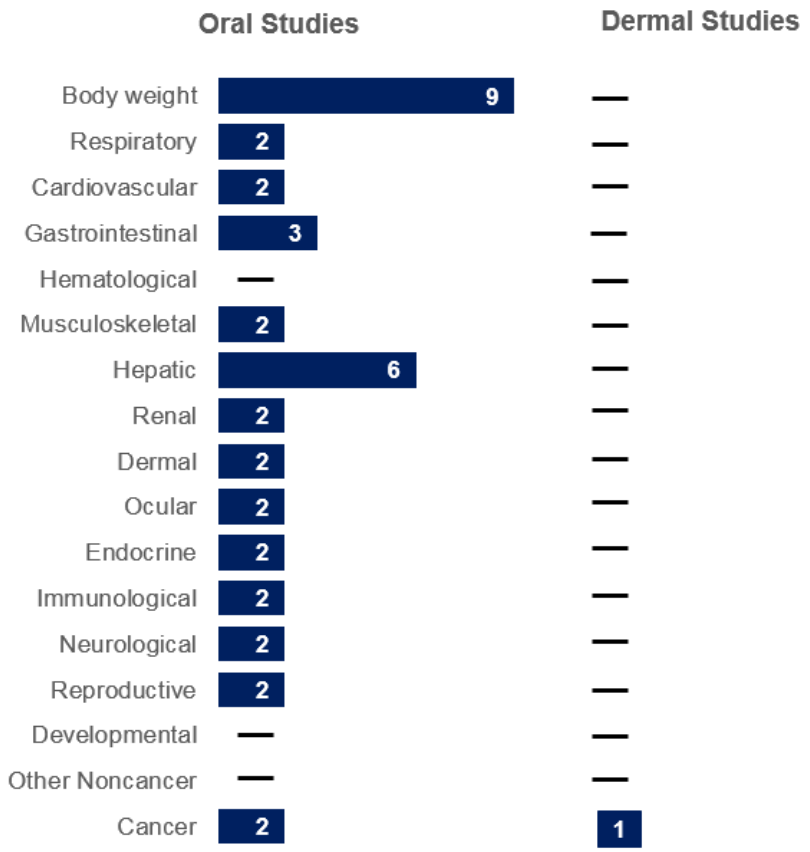
6.2 IDENTIFICATION OF DATA NEEDS

Missing information in Figure 6-1 should not be interpreted as a “data need”. A data need, as defined in ATSDR’s *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Figure 6-1. Summary of Existing Health Effects Studies on 1,2-Diphenylhydrazine By Route and Endpoint*

Potential body weight, hepatic, gastrointestinal, and cancer effects were the most studied endpoints

The majority of the studies examined oral exposure in **animals**; no data were identified for **humans**



Acute-Duration MRLs. Information is not available on the health effects of 1,2-diphenylhydrazine resulting from inhalation exposure in humans or animals. Because 1,2-diphenylhydrazine is a solid with a low vapor pressure at ambient temperatures, it is highly unlikely that inhalation exposure to this chemical in the vapor state would occur. However, the possibility of inhalation exposure to dusts of 1,2-diphenyl-hydrazine either free or adsorbed to soil is conceivable. Therefore, acute studies of inhalation exposure to dusts of 1,2-diphenylhydrazine could be designed to provide information on possible toxic effects and exposure levels that cause effects. No studies were located regarding acute oral exposure in humans. The only pertinent acute exposure toxicity studies of 1,2-diphenylhydrazine were conducted in rats; these consist of an oral LD_{50} assay and a repeated-dose study, which did not find adverse hepatic or body weight effects. Additional acute oral exposure studies that could identify the critical targets of toxicity and provide dose-response data are needed for derivation of an acute MRL.

Intermediate-Duration MRLs. No information was located regarding intermediate-duration inhalation exposure to 1,2-diphenylhydrazine in humans or animals. As discussed for acute-duration exposure, 1,2-diphenylhydrazine is a solid with a low vapor pressure at ambient temperature, which makes inhalation exposure to this chemical in the vapor state unlikely. However, the possibility of inhalation exposure to dusts of 1,2-diphenylhydrazine, either free or adsorbed to soil, is conceivable. Therefore, intermediate-duration studies of inhalation exposure to dusts of 1,2-diphenylhydrazine could be designed to provide information on possible toxic effects and exposure levels that cause effects. Data were considered adequate to derive a provisional intermediate-duration oral MRL for 1,2-diphenylhydrazine. However, additional studies examining a wide range of endpoints would support the identification of the liver as the most sensitive target of toxicity.

Chronic-Duration MRLs. No studies were located regarding chronic inhalation exposure to 1,2-diphenylhydrazine in humans or animals. As discussed for acute- and intermediate-duration exposure, 1,2-diphenylhydrazine is a solid with a low vapor pressure at ambient temperature, which makes inhalation exposure this chemical in the vapor state unlikely. However, the possibility of inhalation exposure to dusts of 1,2-diphenylhydrazine either free or adsorbed to soil is conceivable. Therefore, chronic-duration studies of inhalation exposure to dusts of 1,2-diphenylhydrazine could be designed to provide information on possible toxic effects and exposure levels that cause effects. The NCI (1978) bioassay of 1,2-diphenylhydrazine provides the only sufficient chronic oral toxicity data for this chemical. This study was not, however, subjected to the peer-review process used for current NTP bioassays, and it inadequately evaluated non-neoplastic effects. Additional studies would be particularly useful for corroborating and more fully characterizing 1,2-diphenylhydrazine-induced systemic toxicity. In particular, more studies could provide information on cause(s) of death due to chronic exposure, and delineate carcinogenic and non-carcinogenic doses.

Health Effects. A small number of studies have evaluated the toxicity of 1,2-diphenylhydrazine. The available studies have found liver, lung, gastrointestinal, and cancer effects following oral exposure. No inhalation studies were identified and the only dermal study was of poor quality and only examined cancer endpoints. Acute-, intermediate-, and chronic-duration inhalation, oral, and dermal studies examining a wide range of potential targets of toxicity are needed to identify the critical targets and effect levels. Additionally, studies are needed to evaluate immune, neurological, and reproductive function and developmental endpoints to assess whether these systems are targets of toxicity.

Epidemiology and Human Dosimetry Studies. Health effects of 1,2-diphenylhydrazine have not been described in humans. As discussed in Chapter 5, the potential for environmental exposure to 1,2-diphenylhydrazine is extremely low. Although dermal exposure to 1,2-diphenylhydrazine could occur at a contaminated waste site, it is highly unlikely that segments of the general population will be exposed to 1,2-diphenylhydrazine.

Biomarkers of Exposure and Effect. No biomarkers are known that are specific for 1,2-diphenylhydrazine exposure. If 1,2-diphenylhydrazine or its metabolites in urine can be correlated with exposure, it may be possible to monitor humans for exposure. No biomarkers of effect have been identified.

Absorption, Distribution, Metabolism, and Excretion. The general metabolic pathways of 1,2-diphenylhydrazine are identifiable based on limited evidence for 1,2-diphenylhydrazine in oral, intratracheal, and injection experiments with rats, metabolism data for azobenzene (which is metabolized to 1,2-diphenylhydrazine), and metabolism data for aniline (an initial metabolite). The relative contribution of the different pathways is not established. Although oral absorption of 1,2-diphenyl-hydrazine and urinary excretion of 1,2-diphenylhydrazine and its metabolites are apparent, there is no information on the rate and extent of absorption, or excretion, or tissue distribution following oral exposure. Investigations of the toxicokinetics of 1,2-diphenylhydrazine following dermal exposure have not been conducted. Additional studies of absorption, distribution, metabolism, and excretion in animals by the oral and dermal routes of exposure would provide information needed for sufficient characterization of the toxicokinetics of 1,2-diphenylhydrazine. Studies addressing differences in metabolism between oral and dermal routes would be particularly informative, as benzidine may be formed by acidity in the stomach.

Comparative Toxicokinetics. No data are available to determine if there are differences in the toxicokinetics of 1,2-diphenylhydrazine among species. Toxicokinetic studies with different species could help explain observed differences in toxicity and carcinogenicity between rats and mice, and help identify the animal species that serves as the best model for extrapolating results to humans.

Children's Susceptibility. No studies have evaluated the toxicity of 1,2-diphenylhydrazine in children or young animals. Studies in young animals would be useful to address potential concerns that children may be more susceptible to the toxicity of 1,2-diphenylhydrazine than adults. As previously noted, developmental toxicity studies are also needed.

Physical and Chemical Properties. Physical and chemical properties are essential for estimating the partitioning of a chemical in the environment. Data are available for only a few physical and chemical properties of 1,2-diphenylhydrazine, and most of these have limited experimental descriptions. Therefore, an evaluation of the accuracy of the data is difficult. Specifically, measured solubility, vapor pressure, K_{oc}, pKa, and Henry's Law constant at environmentally significant temperatures would help to remove any doubt concerning the accuracy of the partitioning estimates, especially in circumstances where 1,2-diphenylhydrazine does not oxidize rapidly (such as when high concentrations are present). These data form the basis of much of the input requirements for environmental models that predict the behavior of a chemical under specific conditions, including hazardous waste landfills. In addition, the uncertainty in these measurements can be used to estimate the sensitivity of these properties in determining the overall fate of 1,2-diphenylhydrazine in the environment.

Production, Import/Export, Use, Release, and Disposal. Production methods for 1,2-diphenylhydrazine are well described in the literature (including the patent literature); there does not appear to be a need for further information in this area. Uses of 1,2-diphenylhydrazine are documented, but no recent production figures or detailed descriptions of uses are available. This information is useful for estimating the potential for environmental releases from manufacturing and use industries as well as the potential environmental burden, but it is difficult to obtain in the detail desired since it is considered confidential business information for those industries that manufacture 1,2-diphenylhydrazine. Release information is similar to use information in that it is not obtained easily and can be used to estimate environmental burdens and potentially exposed populations. TRI will provide some of this information in the future. Disposal information is useful for determining environmental burden and potential concentrations where environmental exposures may be high. Data on different disposal methods for 1,2-diphenylhydrazine are lacking.

Environmental Fate. The environmental fate and transport of 1,2-diphenylhydrazine are influenced by its rapid oxidation under aerobic conditions. Direct photolysis and biodegradation studies are lacking, but are not likely important due to the rapid rate of oxidation. A data need exists to study the fate of 1,2-diphenylhydrazine under anaerobic conditions, which may be found in anoxic layers of sediment or groundwater.

Bioavailability from Environmental Media. No studies were located regarding the bioavailability of 1,2-diphenylhydrazine from environmental media, but lack of these data does not necessarily indicate a

lack of bioavailability. As exposure to 1,2-diphenylhydrazine could occur at waste sites by dermal contact with contaminated soil or by ingestion of contaminated soil, it would be useful to know if dermal or oral absorption of 1,2-diphenylhydrazine from environmental media could occur. Information on dermal absorption of 1,2-diphenylhydrazine from other media is not available, but qualitative evidence indicates that 1,2-diphenylhydrazine in diet or oil media is absorbed from the gastrointestinal tract.

Food Chain Bioaccumulation. 1,2-Diphenylhydrazine reacts rapidly in water to form azobenzene and other oxidation products (the half-life in waste water is 60 minutes). Because of this and based upon the log octanol/water partition coefficient, no bioaccumulation is expected in any aquatic organism.

Exposure Levels in Environmental Media. Environmental monitoring data are not available or are of questionable accuracy for water, soil, and air. These data would be helpful in determining the ambient concentrations of 1,2-diphenylhydrazine so that exposure estimates for the general population could be made as well as 1,2-diphenylhydrazine exposure estimates for terrestrial and aquatic organisms.

Exposure Levels in Humans. The database for exposure levels in humans is very limited, and it is unclear if an exposed population exists given the rapid disappearance of 1,2-diphenylhydrazine from the environment. While a more complete database would be helpful in determining the current exposure levels and thereby estimating the average daily dose associated with various scenarios (e.g., living near a hazardous waste site, taking phenylbutazone), a number of factors limit establishing such a program, including the lack of appropriate analytical methods.

Exposures of Children. No data were located on exposures in children. See the previous section for issues relating to collecting monitoring data.

Analytical Methods. No adequate methods are available for the analysis of 1,2-diphenylhydrazine in biological materials. If this information were available, it would allow both investigators and reviewers to assess the accuracy and uncertainty of the methods used in toxicological studies. Furthermore, the ready availability of tested analytical methods, including sample preservation, would permit a standardized approach to the analysis of biological materials to assist in measuring human exposure and monitoring effects in humans. Adequate methods appear to be available for the analysis of 1,2-diphenyl-hydrazine metabolites in biological materials. Metabolites include azobenzene and aniline, both of which appear to be amenable to analysis by standard methods. 1,2-Diphenylhydrazine and its metabolites, however, have not been established as a quantitative biomarker of exposure to 1,2-diphenylhydrazine.

While analytical methods appear to be available for the analysis of 1,2-diphenylhydrazine, no methods were found for the preservation of 1,2-diphenylhydrazine in ambient air, water, or soil samples. Since 1,2-diphenylhydrazine is rapidly oxidized to azobenzene and has been previously reported to decompose instantaneously to azobenzene when introduced to the GC injection port (Riggin and Howard 1979), most GC analysis of 1,2-diphenylhydrazine are calibrated using azobenzene and the results are reported as a combination of both of these compounds.

6.3 ONGOING STUDIES

No ongoing studies were identified for 1,2-diphenylhydrazine (NIH Reporter 2017).

CHAPTER 7. REGULATIONS AND GUIDELINES

Pertinent international and national regulations, advisories, and guidelines regarding 1,2-diphenylhydrazine in air, water, and other media are summarized in Table 7-1. This table is not an exhaustive list, and current regulations should be verified by the appropriate regulatory agency.

ATSDR develops MRLs which are substance specific guidelines intended to serve as screening levels by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites. See Section 1.3 and Appendix A for detailed information on the MRLs for 1,2-diphenylhydrazine.

Table 7-1. Regulations and Guidelines Applicable to 1,2-Diphenylhydrazine

Agency	Description	Information	Reference
		Air	
EPA	RfC	Not assessed	IRIS 2006
		Water & Food	
EPA	Drinking water standards and health advisories	Not listed	EPA 2012
	National primary drinking water regulations	Not listed	EPA 2009
	RfD	Not assessed	IRIS 2006
WHO	Drinking water quality guidelines	Not listed	WHO 2017
FDA	EAFUS	Not listed[a]	FDA 2013
		Cancer	
HHS	Carcinogenicity classification	Reasonably anticipated to be a human carcinogen	NTP 2016
EPA	Carcinogenicity classification	B2[b]	IRIS 2006
IARC	Carcinogenicity classification	Not evaluated	IARC 2017
		Occupational	
OSHA	PEL (8-hour TWA) for general industry, construction, and shipyards	Not listed	OSHA 2016a, 2016b, 2016c
NIOSH	REL (up to 10-hour TWA)	Not listed	NIOSH 2016

Table 7-1. Regulations and Guidelines Applicable to 1,2-Diphenylhydrazine

Agency	Description	Information	Reference
	Emergency Criteria		
EPA	AEGLs-air	Not listed	EPA 2016
AIHA	ERPGs	Not listed	AIHA 2015
DOE	PACs-air		DOE 2018a
	PAC-1[c]	120 mg/m^3	
	PAC-2[c]	1,300 mg/m^3	
	PAC-3[c]	7,900 mg/m^3	

[a]The EAFUS list of substances contains ingredients added directly to food that FDA has either approved as food additives or listed or affirmed as GRAS.
[b]B2: probable human carcinogen.
[c]Definitions of PAC terminology are available from DOE (2018b). PAC values are based on available 60-minute AEGL, ERPG, or TEEL values.

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = acute exposure guideline level; AIHA = American Industrial Hygiene Association; DOE = Department of Energy; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; ERPG = emergency response planning guidelines; FDA = Food and Drug Administration; GRAS = generally recognized as safe; HHS = Department of Health and Human Services; IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = Protective Action Criteria; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TEEL = Temporary Emergency Exposure Limit; TLV = threshold limit values; TWA = time-weighted average; WHO = World Health Organization

CHAPTER 8. REFERENCES

ACGIH. 2016. CAS Number Index. TLVs and BEIs based on the documentation of the threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH: American Conference of Governmental Industrial Hygienists. February 28, 2017.

*Ahuja S, Thompson G, Smith J. 1988. Trace/ultratrace analyses of unstable compounds - investigations on hydrazobenzene and azobenzene. J Res Natl Bur Stand 93:344-347.

*AIHA. 2015. Current ERPG Values (2015). Fairfax, VA: American Industrial Hygiene Association. https://www.aiha.org/get-involved/AIHAGuidelineFoundation/EmergencyResponsePlanningGuidelines/Documents/2015%20ERPG%20Levels.pdf. March 22, 2016.

*Aldrich Catalog. 1988. Aldrich catalog handbook. Milwaukee, WI: Aldrich Chemical Company, Inc., 642.

*Alvarez, C. 1989. Fabricolor, Patterson, NJ. Transcribed telephone conversation with Dr. D. Anthony Gray of Syracuse Research Corporation.

Asafu-Adjaye EB, Yun JI, Su SY. 1985. Multi-component mixture analysis using room-temperature phosphorimetry. Anal Chem 57:904-907.

Ashby J, Tennant RW. 1988. Chemical structure, salmonella mutagenicity and extent of carcinogenicity as indicators of genotoxic carcinogenesis among 22 chemicals tested in rodents by the U.S. NCI/NTP. Mutat Res 204:17-115.

*Atkinson R. 1985. Kinetics and mechanisms of the gas-phase reactions of the hydroxyl radical with organic compounds under atmospheric conditions. Chem Rev 8:69-201.

*Atkinson R. 1987. A structure-activity relationship for the estimation of rate constants for the gas-phase reaction of OH radicals with organic compounds. Int J Chem Kinet 19:799-828.

*ATSDR. 1989. Decision guide for identifying substance-specific data needs related to toxicological profiles; Notice. Agency for Toxic Substances and Disease Registry. Fed Regist 54(174):37618-37634.

*ATSDR. 1990. Toxicological profile on 1,2-diphenylhydrazine. Agency for Toxic Substances and Disease Registry. https://www.atsdr.cdc.gov/ToxProfiles/tp136.pdf. October 2, 2017.

*ATSDR. 2017. 1,2-Diphenylhydrazine. Full SPL data. Substance priority list (SPL) resource page. Agency for Toxic Substances and Disease Registry, Centers for Disease Control and Prevention. http://www.atsdr.cdc.gov/SPL/resources/index.html. October 6, 2017.

*Barnes D, Bellin J, DeRosa C, et al. 1987. Reference dose (RfD): Description and use in health risk assessments. Volume I, Appendix A: Integrated risk information system supportive documentation. Washington, DC: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment. EPA600886032a.

*Barnes DG, Dourson M. 1988. Reference dose (RfD): Description and use in health risk assessments. Regul Toxicol Pharmacol 8(4):471-486.

*Barnhart, ER. 1988. Physicians' desk reference. Oradell, NJ: Medical Economics Company Inc., 854-855, 979-981.

*Beard RR, JT Noe. 1981. Aromatic nitro and amino compounds. In: Clayton GD, Clayton RE, eds. Patty's industrial hygiene and toxicology. Vol 2A. 3rd ed. New York, NY: John Wiley and Sons, 213-2489.

*Bolton GC, Griffiths IA. 1978. Metabolism of hydrazines and hydrazides by the intestinal microflora. Experientia (Switzerland) 34:1484-1486.

---

* Cited in text

+ Cited in supplemental document

8. REFERENCES

Brusick D. 1983. Evaluation of chronic rodent bioassays and Ames assay tests as accurate models for predicting human carcinogens. In: Milman HA, ed. Application of biological markers for carcinogen testing. New York: Plenum Press, 153-163.

*Camanzo J, Rice CP, Jude DJ, et al. 1987. Organic priority pollutants in nearshore fish from 14 Lake Michigan tributaries and embayments, 1983. J Great Lakes Res 13:296-309.

*CAS. 1988. Chemical Abstract Services Online Registry File. December 6, 1988.

*Clewell HJ, Andersen ME. 1985. Risk assessment extrapolations and physiological modeling. Toxicol Ind Health 1(4):111-131.

CLPSDB. 1987. Contract Laboratory Program Statistical Data Base. April 13, 1987.

*Dean J, ed. 1985. Lange's handbook of chemistry. 13th ed. New York, NY: McGraw-Hill Book Co., 7-368.

*De Vault DS. 1985. Contaminants in fish from Great Lakes harbors and tributary mouths. Arch Environ Contam Toxicol 14:587-594.

*Dietrich MJ, Randall TL, Canney PJ. 1985. Wet air oxidation of hazardous organics in wastewater. Environ Prog 4:171-177.

+*Dodd DE, Pluta LJ, Sochaski MA, et al. 2012. Subchronic hepatotoxicity evaluation of hydrazobenzene in Fischer 344 rats. Int J Toxicol 31(6):564-571. 10.1177/1091581812465322.

*DOE. 2018a. Table 3: Protective Action Criteria (PAC) Rev. 29a based on applicable 60-minute AEGLs, ERPGs, or TEELs. The chemicals are listed by CASRN. June 2018. Oak Ridge, TN: U.S. Department of Energy. https://sp.eota.energy.gov/pac/docs/Revision_29A_Table3.pdf. July 26, 2018.

*DOE. 2018b. Protective Action Criteria (PAC) with AEGLs, ERPGs, & TEELs: Rev. 29A, June 2018. Oak Ridge, TN: U.S. Department of Energy. https://sp.eota.energy.gov/pac/. July 26, 2018.

*Dunkel VC, Zeiger E, Brusick D, et al. 1985. Reproducibility of microbial mutagenicity assays: II. Testing of carcinogens and noncarcinogens in *Salmonella tvphimurium* and *Escherichia coli*. Environ Mutagen 7:1-19, 37, 155-158.

*Dutkiewicz T, Szymanska J. 1973. [Chromatographic determination of hydrazobenzene metabolites in rats.] Bromatol Chem Toksykol 6:323-327. (Polish)

EPA. 1980. Ambient water quality criteria for diphenylhydrazine. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, for the Office of Water Regulations and Standards. EPA440580062.

EPA. 1986. Reference values for risk assessment. Cincinnati, OH: U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, for the Office of Solid Waste.

EPA. 1987a. USEPA Contract Laboratory Program statement of work for organics analysis. Dated l0/86, revised 8/87.

EPA. 1987b. Hazardous substances; reportable quantity adjustments; proposed rules. U.S. Environmental Protection Agency. 40 CFR Parts 117 and 302. Fed Regist 52:8140-8152.

EPA. 1988a. Integrated Risk Information System (IRIS). Risk estimates for carcinogenicity for 1,2-diphenylhydrazine. Online. (Verification date 3/1/88). Cincinnati, OH: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office.

EPA. 1988b. Integrated Risk Information System (IRIS). Risk estimates for carcinogenicity for aniline, Online. (Verification date 9/7/88). Cincinnati, OH: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office.

EPA. 1988c. Integrated Risk Information System (IRIS). Risk estimates for carcinogenicity for benzidine. Online. (Verification date 9/7/88). Cincinnati, OH: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office.

8. REFERENCES

EPA. 1989. Interim methods for development of inhalation references doses. Washington, DC: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment. EPA 600888066F.

*EPA. 2005. Toxic chemical release inventory reporting forms and instructions: Revised 2004 version. Section 313 of the Emergency Planning and Community Right-to-Know Act (Title III of the Superfund Amendments and Reauthorization Act of 1986). U.S. Environmental Protection Agency, Office of Environmental Information. EPA260B05001.

*EPA. 2009. National primary drinking water regulations. Washington, DC: U.S. Environmental Protection Agency, Office of Ground Water and Drinking water. EPA816F090004. https://www.epa.gov/sites/production/files/2016-06/documents/npwdr_complete_table.pdf. February 28, 2017.

*EPA. 2012. Drinking water standards and health advisories. Washington, DC: U.S. Environmental Protection Agency, Office of Water. EPA822S12001. https://www.epa.gov/sites/production/files/2015-09/documents/dwstandards2012.pdf. February 28, 2017.

*EPA. 2016. Acute Exposure Guideline Levels (AEGLs) values. U.S. Environmental Protection Agency. https://www.epa.gov/aegl/access-acute-exposure-guideline-levels-aegls-values#chemicals. May 11, 2017.

*Fabre H, Hussam-Eddine N, Mandrou B. 1984. Stability-indicating assay for phenylbutazone: High-performance liquid-chromatographic determination of hydrazobenzene and azobenzene in degraded aqueous phenylbutazone solutions. J Pharm Sci 73:1706-1709.

*FDA. 2009. Determination that Thorazine (chlorpromazine hydrochloride) injection and 18 other drug products were not withdrawn from sale for reasons of safety or effectiveness. U.S. Food and Drug Administration. Fed Regist 74(113):28255-29256.

*FDA. 2013. Everything Added to Food in the United States (EAFUS). Washington, DC: U.S. Food and Drug Administration. http://www.accessdata.fda.gov/scripts/fcn/fcnnavigation.cfm?rpt=eafuslisting. February 28, 2017.

*FDA. 2016. Product safety information. Phenylbutazone in horses- veterinarians. U.S. Food and Drug Administration. https://www.fda.gov/animalveterinary/safetyhealth/productsafetyinformation/ucm186621.htm. June 12, 2017.

*Ferber KH. 1978. Benzidine and related biphenyldiamines. In: Encyclopedia of chemical technology, Vol. 3. 3rd ed. New York, NY: McGraw-Hill Book Co., 772-777.

FSTRAC. 1988. Federal-State Toxicology and Regulatory Alliance Committee. Chemical Communication Subcommittee. March 1988.

*Galloway SM, Armstrong MJ, Reuben C, et al. 1987. Chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells: Evaluations of 108 chemicals. Env Mol Mutagen 10(Supp 10):1-35.

*Genin VA, Medvedovskiy AG, Voronin VM. 1975. [Increased carcinogenic activity during joint effect of hydrobenzene (sic) and benzidine sulfate.] Gig Tr Prof Zabol 6:28-31. (Russian)

Gold LS, Ward JM, Bernstein L, et al. 1986. Association between carcinogenic potency and tumor pathology in rodent carcinogenesis bioassays. Fundam Appl Toxicol 6:677-690.

Graffeo AP, Riggin RM. 1978. The application of electrochemical detection to the HPLC analysis of nonvolatile pollutants. In: Proceedings: 4th Joint Conference on Sensory Environmental Pollution, 637-639.

Gurka DF, Umana M, Pellizzari ED, et al. 1985. The measurement of on-the fly Fourier transform infrared reference spectra of environmentally important compounds. Appl Spectrosc 39:297-303.

*Hall LW Jr., Pinkney AE, Horseman LO, et al. 1985. Mortality of striped bass larvae in relation to contaminants and water quality in a Chesapeake Bay tributary. Trans Am Fish Sot 114:861-868.

*Hansch C, Leo AJ. 1985. Medchem Project. Claremont CA: Pomona College. Issue No. 26.

8. REFERENCES

*Haworth S, Lawlor T, Mortelmas K, et al. 1983. Salmonella mutagenicity test rules for 250 chemicals. Environ Mutagen 5(Suppl. 1):21, 37-38, 102.

Hess GG, McKenzie DE, Hughes BM. 1986. Selective preconcentration of polynuclear aromatic hydrocarbons and polychlorinated biphenyls by in situ metal hydroxide precipitation. J Chromatogr 366:197-204.

HSDB. 1988. Hazardous Substances Data Bank. Bethesda, MD: National Library of Medicine, National Toxicology Information Program. December 5, 1988.

*Hughes DW. 1981. Malonic acid and derivatives. In: Kirk-Othmer encyclopedia of chemical technology. Vol. 14. 3rd ed. New York, NY: Wiley-Interscience, 794, 803-810.

Hurt K, Marhold J, Merhaut J. 1961. Occupational tumours of the urinary tract. Neoplasma 8:551-560.

*IARC. 1972. IARC monographs on the evaluation of carcinogenic risk of chemicals to humans. Vol. 1: Benzidine. Lyon, France: World Health Organization.

*IARC. 2017. Agents classified by the IARC Monographs, Volumes 1–118. Lyon, France: International Agency for Research on Cancer. http://monographs.iarc.fr/ENG/Classification/List_of_Classifications.pdf. June 6, 2017.

*IRIS. 2006. 1,2-Diphenylhydrazine; CASRN 122-66-7. Integrated Risk Information System. Washington, DC: U.S. Environmental Protection Agency. https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0049_summary.pdf. May 10, 2017.

*Kenaga EE. 1980. Predicted bioconcentration factors and soil sorption coefficients of pesticides and other chemicals. Ecotox Environ Safety 4:26-38.

*Kitchin KT, Brown JL. 1994. Dose-response relationship for rat liver DNA damage caused by 49 rodent carcinogens. Toxicology 88(1-3):31-49.

+*Kitchin KT, Brown JL, Kulkarni AP. 1992. Predictive assay for rodent carcinogenicity using *in vivo* biochemical parameters: Operational characteristics and complementarity. Mutat Res 266(2):253-272.

*Kornis G. 1982. Pyrazoles, pyrazolines, pyrazolones. In: Kirk-Othmer Encyclopedia of chemical technology. Vol. 19. 3rd ed. McGraw-Hill Book Co., 448-451.

*Krishnan K, Anderson ME, Clewell HJ, et al. 1994. Physiologically based pharmacokinetic modeling of chemical mixtures. In: Yang RSH, ed. Toxicology of chemical mixtures. Case studies, mechanisms, and novel approaches. San Diego, CA: Academic Press, 399-437.

*Kurlyandskiy BA, Medvedovskiy AG, Genin VA, et al. 1976. [Experimental study of the combined effect of some diphenyl amino derivatives for the purpose of preventing occupational bladder tumors.] Gig Tr Prof Zabol 5:34-38. (Russian)

Lao RC, Thomas RS, Bastien P, et al. 1982. Analysis of organic priority and nonpriority pollutants in environmental samples by GC/MS/computer systems. Pergamon Ser Environ Sci 7:107-118.

Levene CI. 1961. Structural requirements for lathyrogenic agents. J Exp Med 114:295-310.

*Lurie AP. 1964. Benzidine and related diaminobiphenyls. In: Encyclopedia of chemical technology. Vol. 3. 2nd ed. McGraw-Hill Book Co., 3:408, 413, 420.

*Lyman WJ, Reel WF, Rosenblatt DH. 1982. Handbook of chemical property estimation methods: Environmental behavior of organic compounds. New York: McGraw-Hill Book Co., 4-9; 15-16.

*Mabey WR, Smith JH, Pod011 RT, et al. 1982. Aquatic fate process data for organic priority pollutants. Washington, DC: U.S. Environmental Protection Agency. EPA440481014.

*Macholz R, Kujawa M, Schulze J, et al. 1985. The metabolism of some xenobiotics in germ-free and conventional rats. Arch Toxicol 8:373-376.

Mansour M, Parlar H, Korte F. 1975. Ecological chemistry. CI. Reaction behavior of 3,4-dichloraniline and 3,4-dichlorophenol in solution as a solid and in gas phase during UV radiation. Chemosphere 4:235-240.

Marhold J. 1951. [A case of tumour of the bladder following exposure to benzidine.] Pracovni Lekarstvi 31272-274. (Czech)

8. REFERENCES

Marhold J. 1953. [Second case of urinary bladder tumour following work with interproducts of dyes.] Procovni Lekarstvi 4:347. (Czech). (Summarized in Occupational Safety and Health Database, Dialog File 161, NIOSH Accession 00021815.)

+*Marhold J, Matrka M, Hub H, et al. 1968. The possible complicity of diphenyline in the origin of tumors in the manufacture of benzidine. Neoplasma 15:3-10.

*Maronpot RR, Montgomery CA, Boorman GA, et al. 1986a. National Toxicology Program nomenclature for hepatoproliferative lesions of rats. Toxicol Pathol 14(2):263-273.

*Maronpot RR, Shimkin MB, Witschi HP, et al. 1986b. Strain A mouse pulmonary tumor test results for chemicals previously tested in the National Cancer Institute carcinogenicity tests. J Natl Cancer Inst 76:1101-1112.

Maronpot RR, Witschi HP, Smith LH, et al. 1983. Recent experience with the strain A mouse pulmonary tumor bioassay model. Environ Sci Res 27:341-349.

Matsui F, Lovering EG, Curran NM, et al. 1983. Determination of azobenzene and hydrazobenzene in phenylbutazone and sulfinpyrazone products by high-performance liquid chromatography. J Pharm Sci 72:1223-1224.

*Melton RG, Coleman WE, Slater RW, et al. 1981. Comparison of Grob closed-loop stripping analysis with other trace organic methods. Adv Identif Anal Org Pollut Water 2:597-673.

Miller HC, James RH, Dickson WR, et al. 1981. Evaluation of methodology for the survey analysis of solid wastes. ASTM Spec Tech Publ 760:240-266.

*NAS/NRC. 1989. Biologic markers in reproductive toxicology. Washington, DC: National Academy of Sciences/National Research Council. National Academy Press, 15-35.

NATICH. 1988. National Air Toxics Information Clearinghouse. Data base report on state, local and EPA air toxics activities. July, 1988. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards.

+*NCI. 1978. Bioassay of hydrazobenzene for possible carcinogenicity. NCI Carcinogenesis Technical Report Series No. 92. Washington, DC: U.S. Department of Health, Education, and Welfare, National Cancer Institute. DHEW Publication No. (NIH) 78-1342.

*Neely WB, Blau GE, eds. 1985. Environmental exposure from chemicals. Vol. 1. Boca Raton, FL: CRC Press, Inc.

*NIOSH. 1988. National Occupational Exposure Survey (NOES). Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health.

*NIOSH. 2016. NIOSH pocket guide to chemical hazards. Index of Chemical Abstracts Service Registry Numbers (CAS No.). Atlanta, GA: National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention. https://www.cdc.gov/niosh/npg/npgdcas.html. May 11, 2017.

*NRC. 1981. Metabolism of aromatic amines. In: Aromatic amines: An assessment of the biological and environmental effects. Washington, DC: National Research Council. NTIS PB83133058, 40-59.

*NTP. 2013. Draft OHAT approach for systematic review and evidence integration for literature-based health assessments- February 2013. National Toxicology Program, U.S. Department of Health and Human Services, Office of Health Assessment and Translation. https://ntp.niehs.nih.gov/ntp/ohat/evaluationprocess/draftohatapproach_february2013.pdf. April 13, 2016.

*NTP. 2015. Handbook for conducting a literature-based health assessment using OHAT approach for systematic review and evidence integration. National Toxicology Program, U.S. Department of Health and Human Services, Office of Health Assessment and Translation. http://ntp.niehs.nih.gov/ntp/ohat/pubs/handbookjan2015_508.pdf. October 2, 2015.

8. REFERENCES

*NTP. 2016. Hydrazobenzene, CAS No. 122-66-7. Report on Carcinogens, Fourteenth Edition. Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program. https://ntp.niehs.nih.gov/ntp/roc/content/profiles/hydrazobenzene.pdf. June 6, 2017.

*Ohnishi S, Murata M, Oikawa S, et al. 2000. Copper-dependent DNA damage induced by hydrazobenzene, an azobenzene metabolite. Free Radic Res 32(6):469-478.

*OSHA. 2016a. Subpart D Occupational health and environment controls. Section 1926.55 - Gases, vapors, fumes, dusts, and mists. Appendix A to Part 1926.55 - threshold limit values of airborne contaminants for construction. Occupational Safety and Health Standards. Code of Federal Regulations 29 CFR 1926.55. https://www.gpo.gov/fdsys/pkg/CFR-2016-title29-vol8/pdf/CFR-2016-title29-vol8-sec1926-55.pdf. March 6, 2017.

*OSHA. 2016b. Subpart Z - Toxic and hazardous substances. Air contaminants. Occupational Safety and Health Standards. Code of Federal Regulations 29 CFR 1910.1000. https://www.gpo.gov/fdsys/pkg/CFR-2016-title29-vol6/pdf/CFR-2016-title29-vol6-sec1910-1000.pdf. March 6, 2017.

*OSHA. 2016c. Subpart Z - Toxic and hazardous substances. Air contaminants. Table Z - Shipyards. Occupational Safety and Health Standards. Code of Federal Regulations 29 CFR 1915.1000. https://www.gpo.gov/fdsys/pkg/CFR-2016-title29-vol7/pdf/CFR-2016-title29-vol7-sec1915-1000.pdf. March 6, 2017.

*Patterson JW, Kodukala PS. 1981. Biodegradation of hazardous organic pollutants. Chem Eng Prog 77:48-55.

*Pfordte K. 1973. [Acute toxicity and methemoglobin-forming properties of some industrial noxae: Nitrobenzene and its reduction products.] Zeitschrift fuer die Gesamte Hygiene und Ihre Grenzgebiete 19:35-39. (German)

Phai LD, Reuter G. 1976. [Secretion of organic compounds by microorganisms in presence of diphenyl amine.] Allg Mikrobiol 26:369-375. (German)

+*Pliss GB. 1974. [Carcinogenic properties of hydrazo-benzene.] Vopr Onkol 20:53-57. (Russian)

Poctova M, Kakac B. 1981. [Determination of azobenzene and hydrazobenzene in ketazone (kebuzone) pharmaceutical preparations.] Cesk Farm 30:159-161. (Czech)

*Reinhardt CF, Brittelli MR. 1981. Heterocyclic and miscellaneous nitrogen compounds. Hydrazine. In: Clayton GD, Clayton FE, eds. Patty's industrial hygiene and toxicology. Vol. 2A. 3rd ed. New York, NY: John Wiley and Sons, 2791-2822.

*Riggin RM, Howard CC. 1979. Determination of benzidine, dichlorobenzidine, and diphenylhydrazine in aqueous media by high performance liquid chromatography. Anal Chem 51:210-214.

*Riggin RM, Howard CC. 1982. Determination of benzidines in industrial and municipal wastewaters. Cincinnati, OH: U.S. Environmental Protection Agency, Environmental Monitoring and Support Laboratory. EPA600S482022.

*Rooney AA, Boyles AL, Wolfe MS, et al. 2014. Systematic review and evidence integration for literature-based environmental health science assessments. Environ Health Perspect 122(7):711-718. 10.1289/ehp.1307972.

*Sadtler Index. n.d. UV spectrum 4611. Philadelphia, PA: Samuel P. Sadtler and Son, Inc.

*Sandridge RL, Staley HB. 1978. Amines by reduction. In: Encyclopedia of chemical technology. Vol. 2. 3rd ed. McGraw-Hill Book Co., 355-376.

*SANSS. 1988. Structure and Nomenclature Search System. December 5, 1988.

+*Schafer EW, Bowles WA. 1985. Acute oral toxicity and repellence of 933 chemicals to house and deer mice. Arch Environ Contam Toxicol 14:111-129.

*Seiler JP. 1977. Inhibition of testicular DNA synthesis by chemical mutagens and carcinogens. Preliminary results in the validation of a novel short term test. Mutat Res 46:305-310.

*Shabad IX, Genin VA. 1975. [Combined action of amino-substituted biphenyl causing bladder tumors.] Urol Nefrol 1:38-42. (Russian)

*Spitz S, Maguigan WH, Dobriner K. 1950. The carcinogenic action of benzidine. Cancer 3:789-804.

8. REFERENCES

*Tabak HH, Quave SA, Mashni CI. 1981a. Biodegradability studies for predicting the environmental fate of organic priority pollutants. In: Washington, DC: Symposium proceedings of 94th annual meeting Association of Official Analytical Chemistry: Test protocols for environmental fate and movement of toxicants, 267-328.

*Tabak HH, Quave SA, Mashni CI, et al. 1981b. Biodegradability studies with organic priority pollutant compounds. J Water Pollut Contr Fed 53:1503-1518.

*Tang JIS, Yen TF, Kawahara FK. 1983. Separation and identification of the organic species in coal conversion process wastewater. In: Symposium: Chem Geochem Aspects Fossil Energy, 85-106.

*TRI16 2017. TRI explorer: Providing access to EPA's toxics release inventory data. Washington, DC: Office of Information Analysis and Access. Office of Environmental Information. U.S. Environmental Protection Agency. Toxics Release Inventory. http://www.epa.gov/triexplorer/. September 29, 2017.

*USITC. 1979. United States International Trade Commission. Synthetic organic chemicals. U.S. production and sales, 1978. Washington, DC: U.S. Government Printing Office, 2.

Vigliani EC, Barsotti M. 1962. Environmental tumors of the bladder in some Italian dye-stuff factories. Acta Unio Internat Contra Cancrum 18:669-675.

*Weber EJ, Wolfe NL. 1986. Kinetic studies of aromatic azo compounds in anaerobic sediment/water systems [abstract]. In: 191st National meeting: American Chemical Society Division of Environmental Chemistry 26:239-40.

*Weber EJ, Wolfe NL. 1987. Kinetic studies of the reduction of aromatic azo compounds in anaerobic sediment/water systems. Environ Toxicol Chem 6:911-919.

Weisburger EK. 1983. Species differences in response to aromatic amines. Basic Life Sci 27:23-47.

Werner R. Uehleke H, Wohrlin R. 1976. Reduction of azobenzene to hydrazobenzene by liver fractions. Naunyn-Schmeidebergs Arch Pharmacol 293:54.

*WHO. 2010. Guidelines for indoor air quality: Selected pollutants. Geneva, Switzerland: World Health Organization. http://www.euro.who.int/__data/assets/pdf_file/0009/128169/e94535.pdf. January 08, 2014.

*WHO. 2017. Guidelines for drinking-water quality. Fourth edition incorporating the first addendum. Geneva, Switzerland: World Health Organization. http://apps.who.int/iris/bitstream/10665/254637/1/9789241549950-eng.pdf?ua=1. February 28, 2017.

*Williams RT. 1959. The metabolism of dyestuffs and other colouring matters. In: Detoxication mechanisms. The metabolism and detoxication of drugs, toxic substances and other organic compounds. 2nd ed. New York, NY: John Wiley and Sons, Inc., 472-488.

*Yoon JS, Mason JM, Valencia R, et al. 1985. Chemical mutagenesis testing in Drosophila. IV. Results of 45 coded compounds tested for the National Toxicology Program. Environ Mutagen 7:349-367.

Zeiger E. 1987. Carcinogenicity of mutagens: Predictive capability of the Salmonella mutagenesis assay for rodent carcinogenicity. Cancer Res 47:1287-1296.

APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified route and duration of exposure. MRLs are based on noncancer health effects only; cancer effects are not considered. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the NOAEL/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (≥365 days) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive substance-induced endpoint considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

APPENDIX A

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Human Health Sciences, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published MRLs. For additional information regarding MRLs, please contact the Division of Toxicology and Human Health Sciences, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop S102-1, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2-Diphenylhydrazine
CAS Numbers: 122-77-6
Date: December 1990
March 2017—Updated literature search
Profile Status: Draft 5
Route: Inhalation
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration inhalation MRL.

Rationale for Not Deriving an MRL: No acute-duration inhalation studies were identified for 1,2-diphenylhydrazine.

Agency Contact (Chemical Manager): Sam Keith, M.S., C.H.P.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2-Diphenylhydrazine
CAS Numbers: 122-77-6
Date: December 1990
March 2017—Updated literature search
Profile Status: Draft 5
Route: Inhalation
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration inhalation MRL.

Rationale for Not Deriving an MRL: No intermediate-duration inhalation studies were identified for 1,2-diphenylhydrazine.

Agency Contact (Chemical Manager): Sam Keith, M.S., C.H.P.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2-Diphenylhydrazine
CAS Numbers: 122-77-6
Date: December 1990
March 2017—Updated literature search
Profile Status: Draft 5
Route: Inhalation
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration inhalation MRL.

Rationale for Not Deriving an MRL: No chronic-duration inhalation studies were identified for 1,2-diphenylhydrazine.

Agency Contact (Chemical Manager): Sam Keith, M.S., C.H.P.

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2-Diphenylhydrazine
CAS Numbers: 122-77-6
Date: May 2019
Profile Status: Final, Draft for Public Comment
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration oral MRL.

Rationale for Not Deriving an MRL: The acute-duration oral database was not considered suitable for derivation of an MRL because lethality was the only adverse effect observed in the available studies.

The Dodd et al. (2012) study of 1,2-diphenylhydrazine is the only acute oral toxicity study that evaluated endpoints other than lethality. The study found no adverse alterations in body weight, liver weight, liver enzymes, or liver histopathology in rats treated with 1,2-diphenyhydrazine for 5 days or 2 weeks at doses as high as 15.5 mg/kg/day.

Agency Contact (Chemical Manager): Sam Keith, M.S., C.H.P.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2-Diphenylhydrazine
CAS Numbers: 122-77-6
Date: May 2019
Profile Status: Final, Draft for Public Comment
Route: Oral
Duration: Intermediate
MRL: 0.05 mg/kg/day (provisional)
Critical Effect: Hepatic effects
Reference: Dodd et al. 2012
Point of Departure: NOAEL of 4.8 mg/kg/day
Uncertainty Factor: 100
LSE Graph Key: 6
Species: Rat

MRL Summary: A provisional intermediate oral MRL of 0.05 mg/kg/day was derived for 1,2-diphenyl-hydrazine. The provisional MRL is based on a NOAEL of 4.80 mg/kg/day for hepatic effects in rats exposed to 1,2-diphenylhydrazaine in the diet for 13 weeks (Dodd et al. 2012). This NOAEL was divided by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 to account for intra-human variation).

Selection of the Critical Effect: Three studies have evaluated toxicity of 1,2-diphenyhydrazine following intermediate-duration oral exposure. Effects identified include death, gastrointestinal effects, and hepatic effects (Dodd et al. 2012; Marhold et al. 1968; NCI 1978). Increases in mortality were observed in rats at 54 mg/kg/day (NCI 1978) and in mice exposed to 390 mg/kg/day (NCI 1978). An increase in intestinal hemorrhage was reported in mice exposed to 390 mg/kg/day for 4 weeks (NCI 1978); gastrointestinal effects were not observed in similarly exposed rats. Dodd et al. (2012) reported significant increases in the incidences of hypertrophy, eosinophilic granular cytoplasm, and bile duct duplication in the livers of rats exposed to ≥10.3 mg/kg/day for 13 weeks, but not after 4 weeks of exposure. At 15.5 mg/kg/day, macrovesiculation was also observed in the liver of rats exposed for 13 weeks (Dodd et al. 2012). No other intermediate-duration studies included histological examination of the liver. Based on the limited available data, the liver appears to be the most sensitive target of toxicity. This is supported by liver effects (fatty metamorphosis or coagulative necrosis) in rats and mice chronically exposed to 1,2-diphenylhydrazine in the diet (NCI 1978).

Selection of the Principal Study: Due to incomplete details of study design and lack of histopathology data in the 4-week dose-finding study (NCI 1978) and the Marhold et al. (1968) study, derivation of the provisional MRL for hepatic effects is based on findings in the multi-dose study by Dodd et al. (2012). The selected study provides the best available data for characterizing the dose-response relationship for liver effects in laboratory animals orally exposed to 1,2-diphenylhydrazine for intermediate durations and it identified the lowest reliable LOAEL value.

Summary of the Principal Study:

Dodd DE, Pluta LJ, Sochaski MA, et al. 2012. Subchronic hepatotoxicity evaluation of hydrazobenzene in Fischer 344 rats. Int J Toxicol 31: 564-571.

Groups of male Fischer 344 rats (minimum 10/group) were exposed to 0, 5, 20, 80, 200, or 300 ppm 1,2-diphenylhydrazine in the diet for 4 or 13 weeks. Mean administered doses, calculated from weekly food consumption and analytic diet concentration data, were reported to be 0, 0.32, 1.26, 4.80, 10.3, and

15.5 mg/kg/day. Endpoints evaluated included clinical observations, body weight, food consumption, serum chemistry, liver weights, gross pathology, and liver histopathology. Significant, but marginal decreases in body weights (up to ~6% decrease, compared with control values) beginning at 8 weeks occurred in animals exposed to 15.5 mg/kg/day. There were no clinical signs of toxicity or gross pathology throughout the study or at necropsy. Microscopic alterations in the liver, including slight/mild hypertrophy, minimal eosinophilic granular cytoplasm, multifocal bile duct duplications, and multifocal macrovesiculation, an indicator of lipid accumulation within hepatocytes, were observed only at 13 weeks at doses ≥10.3 mg/kg/day; the incidences of these lesions are presented in Table A-1. Relative liver weights also significantly increased (7.7 and 4.4%) at 4 and 13 weeks in 10.3 mg/kg/day rats, and showed concentration dependence, with increases of 8.5 and 10.7% at the same time points after treatment with 15.5 mg/kg/day. No consistent changes in serum alanine aminotransferase, total bilirubin, or lactate dehydrogenase were observed at any dose, but serum aspartate aminotransferase decreased by 26% at 13 weeks after treatment with 15.5 mg/kg/day. Decreases in serum alkaline phosphatase occurred beginning at a dose of 1.26 mg/kg/day at 13 weeks, but were also observed at earlier time points at higher doses; the toxicological significance of the decreases in alkaline phosphatase is not known. The investigators noted that the decreases were unexpected and did not correlate with other liver effects (Dodd et al. 2012).

Table A-1. Incidences of Liver Lesions in Rats Exposed to 1,2-Diphenylhydrazine in the Diet for 13 Weeks

	Dose (mg/kg/day)					
	0	0.32	1.26	4.80	10.3	15.5
Slight/mild hypertrophy (diffuse)	0/12	0/10	0/10	0/10	10/10	10/10
Slight/mild macrovesiculation (multifocal)	0/12	0/10	0/10	0/10	1/10	10/10
Minimal eosinophilic granular cytoplasm	0/12	0/10	0/10	0/10	10/10	9/10
Minimal to slight/mild bile duct duplication (multifocal)	0/12	0/10	0/10	0/10	8/10	10/10

Source: Dodd et al. 2012

Selection of the Point of Departure for the Provisional MRL: Data were not amenable to benchmark dose modeling due to the steep dose-response curve and the lack of information between the extremes of the control incidence (0%) and the maximal response (≥80%). Using a NOAEL/LOAEL approach, the NOAEL of 4.8 mg/kg/day was selected as the basis of the provisional MRL

Adjustment Intermittent Exposure: Not applicable.

Uncertainty Factor: The NOAEL of 4.8 mg/kg/day was divided by a total uncertainty factor of 100:

- 10 for animal to human extrapolation
- 10 for human variability

Other Additional Studies or Pertinent Information: In a chronic-duration study, dietary exposure to 1,2-diphenylhydrazine resulted in interstitial inflammation in the lungs, hyperkeratosis/acanthosis in the stomach, and fatty metamorphosis in the liver of rats exposed for 78 weeks (NCI 1978). Coagulative necrosis was also observed in the livers of female mice exposed to 52 mg/kg/day (NCI 1978). The results of the NCI (1978) study support the selection of the liver lesions as the most sensitive effect.

Agency Contact (Chemical Manager): Sam Keith, M.S., C.H.P.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2-Diphenylhydrazine
CAS Numbers: 122-77-6
Date: December 1990
March 2017—Updated literature search
Profile Status: Draft 5
Route: Oral
Duration: Chronic

MRL Summary: The available chronic oral data (NCI 1978) were not considered adequate for derivation of a chronic oral MRL.

Rationale for Not Deriving an MRL: The only available chronic-duration oral study was not considered suitable for derivation of an MRL due to the long duration (28–30 weeks) between exposure termination and histological examination and methodological problems with the only available study.

The NCI (1978) bioassay of 1,2-diphenylhydrazine provides the only sufficient chronic oral toxicity data for this chemical. In this study, rats and mice were exposed to 1,2-diphenylhydrazine in the diet for 78 weeks followed by a 28–30-week observation period. The facilities supplying the rats, the diet, and the bedding used for low-dose rats and their controls differed from those used for the high-dose rats and their controls. Additionally, the low-dose control group and low- and high-dose exposed rats were housed in a different room than the high-dose control group. Similar differences in animal husbandry were noted for the mice. All animals, regardless of time or reason for death, whether due to lethality, sacrifice when moribund, or at study termination, were necropsied and were included in histopathological incidence evaluations. Significant increases in mortality were observed in female rats exposed to 9.2 mg/kg/day and in male and female mice exposed to 69 mg/kg/day; times and causes of death were not provided (NCI 1978). Non-neoplastic alterations included interstitial lung inflammation, acanthosis of the stomach, hyperkeratosis of the stomach, and fatty metamorphosis in the liver; the NOAEL and LOAEL values for these effects are presented in Table A-2. Although the study identifies 3.7 mg/kg/day as the lowest LOAEL for interstitial lung inflammation and acanthosis of the stomach in female rats, there is some uncertainty with this categorization, since the incidences of these lesions were not significantly increased at the higher dose level (9.2 mg/kg/day). Adding to the uncertainty is the inconsistency of these effects between the low dose control group and the high dose control group; for example, incidences of lung interstitial inflammation was 0/47 for the low dose female controls and 6/50 in the high dose female controls (in males, the incidences were 0/47 and 4/48 in low- and high-dose controls). In addition to these non-neoplastic lesions, increases in the incidence of neoplastic lesions were observed, including hepatocellular carcinomas in male rats exposed to ≥6.3 mg/kg/day and female mice exposed to 69 mg/kg/day, neoplastic nodules in the livers of female rats exposed to 9.2 mg/kg/day, combined squamous cell carcinomas/papillomas in the ear canal, Zymbal's gland, and skin of the ear in male rats exposed to 24 mg/kg/day, adrenal gland pheochromacytomas in male rats exposed to 24 mg/kg/day, and mammary gland adenocarcinomas in female rats exposed to 9.2 mg/kg/day (NCI 1978).

Table A-2. Summary of Relevant NOAEL and LOAEL Values in Rats and Mice Following Chronic-Duration Oral Exposure to 1,2-Diphenylhydrazine[a]

	Males		Females	
	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)
Fischer 344 rats				
Increased mortality				9.2
Decreased body weight gain	6.	24	3.7	9.2
Interstitial lung inflammation		6.3		3.7[b]
Acanthosis of stomach	6.3	24		3.7[b]
Hyperkeratosis of stomach	6.3	24	9.2	
Fatty metamorphosis in liver	6.3	24	3.7	9.2[c]
B6C3F1 mice				
Increased mortality		69		69
Decreased body weight	14	69	6.9	69
Coagulative hepatic necrosis			6.9	69

[a]Rats and mice were exposed for 78 weeks followed by a 28–30-week observation period.
[b]This effect was not observed in rats exposed to 9.2 mg/kg/day.
[c]Incidence higher than low-dose control group, but not high-dose control group.

Source: NCI 1978

The NCI (1978) study was not considered suitable for the derivation of a chronic-duration oral MRL due to the lack of dose-response for effects observed at the lowest dose tested, the long recovery period, and some methodological issues with the study design. As summarized in Table A-3, significant increases in the incidence of interstitial lung inflammation and acanthosis of the stomach were observed in female rats at the lowest dose tested (3.7 mg/kg/day), but were not observed at the highest dose (9.2 mg/kg/day). In male rats, an increase in interstitial lung inflammation was observed in male rats at 6.3 and 24 mg/kg/day. Stomach lesions were observed in males at 24 mg/kg/day, but not at 6.3 mg/kg/day. The lack of dose-response relationships increases the uncertainty in assessing whether the effects are due to 1,2-diphenyl-hydrazine exposure. Differences in the source of the animals, housing, and diet between the low-dose controls and exposed animals and the high-dose controls and exposed animals may have also contributed to the observed differences. In addition, the long recovery period complicates the identification of the NOAELs and LOAELs because it is not known if effects occurred at lower doses and the damage was repaired prior to examination.

Table A-3. Incidence of Lung and Stomach Lesions in Rats Following Chronic-Duration Oral Exposure to 1,2-Diphenylhydrazine[a]

		Low dose		High dose
Female rats	Controls	3.7 mg/kg/day	Controls	9.2 mg/kg/day
Interstitial lung inflammation	0/47 (0%)	29/50[b] (58%)	6/50 (12%)	7/50 (14%)
Acanthosis of stomach	0/46 (0%)	6/50[b] (12%)	2/48 (4%)	5/44 (11%)
		Low dose		High dose
Male rats	Controls	6.3 mg/kg/day	Controls	24 mg/kg/day
Interstitial lung inflammation	0/47 (0%)	12/49[b] (24%)	4/48 (8%)	16/48[b] (33%)
Acanthosis of stomach	0/47 (0%)	4/49 (8%)	1/49 (2%)	17/47[b] (36%)

[a]Rats were exposed for 78 weeks followed by a 28–30-week observation period.
[b]Statistically significant differences ($p<0.05$); Fisher Exact Test conducted by ATSDR.

Source: NCI 1978

Agency Contact (Chemical Manager): Sam Keith, M.S., C.H.P.

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR 1,2-DIPHENYLHYDRAZINE

The objective of the toxicological profile is to evaluate the potential for human exposure and the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to 1,2-diphenylhydrazine.

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen was conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions, and regulations/ guidelines data for 1,2-diphenylhydrazine. ATSDR primarily focused on peer-reviewed articles without publication date or language restrictions. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of 1,2-diphenylhydrazine have undergone peer review by at least three ATSDR-selected experts who have been screened for conflict of interest. The inclusion criteria used to identify relevant studies examining the health effects of 1,2-diphenylhydrazine are presented in Table B-1.

Table B-1. Inclusion Criteria for the Literature Search and Screen

Health Effects
Species
Human
Laboratory mammals
Route of exposure
Inhalation
Oral
Dermal (or ocular)
Parenteral (these studies will be considered supporting data)
Health outcome
Death
Systemic effects
Body weight effects
Respiratory effects
Cardiovascular effects
Gastrointestinal effects
Hematological effects
Musculoskeletal effects
Hepatic effects
Renal effects
Dermal effects
Ocular effects
Endocrine effects
Immunological effects
Neurological effects
Reproductive effects
Developmental effects

Table B-1. Inclusion Criteria for the Literature Search and Screen

Other noncancer effects
Cancer
Toxicokinetics
Absorption
Distribution
Metabolism
Excretion
PBPK models
Biomarkers
Biomarkers of exposure
Biomarkers of effect
Interactions with other chemicals

B.1.1 Literature Search

The current literature search was intended to update the health effects sections of the existing toxicological profile for 1,2-diphenylhydrazine (ATSDR 1990), thus, the literature search was restricted to studies published between January 1988 to March 2017. The following main databases were searched in March 2017:

- PubMed
- National Library of Medicine's TOXLINE
- Scientific and Technical Information Network's TOXCENTER

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, and Medical Subject Headings (MeSH) terms for 1,2-diphenylhydrazine. The query strings used for the literature search are presented in Table B-2.

The search was augmented by searching the Toxic Substances Control Act Test Submissions (TSCATS), NTP website, and National Institute of Health Research Portfolio Online Reporting Tools Expenditures and Results (NIH RePORTER) databases using the queries presented in Table B-3. Additional databases were searched in the creation of various tables and figures, such as the TRI Explorer, the Substance priority list (SPL) resource page, and other items as needed. Regulations applicable to 1,2-diphenylhydrazine were identified by searching international and U.S. agency websites and documents.

Review articles were identified and used for the purpose of providing background information and identifying additional references. ATSDR also identified reports from the grey literature, which included unpublished research reports, technical reports from government agencies, conference proceedings and abstracts, and theses and dissertations.

Table B-2. Database Query Strings

Database search date	Query string
PubMed	
03/2017	((1G3CS09TUK[rn] OR 122-66-7[rn] OR "1,2-diphenylhydrazine"[supplementary concept] OR "1,2-diphenylhydrazine"[nm]) AND (1988/01/01 : 3000[dp] OR 1988/01/01 : 3000[mhda])) OR (("(sym)-Diphenylhydrazine"[tw] OR "1,1'-Hydrazodibenzene"[tw] OR "1,2-Diphenylhydrazine"[tw] OR "1,1'-hydrazobis-Benzene"[tw] OR "hydrazodi-Benzene"[tw] OR "1,2-diphenyl-Hydrazine"[tw] OR "Hydrazobenzene"[tw] OR "N, N'-Bianiline"[tw] OR "N, N'-Diphenylhydrazine"[tw] OR "Symmetrical diphenyl hydrazine"[tw]) AND (1988/01/01 : 3000[dp] OR 1988/01/01 : 3000[crdat] OR 1988/01/01 : 3000[edat]))
Toxline	
03/2017	(" (sym) -diphenylhydrazine" OR "1 1'-hydrazodibenzene" OR "1 2-diphenylhydrazine" OR "1 1'-hydrazobis-benzene" OR "hydrazodi-benzene" OR "1 2-diphenyl-hydrazine" OR "hydrazobenzene" OR "n n'-bianiline" OR "n n'-diphenylhydrazine" OR "symmetrical diphenyl hydrazine" OR 122-66-7 [rn]) AND 1988:2017 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org]
Toxcenter	
03/2017	FILE 'TOXCENTER' ENTERED AT 16:44:37 ON 16 MAR 2017 CHARGED TO COST=EH011.13.01.01 L49 292 SEA 122-66-7 L50 280 SEA L49 NOT TSCATS/FS L51 260 SEA L50 NOT PATENT/DT L52 169 SEA L51 AND PY>=1988 ACTIVATE TOXQUERY/Q --------- L53 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L54 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L55 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L56 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L57 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L58 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L59 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L60 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L61 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L62 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?) L63 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) L64 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?)

Table B-2. Database Query Strings

Database search date	Query string
	L65 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
	L66 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L67 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L68 QUE (ENDOCRIN? AND DISRUPT?)
	L69 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L70 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L71 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L72 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)
	L73 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L74 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L75 QUE (NEPHROTOX? OR HEPATOTOX?)
	L76 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L77 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L78 QUE L53 OR L54 OR L55 OR L56 OR L57 OR L58 OR L59 OR L60 OR L61 OR L62 OR L63 OR L64 OR L65 OR L66 OR L67 OR L68 OR L69 OR L70 OR L71 OR L72 OR L73 OR L74 OR L75 OR L76 OR L77
	L79 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?)
	L80 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
	L81 QUE L78 OR L79 OR L80
	L82 QUE (NONHUMAN MAMMALS)/ORGN
	L83 QUE L81 OR L82
	L84 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?)
	L85 QUE L83 OR L84

	L86 125 SEA L52 AND L85
	L87 6 SEA L86 AND MEDLINE/FS
	L88 3 SEA L86 AND BIOSIS/FS
	L89 102 SEA L86 AND CAPLUS/FS
	L90 14 SEA L86 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS)
	L91 117 DUP REM L87 L88 L90 L89 (8 DUPLICATES REMOVED)
	L*** DEL 6 S L86 AND MEDLINE/FS
	L*** DEL 6 S L86 AND MEDLINE/FS

Table B-2. Database Query Strings

Database search date	Query string
	L92 6 SEA L91 L*** DEL 3 S L86 AND BIOSIS/FS L*** DEL 3 S L86 AND BIOSIS/FS L93 2 SEA L91 L*** DEL 102 S L86 AND CAPLUS/FS L*** DEL 102 S L86 AND CAPLUS/FS L94 95 SEA L91 L*** DEL 14 S L86 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) L*** DEL 14 S L86 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) L95 14 SEA L91 L96 111 SEA (L92 OR L93 OR L94 OR L95) NOT MEDLINE/FS SAVE TEMP L96 DIPHEN/A D SCAN L96

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS[a]	
03/2017	Compound searched: 122-66-7
NTP	
03/2017	122-66-7 1,1'-Hydrazodibenzene 1,2-Diphenylhydrazine Hydrazobenzene
NIH RePORTER	
05/2017	Active projects "(sym)-Diphenylhydrazine" OR "1,1'-Hydrazodibenzene" OR "1,2-Diphenylhydrazine" OR "1,1'-hydrazobis-Benzene" OR "hydrazodi-Benzene" OR "1,2-diphenyl-Hydrazine" OR "Hydrazobenzene" OR "N,N'-Bianiline" OR "N,N'-Diphenylhydrazine" OR "Symmetrical diphenyl hydrazine"
Other	Identified throughout the assessment process

[a]Several versions of the TSCATS database were searched, as needed, by CASRN including TSCATS1 via Toxline (no date limit), TSCATS2 via https://yosemite.epa.gov/oppts/epatscat8.nsf/ReportSearch?OpenForm (date restricted by EPA receipt date), and TSCATS via CDAT (date restricted by 'Mail Received Date Range'), as well as google for recent TSCA submissions.

The 2017 results were:

- Number of records identified from PubMed, TOXLINE, and TOXCENTER (after duplicate removal): 175
- Number of records identified from other strategies: 34
- Total number of records to undergo literature screening: 209

B.1.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies on 1,2-diphenylhydrazine:

- Title and abstract screen
- Full text screen

Title and Abstract Screen. Within the reference library, titles and abstracts were screened manually for relevance. Studies that were considered relevant (see Table B-1 for inclusion criteria) were moved to the second step of the literature screening process. Studies were excluded when the title and abstract clearly indicated that the study was not relevant to the toxicological profile.

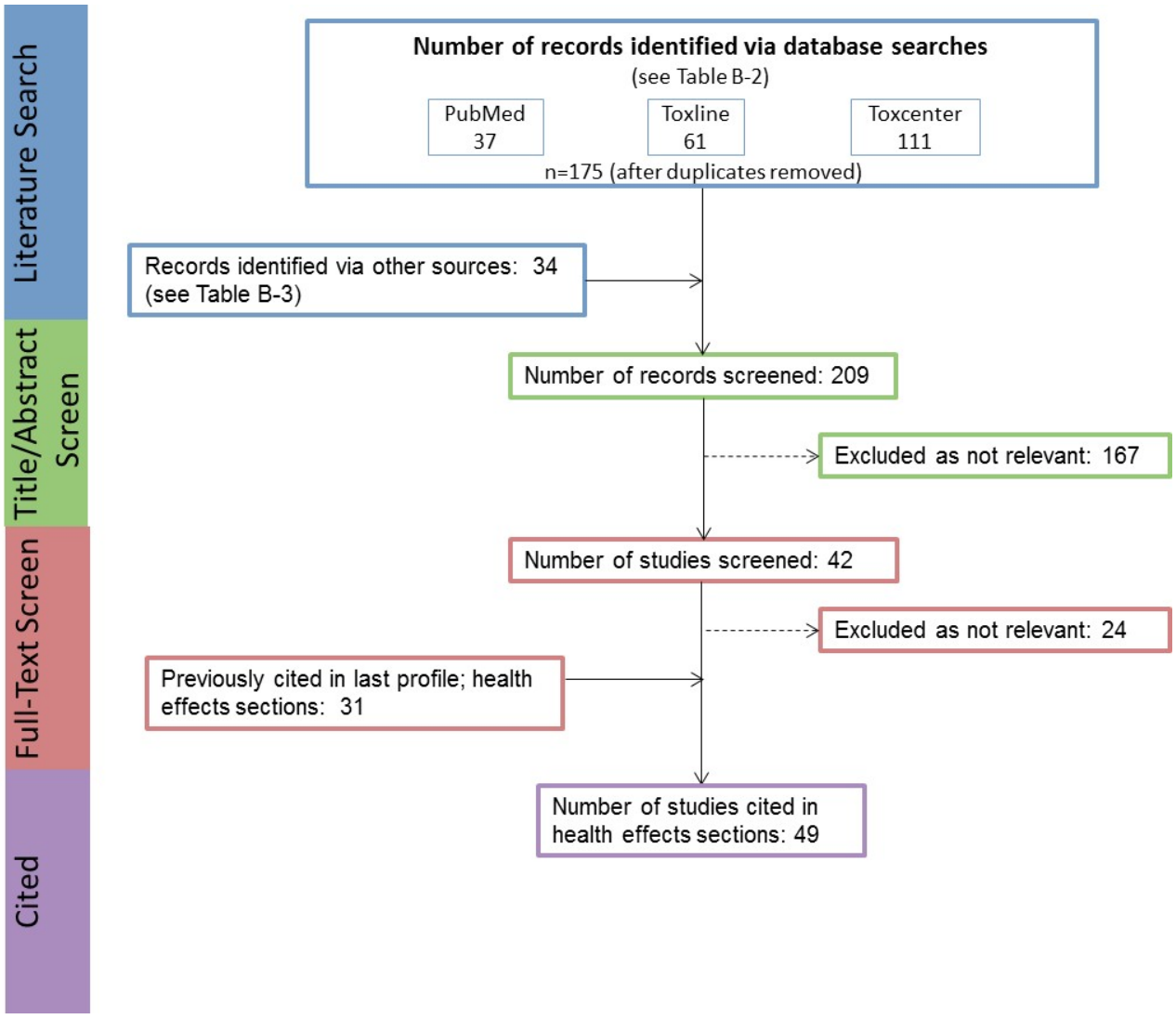
- Number of titles and abstracts screened: 209
- Number of studies considered relevant and moved to the next step: 42

Full Text Screen. The second step in the literature screening process was a full text review of individual studies considered relevant in the title and abstract screen step. Each study was reviewed to determine whether it was relevant for inclusion in the toxicological profile.

- Number of studies undergoing full text review: 42
- Number of studies cited in the health effects sections of the existing toxicological profile (December,1990): 31
- Total number of studies cited in the health effects sections of the updated profile: 49

A summary of the results of the literature search and screening is presented in Figure B-1.

Figure B-1. March 2017 Literature Search Results and Screen for 1,2-Diphenylhydrazine



APPENDIX C. FRAMEWORK FOR ATSDR'S SYSTEMATIC REVIEW OF HEALTH EFFECTS DATA FOR 1,2-DIPHENYLHYDRAZINE

To increase the transparency of ATSDR's process of identifying, evaluating, synthesizing, and interpreting the scientific evidence on the health effects associated with exposure to 1,2-diphenylhydrazine, ATSDR utilized a slight modification of NTP's Office of Health Assessment and Translation (OHAT) systematic review methodology (NTP 2013, 2015; Rooney et al. 2014). ATSDR's framework is an eight-step process for systematic review with the goal of identifying the potential health hazards of exposure to 1,2-diphenylhydrazine:

- Step 1. Problem Formulation
- Step 2. Literature Search and Screen for Health Effects Studies
- Step 3. Extract Data from Health Effects Studies
- Step 4. Identify Potential Health Effect Outcomes of Concern
- Step 5. Assess the Risk of Bias for Individual Studies
- Step 6. Rate the Confidence in the Body of Evidence for Each Relevant Outcome
- Step 7. Translate Confidence Rating into Level of Evidence of Health Effects
- Step 8. Integrate Evidence to Develop Hazard Identification Conclusions

C.1 PROBLEM FORMULATION

The objective of the toxicological profile and this systematic review was to identify the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to 1,2-diphenylhydrazine. The inclusion criteria used to identify relevant studies examining the health effects of 1,2-diphenylhydrazine are presented in Table C-1.

Data from human and laboratory animal studies were considered relevant for addressing this objective. Human studies were divided into two broad categories: observational epidemiology studies and controlled exposure studies. The observational epidemiology studies were further divided: cohort studies (retrospective and prospective studies), population studies (with individual data or aggregate data), and case-control studies.

C.2 LITERATURE SEARCH AND SCREEN FOR HEALTH EFFECTS STUDIES

A literature search and screen was conducted to identify studies examining the health effects of 1,2-diphenylhydrazine. The literature search framework for the toxicological profile is discussed in detail in Appendix B.

Table C-1. Inclusion Criteria for Identifying Health Effect Studies

Species
Human
Laboratory mammals
Route of exposure
Inhalation
Oral
Dermal (or ocular)
Parenteral (these studies will be considered supporting data)
Health outcome
Body weight effects
Respiratory effects
Cardiovascular effects
Gastrointestinal effects
Hematological effects
Musculoskeletal effects
Hepatic effects
Renal effects
Dermal effects
Ocular effects
Endocrine effects
Immunological effects
Neurological effects
Reproductive effects
Developmental effects
Other noncancer effects

C.2.1 Literature Search

As noted in Appendix B, the literature search to update the existing toxicological profile for 1,2-diphenylhydrazine (ATSDR 1990) was restricted to studies published between January 1988 and March 2017. See Appendix B for the databases searched and the search strategy.

A total of 174 unique records relevant to all sections of the toxicological profile were identified from the database queries (Table B-2) and 34 items were identified using additional literature search strategies (Table B-3).

C.2.2 Literature Screening

As described in Appendix B, a two-step process was used to screen the literature search to identify relevant studies examining the health effects of 1,2-diphenylhydrazine.

Title and Abstract Screen. In the Title and Abstract Screen step, 209 records were reviewed; 40 studies were considered to meet the health effects inclusion criteria in Table B-1 and were moved to the next step in the process.

Full Text Screen. In the second step in the literature screening process for the systematic review, a full text review of the 40 health effects studies identified in the update literature was performed. Additionally, 31 studies cited in the existing profile were included in the full study screen bringing the total number of studies for the qualitative review to 71. Of the 71 studies undergoing Full Text Screen, 62 studies did not meet the inclusion criteria in Table C-1; some of the excluded studies were used as background information on toxicokinetics or mechanisms of action or were relevant to other sections of the toxicological profile.

C.3 EXTRACT DATA FROM HEALTH EFFECTS STUDIES

Relevant data extracted from the individual studies selected for inclusion in the systematic review were collected in customized data forms. A summary of the type of data extracted from each study is presented in Table C-2. For references that included more than one experiment or species, data extraction records were created for each experiment or species.

Table C-2. Data Extracted from Individual Studies

Citation
Chemical form
Route of exposure (e.g., inhalation, oral, dermal)
Specific route (e.g., gavage in oil, drinking water)
Species
Strain
Exposure duration category (e.g., acute, intermediate, chronic)
Exposure duration
Frequency of exposure (e.g., 6 hours/day, 5 days/week)
Exposure length
Number of animals or subjects per sex per group
Dose/exposure levels
Parameters monitored
Description of the study design and method
Summary of calculations used to estimate doses (if applicable)
Summary of the study results
Reviewer's comments on the study
Outcome summary (one entry for each examined outcome)
No-observed-adverse-effect level (NOAEL) value
Lowest-observed-adverse-effect level (LOAEL) value
Effect observed at the LOAEL value

A summary of the extracted data for each study is presented in the Supplemental Document for 1,2-Diphenylhydrazine and overviews of the results of the oral and dermal exposure studies (no inhalation exposure studies were identified) are presented in Sections 2.2–2.18 of the profile and oral data are summarized in the Levels Significant Exposures table in Section 2.1 of the profile (Table 2-1).

C.4 IDENTIFY POTENTIAL HEALTH EFFECT OUTCOMES OF CONCERN

Overviews of the potential health effect outcomes for 1,2-diphenylhydrazine identified in animal studies (no human studies were identified) are presented in Table C-3. Animal studies examined a number of endpoints following oral exposure (dermal study only examined cancer endpoints). These studies examined most endpoints and reported respiratory, gastrointestinal, and hepatic effects. Studies examining these potential outcomes were carried through to Steps 4–8 of the systematic review.

APPENDIX C

Table C-3. Overview of the Health Outcomes for 1,2-Diphenylhydrazine Evaluated in Experimental Animal Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological[a]	Neurological[a]	Reproductive[a]	Developmental	Other Noncancer	Caner
Inhalation studies																	
Acute-duration																	
Intermediate-duration																	
Chronic-duration																	
Oral studies																	
Acute-duration	2 0	0 0		0 0			2 0										
Intermediate-duration	5 0			1 1			2 1										
Chronic-duration	2 2	2 2	2 0	2 0		2 0	2 2	2 0	2 0	2 0	2 0	2 0	2 0	2 0	2 0		2 2
Dermal studies																	
Acute-duration																	
Intermediate-duration																	
Chronic-duration																	1 1

Number of studies examining endpoint	0	1	2	3	4	5-9	≥10
Number of studies reporting outcome	0	1	2	3	4	5-9	≥10

[a]Number of studies examining endpoint includes study evaluating histopathology, but not evaluating function.

C.5 ASSESS THE RISK OF BIAS FOR INDIVIDUAL STUDIES

C.5.1 Risk of Bias Assessment

The risk of bias of individual studies was assessed using OHAT's Risk of Bias Tool (NTP 2015). The risk of bias questions for animal experimental studies are presented in Table C-4. Each risk of bias question was answered on a four-point scale:

- **Definitely low risk of bias (++)**
- **Probably low risk of bias (+)**
- **Probably high risk of bias (-)**
- **Definitely high risk of bias (– –)**

In general, "definitely low risk of bias" or "definitely high risk of bias" were used if the question could be answered with information explicitly stated in the study report. If the response to the question could be inferred, then "probably low risk of bias" or "probably high risk of bias" responses were typically used.

Table C-4. Risk of Bias Questionnaire for Experimental Animal Studies

Selection bias
Was administered dose or exposure level adequately randomized?
Was the allocation to study groups adequately concealed?
Performance bias
Were experimental conditions identical across study groups?
Were the research personnel blinded to the study group during the study?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

After the risk of bias questionnaires were completed for the health effects studies, the studies were assigned to one of three risk of bias tiers based on the responses to the key questions listed below and the responses to the remaining questions.

- Is there confidence in the exposure characterization? (only relevant for observational studies)
- Is there confidence in the outcome assessment?
- Does the study design or analysis account for important confounding and modifying variables? (only relevant for observational studies)

First Tier. Studies placed in the first tier received ratings of "definitely low" or "probably low" risk of bias on the key questions **AND** received a rating of "definitely low" or "probably low" risk of bias on the responses to at least 50% of the other applicable questions.

Second Tier. A study was placed in the second tier if it did not meet the criteria for the first or third tiers.

Third Tier. Studies placed in the third tier received ratings of "definitely high" or "probably high" risk of bias for the key questions **AND** received a rating of "definitely high" or "probably high" risk of bias on the response to at least 50% of the other applicable questions.

The results of the risk of bias assessment for the different types of 1,2-diphenylhydrazine health effects studies in animal experimental studies are presented in Table C-5.

APPENDIX C

Table C-5. Summary of Risk of Bias Assessment for 1,2-Diphenylhydrazine—Experimental Animal Studies

Reference	Risk of bias criteria and ratings								
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in exposure characterization?	**Confidence in outcome assessment?***	All measured outcomes reported?	Risk of bias tier
Outcome: Respiratory Effects									
Oral chronic exposure									
NCI 1978 (rat)	+	+	+	+	++	+	+	+	First
NCI 1978 (mouse)	+	+	+	+	++	+	+	+	First
Outcome: Gastrointestinal Effects									
Oral intermediate exposure									
NCI 1978 (mouse, 4-week)	+	+	+	+	+	-	+	-	First
Oral chronic exposure									
NCI 1978 (rat)	+	+	+	+	++	+	+	+	First
NCI 1978 (mouse)	+	+	+	+	++	+	+	+	First
Outcome: Hepatic Effects									
Oral acute exposure									
Dodd et al. 2012 (5-day)	++	+	+	+	++	+	+	++	First
Dodd et al. 2012 (2-week)	++	+	+	+	++	+	+	++	First
Oral intermediate exposure									
Dodd et al. 2012 (4-week)	++	+	+	+	++	+	+	++	First
Dodd et al. 2012 (13-week)	++	+	+	+	++	+	+	++	First

APPENDIX C

Table C-5. Summary of Risk of Bias Assessment for 1,2-Diphenylhydrazine—Experimental Animal Studies

Reference	Risk of bias criteria and ratings								
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in exposure characterization?	**Confidence in outcome assessment?***	All measured outcomes reported?	Risk of bias tier
Oral chronic exposure									
NCI 1978 (rat)	+	+	+	+	++	+	**+**	+	First
NCI 1978 (mouse)	+	+	+	+	++	+	**+**	+	First

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; na = not applicable
*Key question used to assign risk of bias tier

C.6 RATE THE CONFIDENCE IN THE BODY OF EVIDENCE FOR EACH RELEVANT OUTCOME

Confidences in the bodies of human and animal evidence were evaluated independently for each potential outcome. ATSDR did not evaluate the confidence in the body of evidence for carcinogenicity; rather, the Agency defaulted to the cancer weight-of-evidence assessment of other agencies including DHHS, EPA, and IARC. The confidence in the body of evidence for an association or no association between exposure to 1,2-diphenylhydrazine and a particular outcome was based on the strengths and weaknesses of individual studies. Four descriptors were used to describe the confidence in the body of evidence for effects or when no effect was found:

- **High confidence:** the true effect is highly likely to be reflected in the apparent relationship
- **Moderate confidence:** the true effect may be reflected in the apparent relationship
- **Low confidence:** the true effect may be different from the apparent relationship
- **Very low confidence:** the true effect is highly likely to be different from the apparent relationship

Confidence in the body of evidence for a particular outcome was rated for each type of study: case-control, case series, cohort, population, human-controlled exposure, and experimental animal. In the absence of data to the contrary, data for a particular outcome were collapsed across animal species, routes of exposure, and exposure durations. If species (or strain), route, or exposure duration differences were noted, then the data were treated as separate outcomes.

C.6.1 Initial Confidence Rating

In ATSDR's modification to the OHAT approach, the body of evidence for an association (or no association) between exposure to 1,2-diphenylhydrazine and a particular outcome was given an initial confidence rating based on the key features of the individual studies examining that outcome. The presence of these key features of study design was determined for individual studies using four "yes or no" questions, which were customized for epidemiology, human controlled exposure, or experimental animal study designs. Separate questionnaires were completed for each outcome assessed in a study. The key features for experimental animal studies are presented in Table C-6. The initial confidence in the study was determined based on the number of key features present in the study design:

- **High Initial Confidence:** Studies in which the responses to the four questions were "yes".

- **Moderate Initial Confidence:** Studies in which the responses to only three of the questions were "yes".

- **Low Initial Confidence:** Studies in which the responses to only two of the questions were "yes".

- **Very Low Initial Confidence:** Studies in which the response to one or none of the questions was "yes".

Table C-6. Key Features of Study Design for Experimental Animal Studies

A concurrent control group was used
A sufficient number of animals per group were tested
Appropriate parameters were used to assess a potential adverse effect
Appropriate statistical analyses were performed and reported or the data were reported in such a way to allow independent statistical analysis

The presence or absence of the key features and the initial confidence levels for studies examining body weight, respiratory, gastrointestinal, and hepatic effects observed in the animal experimental studies are presented in Table C-7.

Table C-7. Presence of Key Features of Study Design for 1,2-Diphenylhydrazine—Experimental Animal Studies

	Key feature				
Reference	Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	Initial study confidence
Outcome: Respiratory Effects					
Oral chronic exposure					
NCI 1978 (rat)	Yes	Yes	No	Yes	Moderate
NCI 1978 (mouse)	Yes	Yes	No	Yes	Moderate
Outcome: Gastrointestinal Effects					
Oral intermediate exposure					
NCI 1978 (mouse, 4-week)	Yes	No	No	No	Very Low
Oral chronic exposure					
NCI 1978 (rat)	Yes	Yes	No	Yes	Moderate
NCI 1978 (mouse)	Yes	Yes	No	Yes	Moderate
Outcome: Hepatic Effects					
Oral acute exposure					
Dodd et al. 2012 (5-day)	Yes	Yes	Yes	Yes	High
Dodd et al. 2012 (2-week)	Yes	Yes	Yes	Yes	High
Oral intermediate exposure					
Dodd et al. 2012 (4-week)	Yes	Yes	Yes	Yes	High
Dodd et al. 2012 (13-week)	Yes	Yes	Yes	Yes	High
Oral chronic exposure					
NCI 1978 (rat)	Yes	Yes	No	Yes	Moderate
NCI 1978 (mouse)	Yes	Yes	No	Yes	Moderate

A summary of the initial confidence ratings for each outcome is presented in Table C-8. If individual studies for a particular outcome and study type had different study quality ratings, then the highest confidence rating for the group of studies was used to determine the initial confidence rating for the body of evidence; any exceptions were noted in Table C-8.

Table C-8. Initial Confidence Rating for 1,2-Diphenylhydrazine Health Effects Studies

	Initial study confidence	Initial confidence rating
Outcome: Respiratory Effects		
Oral chronic exposure		
Animal studies		
NCI 1978 (rat)	Moderate	Moderate
NCI 1978 (mouse)	Moderate	
Outcome: Gastrointestinal Effects		
Oral intermediate exposure		
Animal studies		
NCI 1978 (mouse, 4-week)	Very Low	Very Low
Oral chronic exposure		
Animal studies		
NCI 1978 (rat)	Moderate	Moderate
NCI 1978 (mouse)	Moderate	
Outcome: Hepatic Effects		
Oral acute exposure		
Animal studies		
Dodd et al. 2012 (5-day)	High	High
Dodd et al. 2012 (2-week)	High	
Oral intermediate exposure		
Animal studies		
Dodd et al. 2012 (4-week)	High	High
Dodd et al. 2012 (13-week)	High	
Oral chronic exposure		
Animal studies		
NCI 1978 (rat)	Moderate	Moderate
NCI 1978 (mouse)	Moderate	

C.6.2 Adjustment of the Confidence Rating

The initial confidence rating was then downgraded or upgraded depending on whether there were substantial issues that would decrease or increase confidence in the body of evidence. The nine properties of the body of evidence that were considered are listed below. The summaries of the assessment of the confidence in the body of evidence for body weight, respiratory, gastrointestinal, and hepatic effects are presented in Table C-9. An overview of the confidence in the body of evidence for all health effects associated with 1,2-diphenylhydrazine exposure is presented in Table C-10.

Table C-9. Adjustments to the Initial Confidence in the Body of Evidence

	Initial confidence	Adjustments to the initial confidence rating	Final confidence
Outcome: Respiratory Effects			
Animal studies	Moderate	-1 inconsistency, -1 imprecision	Very Low
Outcome: Gastrointestinal Effects			
Animal studies	Moderate	-1 inconsistency	Low
Outcome: Hepatic Effects			
Animal studies	High	No adjustments	High

Table C-10. Confidence in the Body of Evidence for 1,2-Diphenylhydrazine

Outcome	Confidence in body of evidence	
	Human studies	Animal studies
Respiratory effects	No data	Very Low
Gastrointestinal effects	No data	Low
Hepatic effects	No data	High

Five properties of the body of evidence were considered to determine whether the confidence rating should be downgraded:

- **Risk of bias.** Evaluation of whether there is substantial risk of bias across most of the studies examining the outcome. This evaluation used the risk of bias tier groupings for individual studies examining a particular outcome (Table C-5). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for risk of bias:
    - No downgrade if most studies are in the risk of bias first tier
    - Downgrade one confidence level if most studies are in the risk of bias second tier
    - Downgrade two confidence levels if most studies are in the risk of bias third tier

- **Unexplained inconsistency.** Evaluation of whether there is inconsistency or large variability in the magnitude or direction of estimates of effect across studies that cannot be explained. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for unexplained inconsistency:
    - No downgrade if there is little inconsistency across studies or if only one study evaluated the outcome
    - Downgrade one confidence level if there is variability across studies in the magnitude or direction of the effect
    - Downgrade two confidence levels if there is substantial variability across studies in the magnitude or direct of the effect

- **Indirectness.** Evaluation of four factors that can affect the applicability, generalizability, and relevance of the studies:
    - Relevance of the animal model to human health—unless otherwise indicated, studies in rats, mice, and other mammalian species are considered relevant to humans

- Directness of the endpoints to the primary health outcome—examples of secondary outcomes or nonspecific outcomes include organ weight in the absence of histopathology or clinical chemistry findings in the absence of target tissue effects
- Nature of the exposure in human studies and route of administration in animal studies—inhalation, oral, and dermal exposure routes are considered relevant unless there are compelling data to the contrary
- Duration of treatment in animal studies and length of time between exposure and outcome assessment in animal and prospective human studies—this should be considered on an outcome-specific basis

Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for indirectness:

- No downgrade if none of the factors are considered indirect
- Downgrade one confidence level if one of the factors is considered indirect
- Downgrade two confidence levels if two or more of the factors are considered indirect

- **Imprecision.** Evaluation of the narrowness of the effect size estimates and whether the studies have adequate statistical power. Data are considered imprecise when the ratio of the upper to lower 95% CIs for most studies is ≥10 for tests of ratio measures (e.g., odds ratios) and ≥100 for absolute measures (e.g., percent control response). Adequate statistical power is determined if the study can detect a potentially biologically meaningful difference between groups (20% change from control response for categorical data or risk ratio of 1.5 for continuous data). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for imprecision:
  - No downgrade if there are no serious imprecisions
  - Downgrade one confidence level for serious imprecisions
  - Downgrade two confidence levels for very serious imprecisions

- **Publication bias.** Evaluation of the concern that studies with statistically significant results are more likely to be published than studies without statistically significant results.
  - Downgrade one level of confidence for cases where there is serious concern with publication bias

Four properties of the body of evidence were considered to determine whether the confidence rating should be upgraded:

- **Large magnitude of effect.** Evaluation of whether the magnitude of effect is sufficiently large so that it is unlikely to have occurred as a result of bias from potential confounding factors.
  - Upgrade one confidence level if there is evidence of a large magnitude of effect in a few studies, provided that the studies have an overall low risk of bias and there is no serious unexplained inconsistency among the studies of similar dose or exposure levels; confidence can also be upgraded if there is one study examining the outcome, provided that the study has an overall low risk of bias

- **Dose response.** Evaluation of the dose-response relationships measured within a study and across studies. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
  - Upgrade one confidence level for evidence of a monotonic dose-response gradient
  - Upgrade one confidence level for evidence of a non-monotonic dose-response gradient where there is prior knowledge that supports a non-monotonic dose-response and a non-monotonic dose-response gradient is observed across studies

- **Plausible confounding or other residual biases.** This factor primarily applies to human studies and is an evaluation of unmeasured determinants of an outcome such as residual bias towards the null (e.g., "healthy worker" effect) or residual bias suggesting a spurious effect (e.g., recall bias). Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
    - Upgrade one confidence level for evidence that residual confounding or bias would underestimate an apparent association or treatment effect (i.e., bias toward the null) or suggest a spurious effect when results suggest no effect

- **Consistency in the body of evidence.** Evaluation of consistency across animal models and species, consistency across independent studies of different human populations and exposure scenarios, and consistency across human study types. Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
    - Upgrade one confidence level if there is a high degree of consistency in the database

C.7 TRANSLATE CONFIDENCE RATING INTO LEVEL OF EVIDENCE OF HEALTH EFFECTS

In the seventh step of the systematic review of the health effects data for 1,2-diphenylhydrazine, the confidence in the body of evidence for specific outcomes was translated to a level of evidence rating. The level of evidence rating reflected the confidence in the body of evidence and the direction of the effect (i.e., toxicity or no toxicity); route-specific differences were noted. The level of evidence for health effects was rated on a five-point scale:

- **High level of evidence:** High confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Moderate level of evidence:** Moderate confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Low level of evidence:** Low confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Evidence of no health effect:** High confidence in the body of evidence that exposure to the substance is not associated with the health outcome
- **Inadequate evidence:** Low or moderate confidence in the body of evidence that exposure to the substance is not associated with the health outcome OR very low confidence in the body of evidence for an association between exposure to the substance and the health outcome

A summary of the level of evidence of health effects for 1,2-diphenylhydrazine is presented in Table C-11.

Table C-11. Level of Evidence of Health Effects for 1,2-Diphenylhydrazine

Outcome	Confidence in body of evidence	Direction of health effect	Level of evidence for health effect
Human studies			
Respiratory effects	No data		No data
Gastrointestinal effects	No data		No data
Hepatic effects	No data		No data
Animal studies			
Respiratory effects	Very Low	Health effect	Inadequate
Gastrointestinal effects	Low	Health effect	Low
Hepatic effects	High	Health effect	High

C.8 INTEGRATE EVIDENCE TO DEVELOP HAZARD IDENTIFICATION CONCLUSIONS

The final step involved the integration of the evidence streams for the human studies and animal studies to allow for a determination of hazard identification conclusions. For health effects, there were four hazard identification conclusion categories:

- **Known** to be a hazard to humans
- **Presumed** to be a hazard to humans
- **Suspected** to be a hazard to humans
- **Not classifiable** as to the hazard to humans

The initial hazard identification was based on the highest level of evidence in the human studies and the level of evidence in the animal studies; if there were no data for one evidence stream (human or animal), then the hazard identification was based on the one data stream (equivalent to treating the missing evidence stream as having low level of evidence). The hazard identification scheme is presented in Figure C-1 and described below:

- **Known:** A health effect in this category would have:
  - High level of evidence for health effects in human studies **AND** a high, moderate, or low level of evidence in animal studies.
- **Presumed:** A health effect in this category would have:
  - Moderate level of evidence in human studies **AND** high or moderate level of evidence in animal studies **OR**
  - Low level of evidence in human studies **AND** high level of evidence in animal studies
- **Suspected:** A health effect in this category would have:
  - Moderate level of evidence in human studies **AND** low level of evidence in animal studies **OR**
  - Low level of evidence in human studies **AND** moderate level of evidence in animal studies
- **Not classifiable:** A health effect in this category would have:
  - Low level of evidence in human studies **AND** low level of evidence in animal studies

Other relevant data such as mechanistic or mode-of-action data were considered to raise or lower the level of the hazard identification conclusion by providing information that supported or opposed biological plausibility.

Two hazard identification conclusion categories were used when the data indicated that there may be no health effect in humans:

- **Not identified** to be a hazard in humans
- **Inadequate** to determine hazard to humans

If the human level of evidence conclusion of no health effect was supported by the animal evidence of no health effect, then the hazard identification conclusion category of "not identified" was used. If the human or animal level of evidence was considered inadequate, then a hazard identification conclusion category of "inadequate" was used. As with the hazard identification for health effects, the impact of other relevant data was also considered for no health effect data.

The hazard identification conclusions for 1,2-diphenylhydrazine are listed below and summarized in Table C-12.

Presumed Health Effects

- Hepatic effects
    - No human data are available on the potential hepatic effects of 1,2-diphenylhydrazine.
    - High level of evidence from intermediate (Dodd et al. 2012) and chronic (NCI 1978) oral studies in rats and chronic oral studies in mice (NCI 1978). No liver effects were observed at exposures of less than 13 weeks in rats (Dodd et al. 2012; NCI 1978) or mice (NCI 1978).

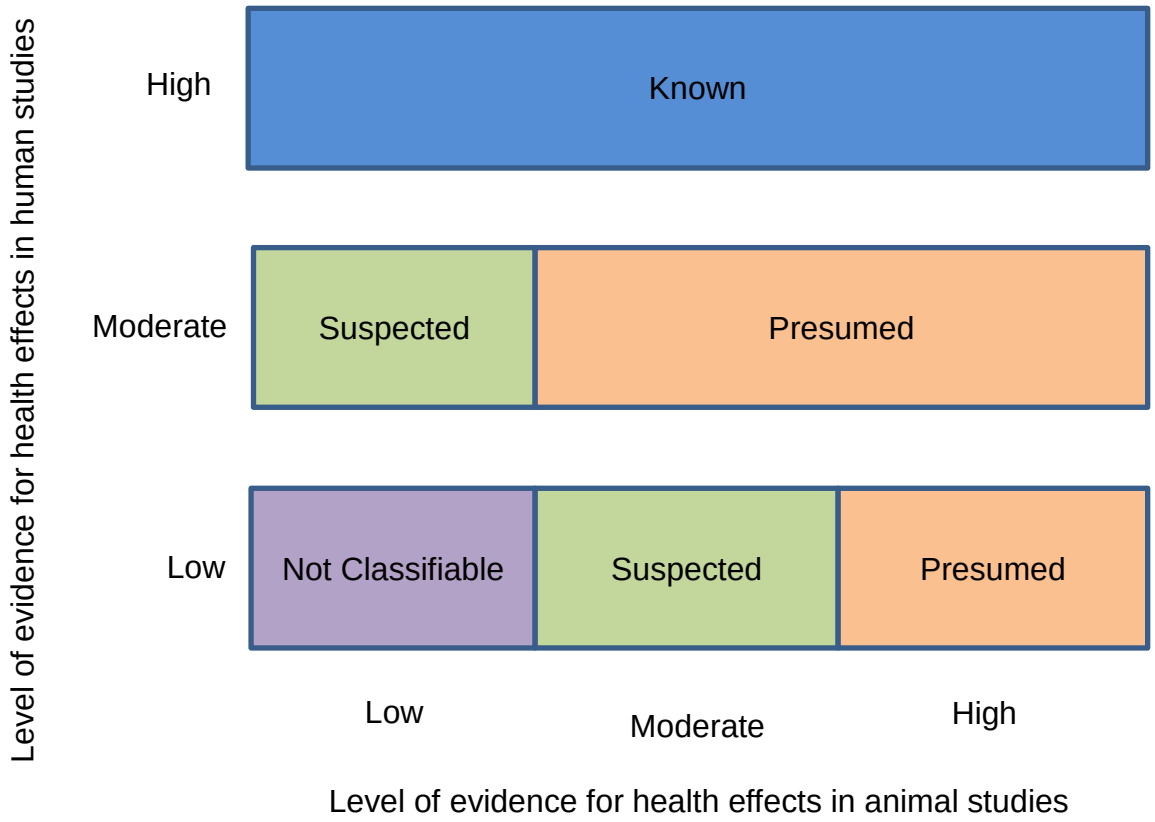
Not Classifiable Effects

- Respiratory effects
    - No human data are available on the potential respiratory effects of 1,2-diphenyl-hydrazine.
    - There is inadequate evidence in animal studies that chronic oral exposure will result in respiratory effects. Interstitial lung inflammation was observed in male rats (NCI 1978); in female rats the incidence was not dose-related. Respiratory effects were not observed in mice following chronic oral exposure (NCI 1978).
- Gastrointestinal effects
    - No human data are available on the potential gastrointestinal effects of 1,2-diphenyl-hydrazine.
    - Low evidence in animals from an intermediate oral study which reported intestinal hemorrhage in mice (NCI 1978) and from a chronic oral study in rats that reported hyperkeratosis and/or acanthosis in rats (NCI 1978); no gastrointestinal effects were observed in mice following chronic oral exposure.

Table C-12. Hazard Identification Conclusions for 1,2-Diphenylhydrazine

Outcome	Hazard identification
Respiratory effects	Not classifiable
Gastrointestinal effects	Not classifiable
Hepatic effects	Presumed

Figure C-1. Hazard Identification Scheme



APPENDIX D. USER'S GUIDE

Chapter 1. Relevance to Public Health

This chapter provides an overview of U.S. exposures, a summary of health effects based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information, and an overview of the minimal risk levels. This is designed to present interpretive, weight-of-evidence discussions for human health endpoints by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

Minimal Risk Levels (MRLs)

Where sufficient toxicologic information is available, ATSDR derives MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a hazardous substance emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Section 1.2, Summary of Health Effects, contains basic information known about the substance. Other sections, such as Section 3.2 Children and Other Populations that are Unusually Susceptible and Section 3.4 Interactions with Other Substances, provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a

substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables that are provided in Chapter 2. Detailed discussions of the MRLs are presented in Appendix A.

Chapter 2. Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species and MRLs to humans for noncancer endpoints. The LSE tables and figures can be used for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE tables and figures follow. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

TABLE LEGEND

See Sample LSE Table (page D-5)

(1) Route of exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically, when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure (i.e., inhalation, oral, and dermal). LSE figures are limited to the inhalation and oral routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures. Profiles with more than one chemical may have more LSE tables and figures.

(2) Exposure period. Three exposure periods—acute (<15 days), intermediate (15–364 days), and chronic (≥365 days)—are presented within each relevant route of exposure. In this example, two oral studies of chronic-duration exposure are reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Figure key. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 51 identified NOAELs and less serious LOAELs (also see the three "51R" data points in sample LSE Figure 2-X).

(4) Species (strain) No./group. The test species (and strain), whether animal or human, are identified in this column. The column also contains information on the number of subjects and sex per group. Chapter 1, Relevance to Public Health, covers the relevance of animal data to human toxicity and Section 3.1, Toxicokinetics, contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(5) Exposure parameters/doses. The duration of the study and exposure regimens are provided in these columns. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 51), rats were orally exposed to “Chemical X” via feed for 2 years. For a

more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Aida et al. 1992).

(6) Parameters monitored. This column lists the parameters used to assess health effects. Parameters monitored could include serum (blood) chemistry (BC), behavioral (BH), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), enzyme activity (EA), food intake (FI), fetal toxicity (FX), gross necropsy (GN), hematology (HE), histopathology (HP), lethality (LE), maternal toxicity (MX), organ function (OF), ophthalmology (OP), organ weight (OW), teratogenicity (TG), urinalysis (UR), and water intake (WI).

(7) Endpoint. This column lists the endpoint examined. The major categories of health endpoints included in LSE tables and figures are death, body weight, respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal, ocular, endocrine, immunological, neurological, reproductive, developmental, other noncancer, and cancer. "Other noncancer" refers to any effect (e.g., alterations in blood glucose levels) not covered in these systems. In the example of key number 51, three endpoints (body weight, hematological, and hepatic) were investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no adverse effects were seen in the organ system studied. The body weight effect reported in key number 51 is a NOAEL at 25.5 mg/kg/day. NOAELs are not reported for cancer and death; with the exception of these two endpoints, this field is left blank if no NOAEL was identified in the study.

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused an adverse health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. Key number 51 reports a less serious LOAEL of 6.1 mg/kg/day for the hepatic system, which was used to derive a chronic exposure, oral MRL of 0.008 mg/kg/day (see footnote "c"). MRLs are not derived from serious LOAELs. A cancer effect level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases. If no LOAEL/CEL values were identified in the study, this field is left blank.

(10) Reference. The complete reference citation is provided in Chapter 8 of the profile.

(11) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. For example, footnote "c" indicates that the LOAEL of 6.1 mg/kg/day in key number 51 was used to derive an oral MRL of 0.008 mg/kg/day.

FIGURE LEGEND

See Sample LSE Figure (page D-6)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the chronic exposure period are illustrated.

(14) Endpoint. These are the categories of health effects for which reliable quantitative data exist. The same health effect endpoints appear in the LSE table.

(15) Levels of exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) LOAEL. In this example, the half-shaded circle that is designated 51R identifies a LOAEL critical endpoint in the rat upon which a chronic oral exposure MRL is based. The key number 51 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 6.1 mg/kg/day (see entry 51 in the sample LSE table) to the MRL of 0.008 mg/kg/day (see footnote "c" in the sample LSE table).

(17) CEL. Key number 59R is one of studies for which CELs were derived. The diamond symbol refers to a CEL for the test species (rat). The number 59 corresponds to the entry in the LSE table.

(18) Key to LSE figure. The key provides the abbreviations and symbols used in the figure.

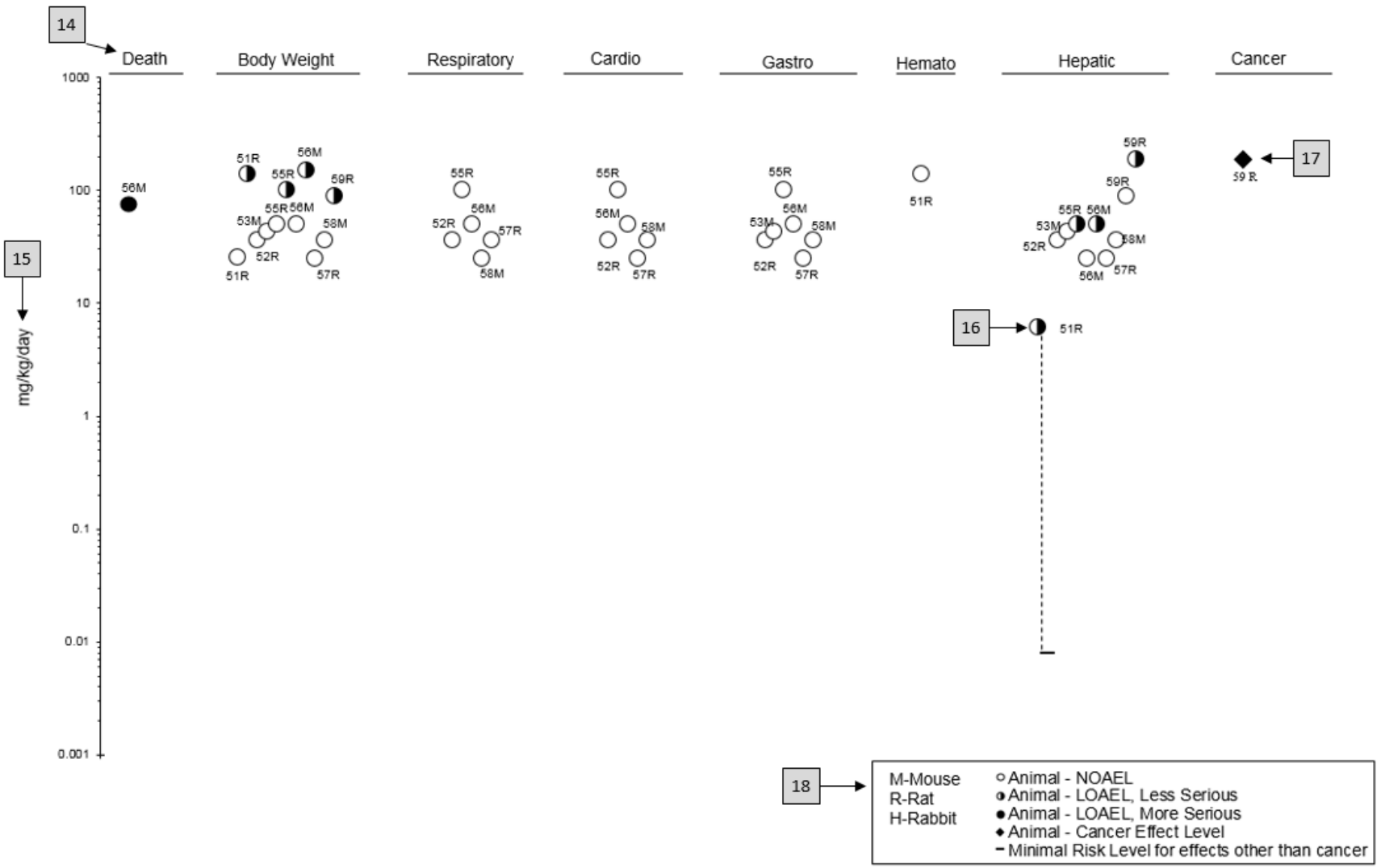
APPENDIX D

Table 2-X. Levels of Significant Exposure to [Chemical X] – Oral (1)

Figure key[a] (3)	Species (strain) No./group (4)	Exposure parameters (5)	Doses (mg/kg/day) (5)	Parameters monitored (6)	Endpoint (7)	NOAEL (mg/kg/day) (8)	Less serious LOAEL (mg/kg/day) (9)	Serious LOAEL (mg/kg/day) (9)	Effect
CHRONIC EXPOSURE (2)									
51	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0, 6.1, 25.5, 138.0 F: 0, 8.0, 31.7, 168.4	CS, WI, BW, OW, HE, BC, HP	Bd wt	25.5	138.0		Decreased body weight gain in males (23–25%) and females (31–39%)
					Hemato	138.0			
					Hepatic		6.1[c]		Increases in absolute and relative weights at ≥6.1/8.0 mg/kg/day after 12 months of exposure; fatty generation at ≥6.1 mg/kg/day in males and at ≥31.7 mg/kg/day in females, and granulomas in females at 31.7 and 168.4 mg/kg/day after 12, 18, or 24 months of exposure and in males at ≥6.1 mg/kg/day only after 24 months of exposure
Aida et al. 1992 (10)									
52	Rat (F344) 78 M	104 weeks (W)	0, 3.9, 20.6, 36.3	CS, BW, FI, BC, OW, HP	Hepatic	36.3			
					Renal	20.6	36.3		Increased incidence of renal tubular cell hyperplasia
					Endocr	36.3			
George et al. 2002									
59	Rat (Wistar) 58M, 58F	Lifetime (W)	M: 0, 90 F: 0, 190	BW, HP	Cancer		190 F		Increased incidence of hepatic neoplastic nodules in females only; no additional description of the tumors was provided
Tumasonis et al. 1985									

[a]The number corresponds to entries in Figure 2-x.
(11) [b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.1 mg/kg/day based on the $BMDL_{05}$ of 10 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).
[c]Used to derive a chronic-duration oral MRL of 0.008 mg/kg/day based on the $BMDL_{10}$ of 0.78 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Figure 2-X. Levels of Significant Exposure to [Chemical X] - Oral



APPENDIX E. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances may find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Relevance to Public Health: The Relevance to Public Health Section provides an overview of exposure and health effects and evaluates, interprets, and assesses the significance of toxicity data to human health. A table listing minimal risk levels (MRLs) is also included in this chapter.

Chapter 2: Health Effects: Specific health effects identified in both human and animal studies are reported by type of health effect (e.g., death, hepatic, renal, immune, reproductive), route of exposure (e.g., inhalation, oral, dermal), and length of exposure (e.g., acute, intermediate, and chronic).
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting.

Pediatrics:
Section 3.2 Children and Other Populations that are Unusually Susceptible
Section 3.3 Biomarkers of Exposure and Effect

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)
Internet: http://www.atsdr.cdc.gov

The following additional materials are available online:

Case Studies in Environmental Medicine are self-instructional publications designed to increase primary health care providers' knowledge of a hazardous substance in the environment and to aid in the evaluation of potentially exposed patients (see https://www.atsdr.cdc.gov/csem/csem.html).

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident (see https://www.atsdr.cdc.gov/MHMI/index.asp). Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs™) provide answers to frequently asked questions about toxic substances (see https://www.atsdr.cdc.gov/toxfaqs/Index.asp).

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015 • Web Page: https://www.cdc.gov/nceh/.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: https://www.cdc.gov/niosh/.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212 • Web Page: https://www.niehs.nih.gov/.

Clinical Resources (Publicly Available Information)

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266 • Web Page: http://www.acoem.org/.

The American College of Medical Toxicology (ACMT) is a nonprofit association of physicians with recognized expertise in medical toxicology. Contact: ACMT, 10645 North Tatum Boulevard, Suite 200-111, Phoenix AZ 85028 • Phone: 844-226-8333 • FAX: 844-226-8333 • Web Page: http://www.acmt.net.

The Pediatric Environmental Health Specialty Units (PEHSUs) is an interconnected system of specialists who respond to questions from public health professionals, clinicians, policy makers, and the public about the impact of environmental factors on the health of children and reproductive-aged adults. Contact information for regional centers can be found at http://pehsu.net/findhelp.html.

The American Association of Poison Control Centers (AAPCC) provide support on the prevention and treatment of poison exposures. Contact: AAPCC, 515 King Street, Suite 510, Alexandria VA 22314 • Phone: 701-894-1858 • Poison Help Line: 1-800-222-1222 • Web Page: http://www.aapcc.org/.

APPENDIX F. GLOSSARY

Absorption—The process by which a substance crosses biological membranes and enters systemic circulation. Absorption can also refer to the taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of ≤14 days, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD) or Benchmark Concentration (BMC)—is the dose/concentration corresponding to a specific response level estimate using a statistical dose-response model applied to either experimental toxicology or epidemiology data. For example, a BMD_{10} would be the dose corresponding to a 10% benchmark response (BMR). The BMD is determined by modeling the dose-response curve in the region of the dose-response relationship where biologically observable data are feasible. The BMDL or BMCL is the 95% lower confidence limit on the BMD or BMC.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Indicators signaling events in biologic systems or samples, typically classified as markers of exposure, effect, and susceptibility.

Cancer Effect Level (CEL)—The lowest dose of a chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-control study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without the outcome.

Case Report—A report that describes a single individual with a particular disease or exposure. These reports may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Reports that describe the experience of a small number of individuals with the same disease or exposure. These reports may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration that must not be exceeded.

Chronic Exposure—Exposure to a chemical for ≥365 days, as specified in the Toxicological Profiles.

Clastogen—A substance that causes breaks in chromosomes resulting in addition, deletion, or rearrangement of parts of the chromosome.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome, and who are disease-free at start of follow-up. Often, at least one exposed group is compared to one unexposed group, while in other cohorts, exposure is a continuous variable and analyses are directed towards analyzing an exposure-response coefficient.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at a specific point in time.

Data Needs—Substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the response or amount of the response.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the effect occurs. Effects include malformations and variations, altered growth, and *in utero* death.

Epidemiology—The investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Excretion—The process by which metabolic waste products are removed from the body.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one-half of a quantity of a chemical from the body or environmental media.

Health Advisory—An estimate of acceptable drinking water levels for a chemical substance derived by EPA and based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH)—A condition that poses a threat of life or health, or conditions that pose an immediate threat of severe exposure to contaminants that are likely to have adverse cumulative or delayed effects on health.

Immunotoxicity—Adverse effect on the functioning of the immune system that may result from exposure to chemical substances.

Incidence—The ratio of new cases of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Metabolism—Process in which chemical substances are biotransformed in the body that could result in less toxic and/or readily excreted compounds or produce a biologically active intermediate.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—The state of being diseased; the morbidity rate is the incidence or prevalence of a disease in a specific population.

Mortality—Death; the mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations, which are changes in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a hazardous substance.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Although effects may be produced at this dose, they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio that is greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) regulatory limit on the amount or concentration of a substance not to be exceeded in workplace air averaged over any 8-hour work shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests (insects or other organisms harmful to cultivated plants or animals).

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic endpoints. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—A type of physiologically based dose-response model that is comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information, including tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as blood:air partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which a group is followed over time and the pertinent observations are made on events occurring after the start of the study.

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation RfC is expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily oral exposure of the human population to a potential hazard that is likely to be without risk of deleterious noncancer health effects during a lifetime. The oral RfD is expressed in units of mg/kg/day.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). RQs are (1) ≥1 pound or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a hazardous substance. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a hazardous substance.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, existing health condition, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio/Relative Risk—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio that is greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Short-Term Exposure Limit (STEL)—A STEL is a 15-minute TWA exposure that should not be exceeded at any time during a workday.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect. The TLV may be expressed as a Time-Weighted Average (TLV-TWA), as a Short-Term Exposure Limit (TLV-STEL), or as a ceiling limit (TLV-C).

Time-Weighted Average (TWA)—An average exposure within a given time period.

Toxicokinetic—The absorption, distribution, metabolism, and elimination of toxic compounds in the living organism.

Toxics Release Inventory (TRI)—The TRI is an EPA program that tracks toxic chemical releases and pollution prevention activities reported by industrial and federal facilities.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL), Reference Dose (RfD), or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis (3 being the approximate logarithmic average of 10 and 1).

Xenobiotic—Any substance that is foreign to the biological system.

APPENDIX G. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

AAPCC	American Association of Poison Control Centers
ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ACMT	American College of Medical Toxicology
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AEGL	Acute Exposure Guideline Level
AIC	Akaike's information criterion
AIHA	American Industrial Hygiene Association
ALT	alanine aminotransferase
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BCF	bioconcentration factor
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
C	centigrade
CAA	Clean Air Act
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
cm	centimeter
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DWEL	drinking water exposure level
EAFUS	Everything Added to Food in the United States
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
ERPG	emergency response planning guidelines
F	Fahrenheit
F1	first-filial generation
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act

FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GGT	γ-glutamyl transferase
GRAS	generally recognized as safe
HEC	human equivalent concentration
HED	human equivalent dose
HHS	Department of Health and Human Services
HPLC	high-performance liquid chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Level of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
MRL	Minimal Risk Level
MS	mass spectrometry
MSHA	Mine Safety and Health Administration
Mt	metric ton
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NCEH	National Center for Environmental Health
ND	not detected
ng	nanogram
NHANES	National Health and Nutrition Examination Survey

NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NTP	National Toxicology Program
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PAC	Protective Action Criteria
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
PEHSU	Pediatric Environmental Health Specialty Unit
PND	postnatal day
POD	point of departure
ppb	parts per billion
ppbv	parts per billion by volume
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure level/limit
REL-C	recommended exposure level-ceiling value
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SD	standard deviation
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase (same as aspartate aminotransferase or AST)
SGPT	serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT)
SIC	standard industrial classification
SMR	standardized mortality ratio
sRBC	sheep red blood cell
STEL	short term exposure limit
TLV	threshold limit value
TLV-C	threshold limit value-ceiling value
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey

USNRC	U.S. Nuclear Regulatory Commission
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result