Toxicological Profile for Nitrophenols

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

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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.

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 due to associated acute, intermediate, and chronic exposures;

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

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 was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

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*Legislative Background

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.

VERSION HISTORY

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April 2022	Draft for public comment toxicological profile released
July 1992	Final toxicological profile released

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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.

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CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

Nitrophenols exist in three isomeric forms: 2-nitrophenol (also called ortho- or o-), 3-nitrophenol (also called meta- or m-), and 4-nitrophenol (also called para- or p-). Nitrophenol isomers (also referred to as mononitrophenols) are primarily used as intermediates to produce dyes, pigments, pharmaceuticals, rubber chemicals, photographic chemicals, and pesticides, including fungicides and lumber preservatives. 2-Nitrophenol is used to manufacture pesticides, fungicides, and other agricultural chemicals. 3-Nitrophenol is used as an indicator and to synthesize some dyestuffs and drugs. 4-Nitrophenol is used to darken leather and to manufacture drugs, fungicides, methyl and ethyl parathion insecticides, and dyes. 2-Nitrophenol is a light yellow, aromatic solid. 3- and 4-Nitrophenol are colorless to pale yellow solids. Nitrophenols are expected to be highly soluble in water. They also have low vapor pressures, and the potential for long range atmospheric transport is therefore low. The atmospheric half-lives of these compounds are 3–18 days.

The general population may be exposed to nitrophenols through the inhalation of ambient air, although there are no recent U.S. air monitoring data for nitrophenols to quantify exposure. Nitrophenol isomers (2-, 3-, and 4-nitrophenol) have been found previously in the air, water, and soil. The primary anthropogenic source of the nitrophenols in air is traffic activity. Nitrophenols are formed in vehicular exhausts following the thermal reaction of fuel with oxides of nitrogen. The nitrophenols are released from exhausts of both gasoline- and diesel-powered vehicles. People who work with or around running gasoline- or diesel-powered motor vehicles may be at risk of higher exposures to nitrophenols. 4-Nitrophenol is also a breakdown product of several pesticides; therefore, workers involved in the application of certain pesticides or individuals living in agricultural areas may be exposed to higher levels of nitrophenols than the general population.

Nitrophenols have not been detected in food. Whether this is because of a lack of effort directed at monitoring these compounds or because they are present at undetectable levels is not known. Therefore, exposure from food sources, although plausible, remains to be demonstrated with actual monitoring data. 4-Nitrophenol has been detected in human urine and hair; however, this detection does not indicate direct exposure to this compound, as exposure to several pesticides can cause excretion of the compound in human urine. 4-Nitrophenol is also a metabolite of nitrobenzene. For more information on environmental levels and the possibilities for exposure to these substances, see Chapter 5.

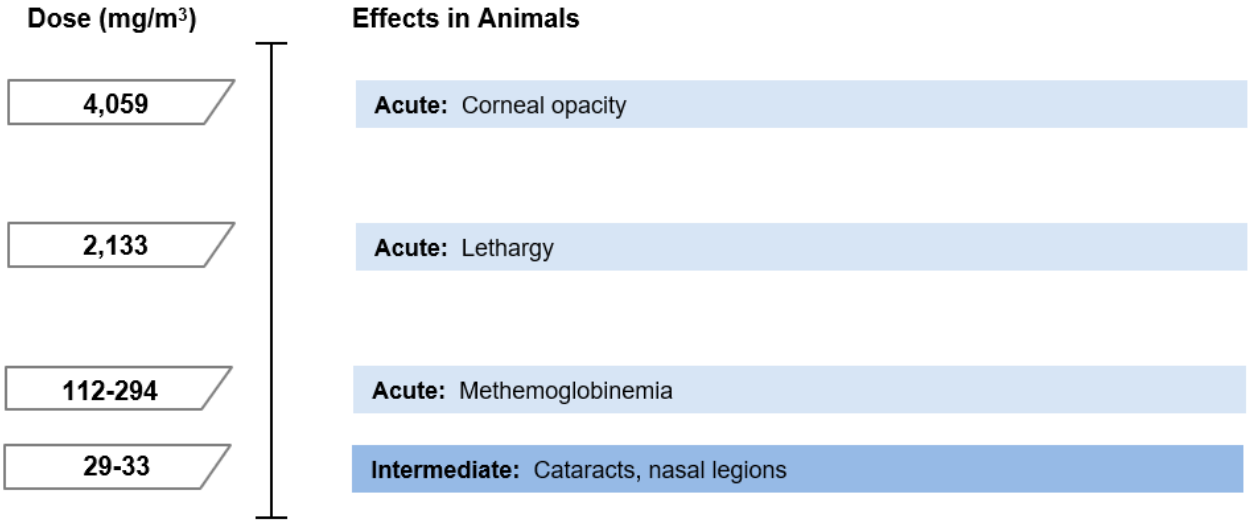
1.2 SUMMARY OF HEALTH EFFECTS

Information on the toxicity of nitrophenols is limited and comes primarily from oral studies on laboratory animals, followed by dermal studies on laboratory animals, and a few inhalation studies on laboratory animals. No human studies that focused specifically on isolated exposure to nitrophenols were identified in the literature. Most animal studies evaluated the toxicity of 4-nitrophenol, including 4 inhalation studies, 15 oral studies, and 8 dermal studies. Studies evaluating 2-nitrophenol included 1 inhalation study, 3 oral studies, and 1 dermal study, while studies evaluating 3-nitrophenol are limited to 2 oral acute lethality studies. Of the available studies, only a few are well-conducted studies evaluating a comprehensive set of endpoints; therefore, the existing experimental animal database is limited regarding the health effects of nitrophenols. Additionally, potential effects following chronic exposure as well as early life stage health effects have not been adequately characterized in the currently available literature.

The available literature indicates that the most sensitive toxicity targets in animals following inhalation exposure to 4-nitrophenol include the hematological system and the eyes. The only available inhalation study evaluating 2-nitrophenol indicates that the upper respiratory system, specifically the nasal cavity, is the most sensitive target of toxicity. Following oral exposure, decreased body weight is the only effect noted at 4-nitrophenol doses below those associated with lethality. The most common effects noted at lethal doses are clinical signs of respiratory distress and neurotoxicity. Figure 1-1 shows the health effects found in animals following inhalation exposure to 2- or 4-nitrophenol; no inhalation data are available for 3-nitrophenol. Figure 1-2 shows health effects found in animals following oral exposure to 4-nitrophenol; the limited number of oral studies evaluating 2- and 3-nitrophenol indicate that they are less toxic than 4-nitrophenol. A systematic review was conducted on body weight effects following oral exposure to 4-nitrophenol, hematological endpoints following inhalation exposure to 4-nitrophenol, and ocular endpoints after exposure to 4-nitrophenol via any route. The number of available studies for 2- and 3-nitrophenol were inadequate to support systematic review. Weight-of-evidence conclusions for 4-nitrophenol are defined in Appendix C. The review resulted in the following hazard identification conclusions:

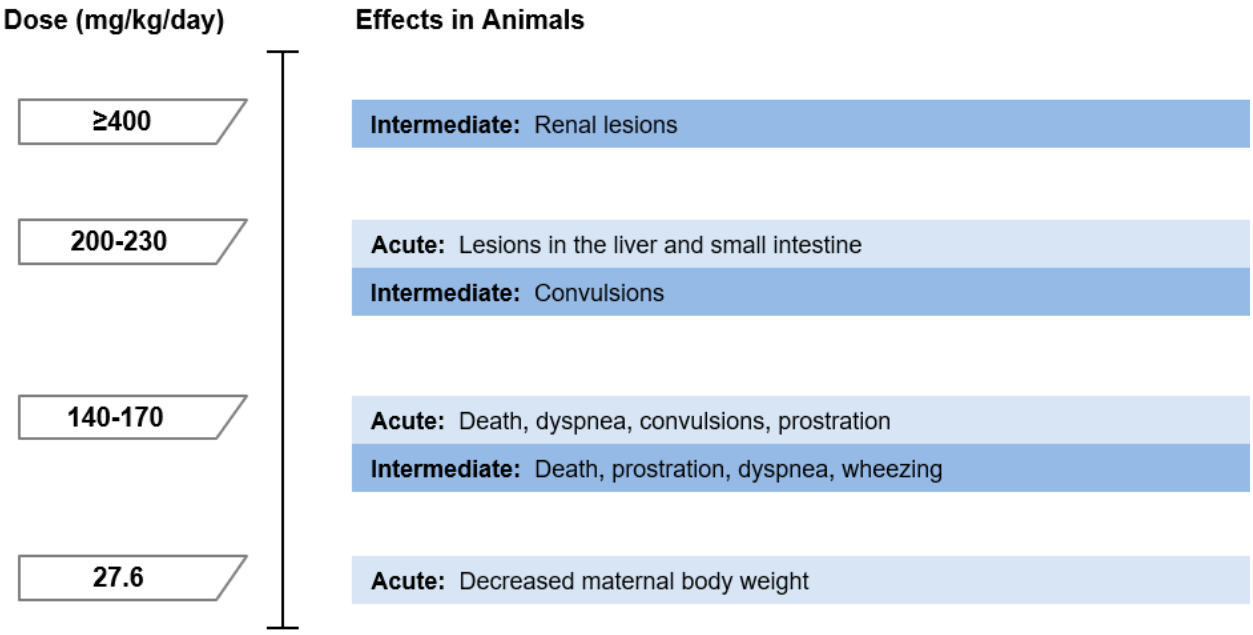
- Ocular effects are a suspected health effect of 4-nitrophenol.
- Body weight effects are not classifiable as a health effect of 4-nitrophenol following oral exposure.
- Hematological effects are not classifiable as a health effect of 4-nitrophenol following inhalation exposure.

Figure 1-1. Health Effects Found in Animals Following Inhalation Exposure to Nitrophenols*



*Includes health effects associated with acute-duration exposure to 4-nitrophenol and intermediate-duration exposure to 2- or 4-nitrophenol. No inhalation studies evaluating 3-nitrophenol were identified.

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



*Includes health effects associated with exposure to 4-nitrophenol.

Body Weight Effects. No human studies evaluating body weight effects following exposure to nitrophenols were identified. Experimental animal studies provide low evidence of an association between oral exposure to 4-nitrophenol and decreased body weight. In rats, decreased maternal body weights were observed following a 10-day gestational exposure to 27.6 mg/kg/day (EPA 1992a). Similar effects in mice were not observed until maternal doses of 400 mg/kg/day (Plasterer et al. 1985). Single acute doses up to 1,000 mg/kg/day were not associated with adverse body weight effects in pregnant rat dams (Abu-Qare et al. 2000; Kavlock 1990). Findings in nonpregnant rats are mixed, with some studies reporting decreased body weights at acute-duration doses of 200 mg/kg/day (Li et al. 2017; Tang et al. 2016), but not others (Koizumi et al. 2001). No body weight effects were noted at doses up to 1,000 mg/kg/day in mice following acute-duration exposure or in rats following intermediate-duration exposure (Hazleton 1989; Koizumi et al. 2001; Plasterer et al. 1985). One gestational gavage study in rats reported no effects on maternal body weight at 2-nitrophenol doses up to 1,000 mg/kg/day (Laughlin et al. 1983). No body weight effects were observed in intermediate-duration inhalation studies with 2- or 4-nitrophenol (Hazleton 1983, 1984), or intermediate- or chronic-duration dermal studies with 4-nitrophenol (NTP 1993; U.S. Army 1985).

Hematological Effects. No human studies evaluating hematological effects following exposure to nitrophenols were identified. Experimental animal studies provide low evidence of an association between inhalation exposure to 4-nitrophenol and adverse hematological effects. Elevated percent methemoglobin was observed following exposure to concentrations ≥112 mg/m^3, with findings persisting after a 14-day recovery period at 2,133 mg/m^3 (Smith et al. 1988). Methemoglobin levels were reportedly "normal" in two rats exposed to 1,304 mg/m^3 for 4 hours (Smith et al. 1988). In an intermediate-duration study, there was no clear evidence for methemoglobinemia in rats following a 4-week exposure to concentrations up to 29.18 mg/m^3 (Hazleton 1983). The lack of clear association could be due to lower exposure levels; however, interpretation of findings is challenging due to a wide variation of methemoglobin levels in this study in both control and exposed animals. Hematological effects were not observed in acute- or intermediate-duration oral studies of 4-nitrophenol in rats (Abu-Qare et al. 2000; Hazleton 1989; Koizumi et al. 2001). In the only study evaluating methemoglobin levels following exposure to 2-nitrophenol, no clear evidence for methemoglobinemia was observed in rats following a 4-week exposure to concentrations up to 61.5 mg/m^3 (Hazleton 1984). No adverse effects in other hematological parameters were noted in any of these studies.

Ocular Effects. No human studies evaluating ocular effects following exposure to nitrophenols were identified. Experimental animal studies provide moderate evidence of an association between

4-nitrophenol exposure and adverse ocular effects. In rats, inhalation exposure has been associated with corneal opacity following acute exposure to 4,059 mg/m^3 (Smith et al. 1988) and cataracts following intermediate-duration exposure to 29.18 mg/m^3 (Hazleton 1983). Corneal effects are likely to have been caused by direct ocular contact with 4-nitrophenol dust; however, a systemic effect cannot be totally excluded in the absence of mechanistic data. In support, ocular instillation studies in rabbits report severe eye irritation, inflammation, corneal cloudiness and neovascularization, and visible damage to the iris in rabbits (EPA 1992b; Monsanto 1983a). No ocular effects were noted in oral or dermal studies of 4-nitrophenol in rodents (Hazleton 1989; NTP 1993). A single intermediate-duration inhalation exposure study of 2-nitrophenol in rats found no ocular effects.

The Integrated Risk Information System (IRIS) of the U.S. Environmental Protection Agency (EPA), the International Agency for Research on Cancer (IARC), and the Department of Health and Human Services (HHS) National Toxicology Program (NTP) have not evaluated the potential for 2-, 3-, or 4-nitrophenol to cause carcinogenicity in humans (IARC 2022; IRIS 2002; NTP 2021).

1.3 MINIMAL RISK LEVELS (MRLs)

Ocular and hematological effects appear to be the most sensitive targets of inhaled 4-nitrophenol, and the upper respiratory tract is the only identified target of inhalation 2-nitrophenol (Figure 1-3). Following oral exposure, decreased body weight was the only effect noted at 4-nitrophenol doses below those associated with lethality (Figure 1-4). The few available studies for 2- and 3-nitrophenol indicate that acute oral toxicity occurs at much higher doses (>900 mg/kg/day), compared to 4-nitrophenol. The sensitive endpoints observed in animal studies are at relatively high doses compared to typical human exposures.

The databases for 2-, 3-, and 4-nitrophenol were all considered inadequate for the derivation of MRLs for any exposure route or duration (Table 1-1). The rationale for not deriving each MRL is discussed in greater detail in Appendix A.

Figure 1-3. Summary of Sensitive Targets of Nitrophenols – Inhalation

Hematological, neurological, and ocular effects are the only toxicity targets identified for 4-nitrophenol inhalation exposure; respiratory effects are the only toxicity target identified for 2-nitrophenol inhalation exposure.

Numbers in circles are the lowest LOAELs for all health effects in animals; no human data were identified.

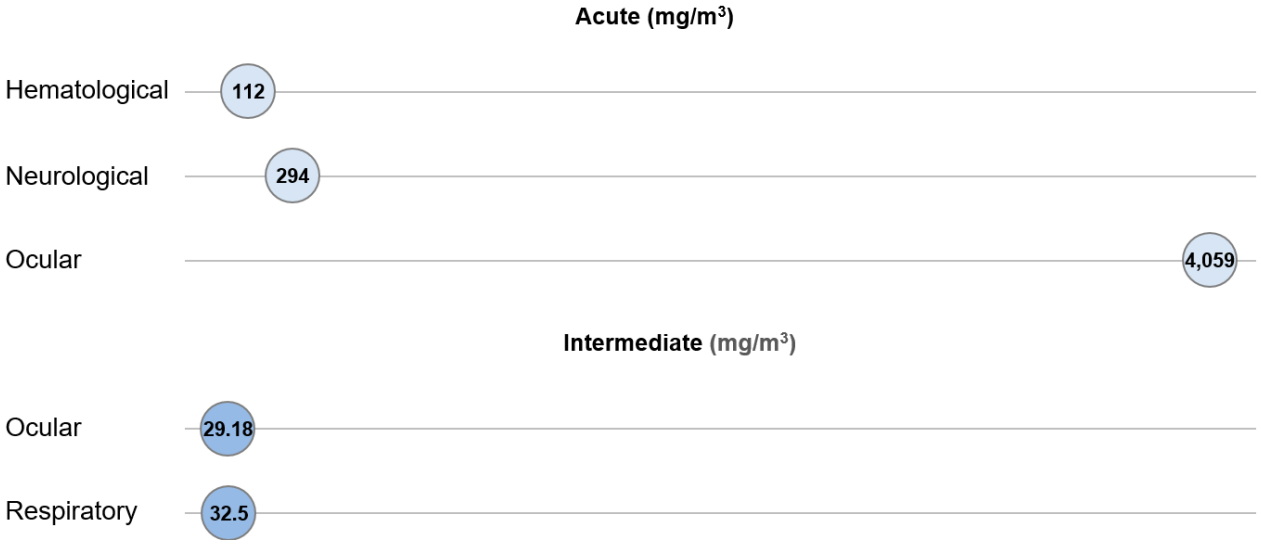


Figure 1-4. Summary of Sensitive Targets of Nitrophenols – Oral

Decreased body weight is the only effect noted following 4-nitrophenol oral exposure at doses lower than those associated with lethality.

Numbers in circles are the lowest LOAELs for all health effects in animals; no human data were identified.

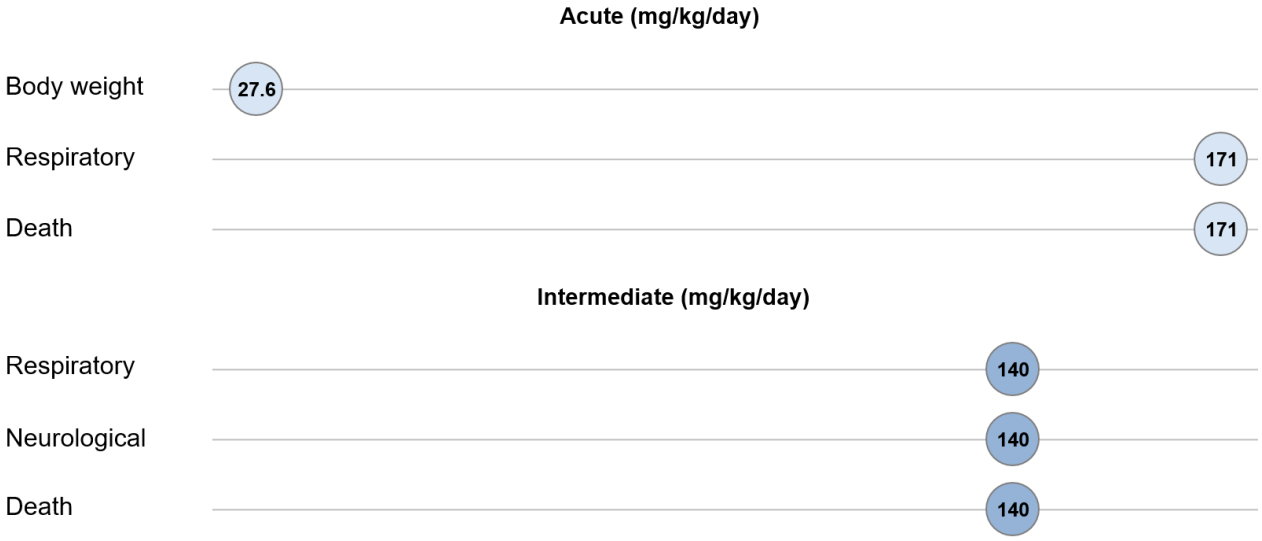


Table 1-1. Minimal Risk Levels (MRLs) for Nitrophenols[a]

No MRLs were derived for any exposure route or duration for 2-, 3-, or 4-Nitrophenol.

[a]See Appendix A for additional information.

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 nitrophenols. 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 nitrophenols, 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 nitrophenols was also conducted; the results of this review are presented in Appendix C.

Animal inhalation studies are presented in Table 2-1 and Figure 2-2, animal oral studies are presented in Table 2-2 and Figure 2-3; and animal dermal studies are presented in Table 2-3.

Levels of significant exposure (LSEs) for each route and duration are presented in tables and illustrated in figures. 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 (SLOAELs) 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 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 the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

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.

The potential health effects of nitrophenols have been evaluated in experimental animal studies only. While several epidemiological studies have evaluated potential associations between health effects and urinary levels of 4-nitrophenol, these studies measure urinary levels as a biomarker for exposure to pesticides that metabolize into 4-nitrophenol (e.g., parathion), rather than assess potential health effects of direct exposure to nitrophenols. Therefore, these studies are not discussed in this profile.

As illustrated in Figure 2-1, most of the health effects data in animals come from oral studies. Animal data are available for each exposure route and exposure duration category; however, there are limited studies available for each. Most of the studies evaluating the toxicity of nitrophenols focus on 4-nitrophenol, while only a few evaluate the toxicity of 2- or 3-nitrophenol. Many of the studies evaluating the toxicity of nitrophenols have evaluated a comprehensive set of endpoints. Lethality and body weight effects are the most examined effects in the literature, followed by reproductive and neurological effects. The genotoxicity of 2-, 3-, and 4-nitrophenol has also been examined.

Research on the health effects of nitrophenols suggest that body weight, hematological, and ocular effects are the most sensitive endpoints of toxicity:

- **Body Weight Effects.** Some studies report decreased body weight in rodents following acute-duration oral exposure to 4-nitrophenol; however, findings were inconsistent and not observed in intermediate-duration oral exposure studies. Adverse body weight effects were not observed

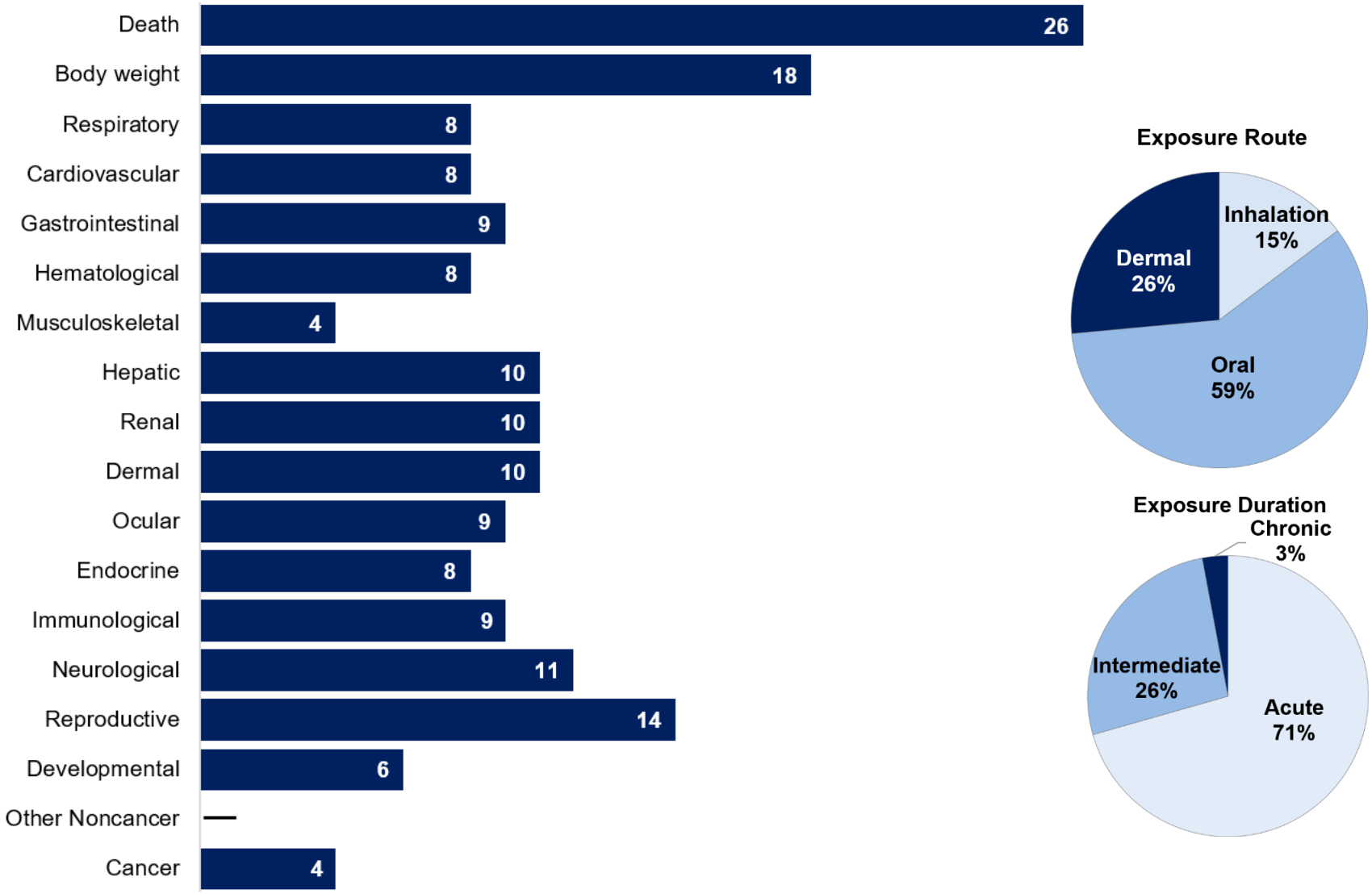
following oral exposure to 2-nitrophenol, inhalation exposure to 2- or 4-nitrophenol, or dermal exposure to 4-nitrophenol.

- **Hematological Endpoints.** Methemoglobinemia was observed in rats following acute-duration inhalation exposure to 4-nitrophenol; however, no clear evidence was observed in an intermediate-duration inhalation study in rats exposed to 4-nitrophenol. No additional hematological effects were noted after inhalation exposure to 4-nitrophenol, and no hematological effects were noted following oral exposure to 4-nitrophenol. Results of a single study investigating hematological effects in animals after 2-nitrophenol inhalation exposure did not observe any exposure-related effects.

- **Ocular Endpoints.** Ocular effects, including corneal opacity and cataracts, have been observed in rats following inhalation exposure to 4-nitrophenol. These effects are likely due to direct corneal contact with dust particles; however, a systemic effect cannot be ruled out. Direct ocular instillation of 4-nitrophenol in rabbits results in severe irritation, inflammation, corneal opacity and neovascularization, and visible destruction of the iris. No ocular effects were found following oral exposure to 4-nitrophenol. Results of a single study investigating ocular effects in animals after 2-nitrophenol inhalation exposure did not observe any exposure-related effects.

Figure 2-1. Overview of the Number of Studies Examining Nitrophenols Health Effects*

Most studies examined the potential lethality, body weight, neurological, and reproductive effects of nitrophenols
Studies evaluated health effects in animals only (counts represent studies examining endpoint)



*Includes studies discussed in Chapter 2. A total of 33 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

Table 2-1. Levels of Significant Exposure to Nitrophenols – Inhalation (mg/m^3)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE									
Smith et al. 1988									**4-nitrophenol**
1	Rat (Crl:CD) 10 M	2 weeks 5 days/week 6 hours/day (H)	0, 294, 2,133	LE, CS, BW, BC, HE, UR, GN, OW, HP	Resp	2,133			
					Cardio	2,133			
					Gastro	2,133			
					Hemato		294		Methemoglobin increased from 0.2% (in controls) to 0.87%
					Hepatic	2,133			
					Renal	2,133			
					Dermal	2,133			
					Ocular	2,133			
					Endocr	2,133			
					Immuno	2,133			
					Neuro	294	2,133		Lethargy
					Repro	2,133			
Smith et al. 1988									**4-nitrophenol**
2	Rat (Crl:CD) 10 M	2 weeks 5 days/week 6 hours/day (H)	0, 26, 112	LE, CS, BW, BC, HE, UR, GN, OW, HP	Resp	112			
					Cardio	112			
					Gastro	112			
					Hemato	26	112		Methemoglobin increased from 0.5% (in controls) to 1.5%
					Hepatic	112			
					Renal	112			
					Dermal	112			
					Ocular	112			
					Endocr	112			
					Immuno	112			
					Neuro	112			
					Repro	112			

Table 2-1. Levels of Significant Exposure to Nitrophenols – Inhalation (mg/m^3)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Smith et al. 1988									**4-nitrophenol**
3	Rat (Crl:CD) 6 M	4 hours (H)	1,304, 4,059	CS	Ocular	1,304		4,059	Corneal opacity
INTERMEDIATE EXPOSURE									
Hazleton 1983									**4-nitrophenol**
4	Rat (Sprague-Dawley) 15 M,15 F	4 weeks 5 days/week 6 hours/day (WB)	0, 1.09, 5.27, 29.18	LE, CS, BW, BC, HE, OP, GN, OW, HP	Bd wt	29.18			
					Resp	29.18			
					Cardio	29.18			
					Gastro	29.18			
					Hemato	29.18			
					Musc/skel	29.18			
					Hepatic	29.18			
					Renal	29.18			
					Dermal	29.18			
					Ocular	5.27 M 29.18 F		29.18 M	Cataracts
					Endocr	29.18			
					Immuno	29.18			
					Neuro	29.18			
					Repro	29.18			
Hazleton 1984									**2-nitrophenol**
5	Rat (Sprague-Dawley) 15 M, 15 F	4 weeks 5 days/week 6 hours/day (WB)	0, 5.0, 32.5, 61.5	LE, CS, BW, BC, HE, OP, GN, OW, HP	Bd wt	61.5			
					Resp	5.0	32.5		Squamous metaplasia of the epithelium lining the nasal turbinates
					Cardio	61.5			
					Gastro	61.5			
					Hemato	61.5			
					Musc/skel	61.5			

Table 2-1. Levels of Significant Exposure to Nitrophenols – Inhalation (mg/m^3)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Hepatic	61.5			
					Renal	61.5			
					Dermal	61.5			
					Ocular	61.5			
					Endocr	61.5			
					Immuno	61.5			
					Neuro	61.5			
					Repro	61.5			

[a]The number corresponds to entries in Figure 2-2; differences in levels of health 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 sex are presented.

BC = blood chemistry; Bd wt or BW = body weight; Cardio = cardiovascular; CS = clinical signs; Endocr = endocrine; F = female(s); Gastro = gastrointestinal; GN = gross necropsy; (H) = head-only; HE = hematology; Hemato = hematological; HP = histopathology; Immuno = immunological; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); Musc/skel = musculoskeletal; Neuro = neurological; NOAEL = no-observed-adverse-effect level; OP = ophthalmology; OW = organ weight; Repro = reproductive; Resp = respiratory; UR = urinalysis; (WB) = whole-body

Figure 2-2. Levels of Significant Exposure to Nitrophenols – Inhalation
Acute (≤14 days)

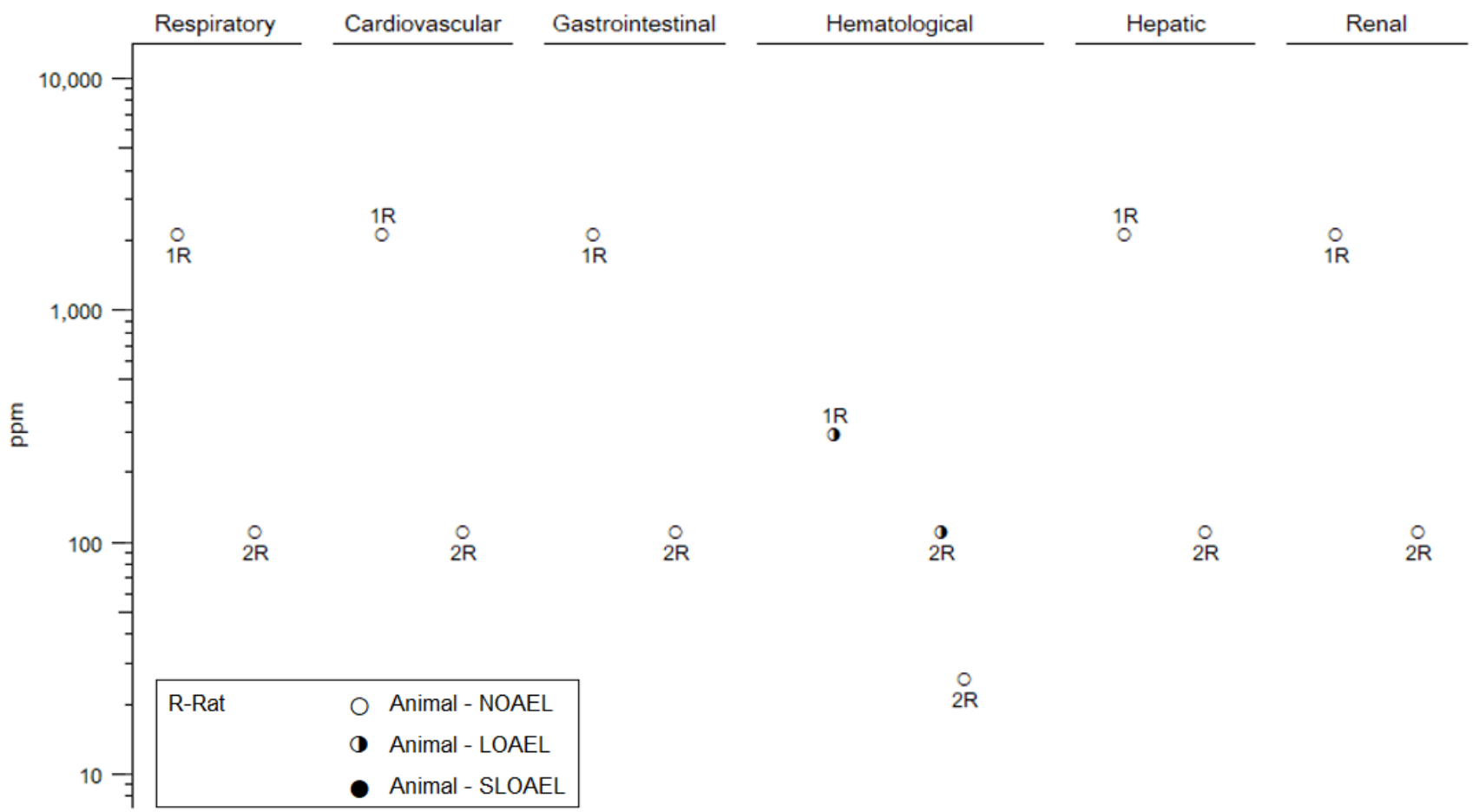


Figure 2-2. Levels of Significant Exposure to Nitrophenols – Inhalation
Acute (≤14 days)

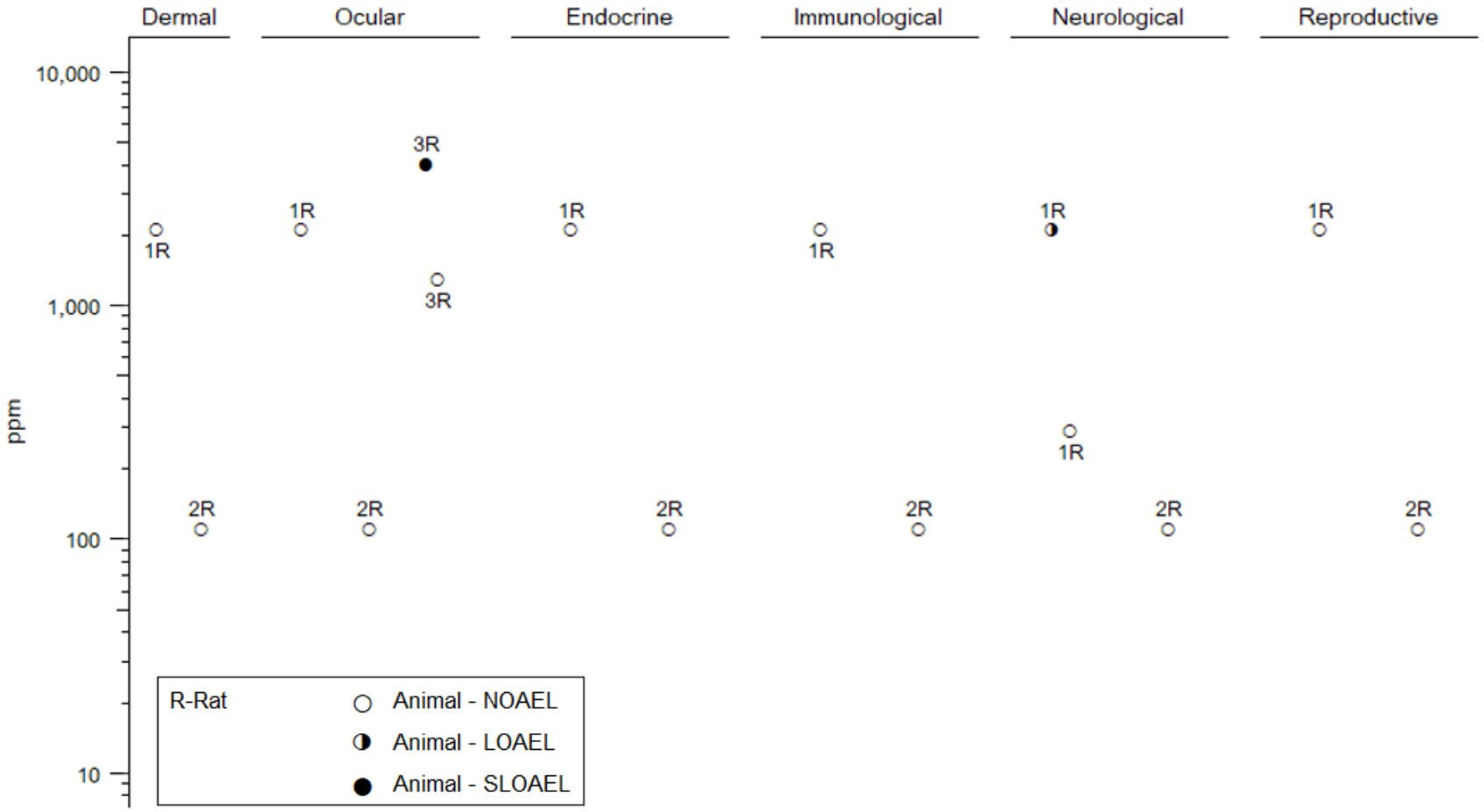


Figure 2-2. Levels of Significant Exposure to Nitrophenols – Inhalation
Intermediate (15-364 days)

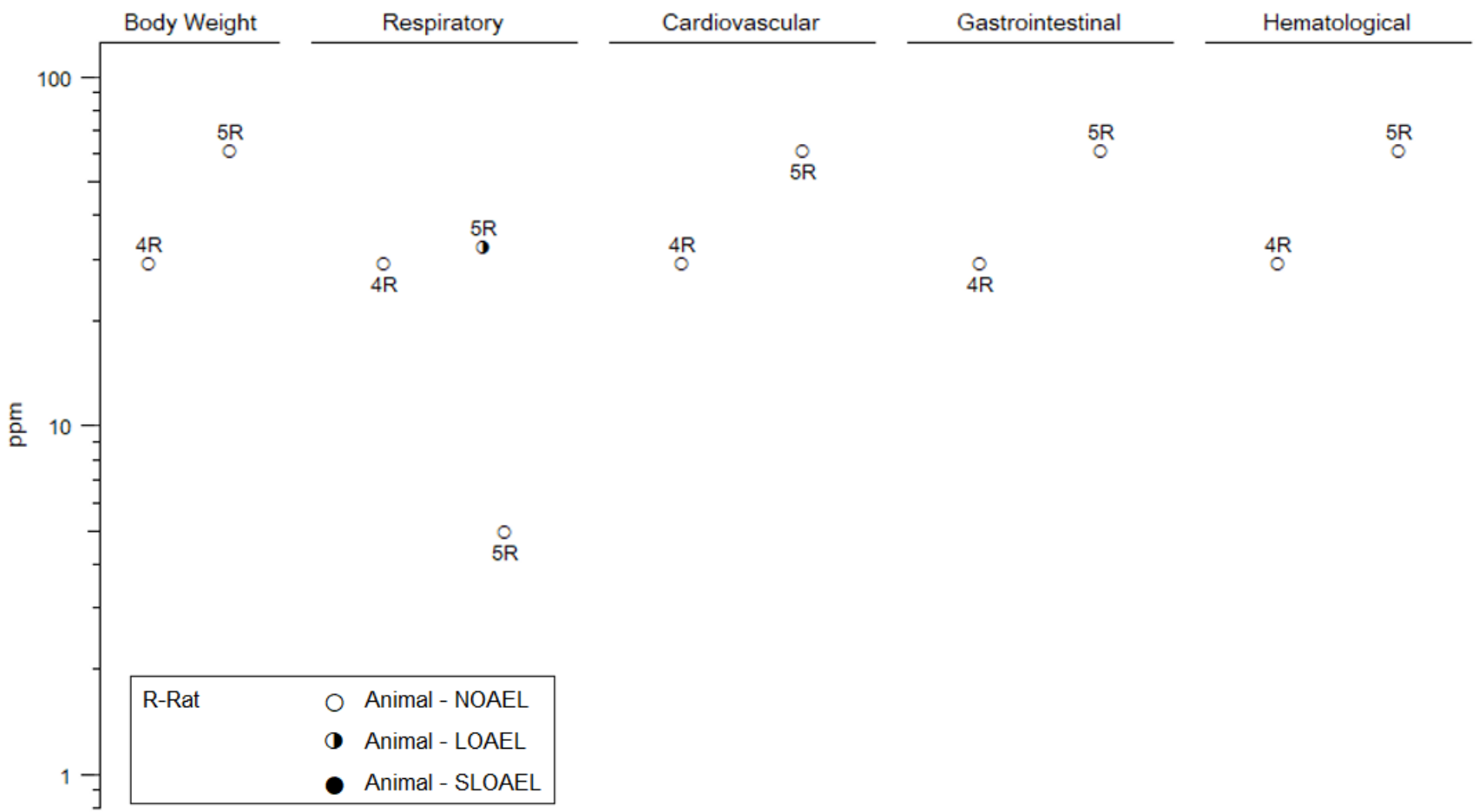


Figure 2-2. Levels of Significant Exposure to Nitrophenols – Inhalation
Intermediate (15-364 days)

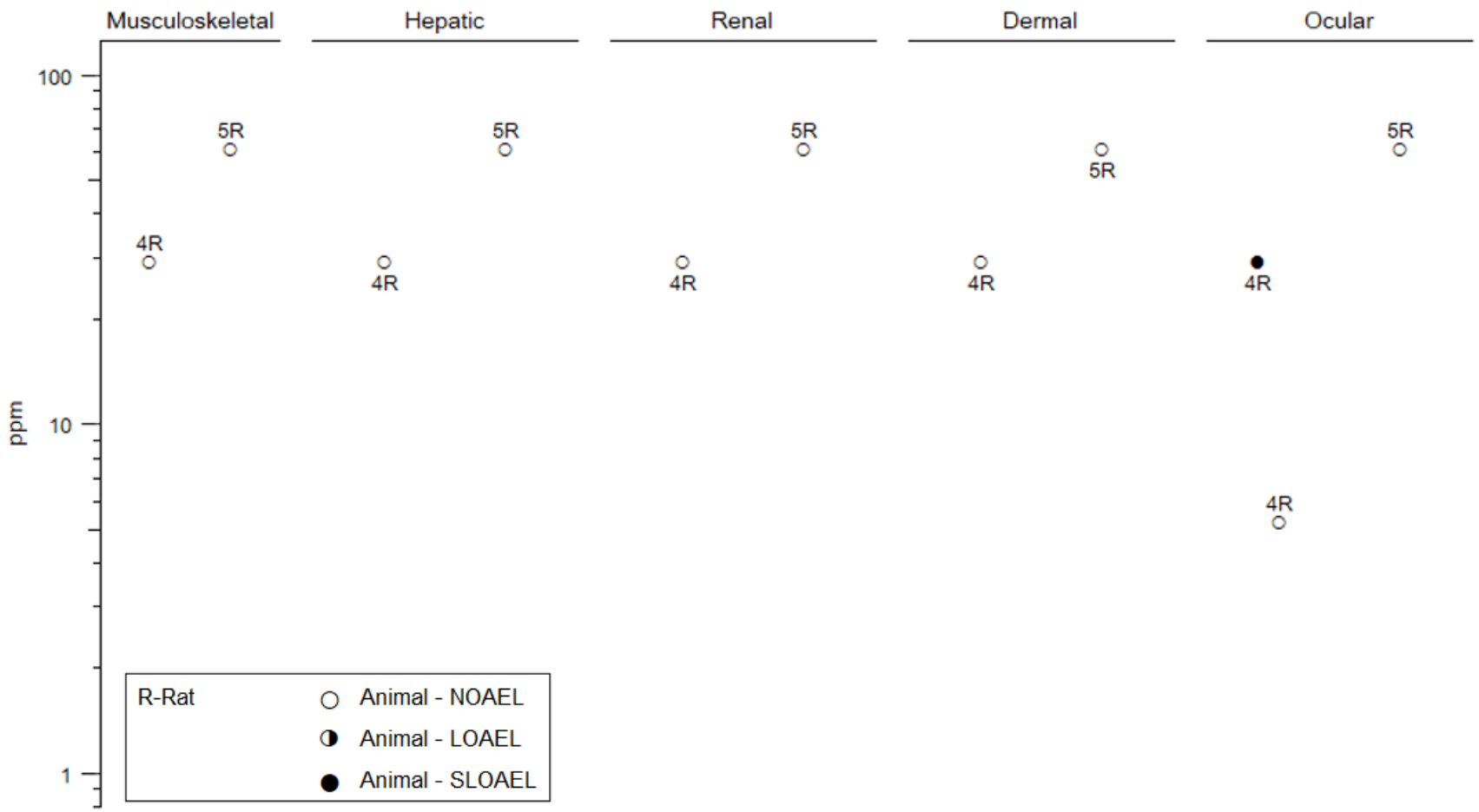


Figure 2-2. Levels of Significant Exposure to Nitrophenols – Inhalation
Intermediate (15-364 days)

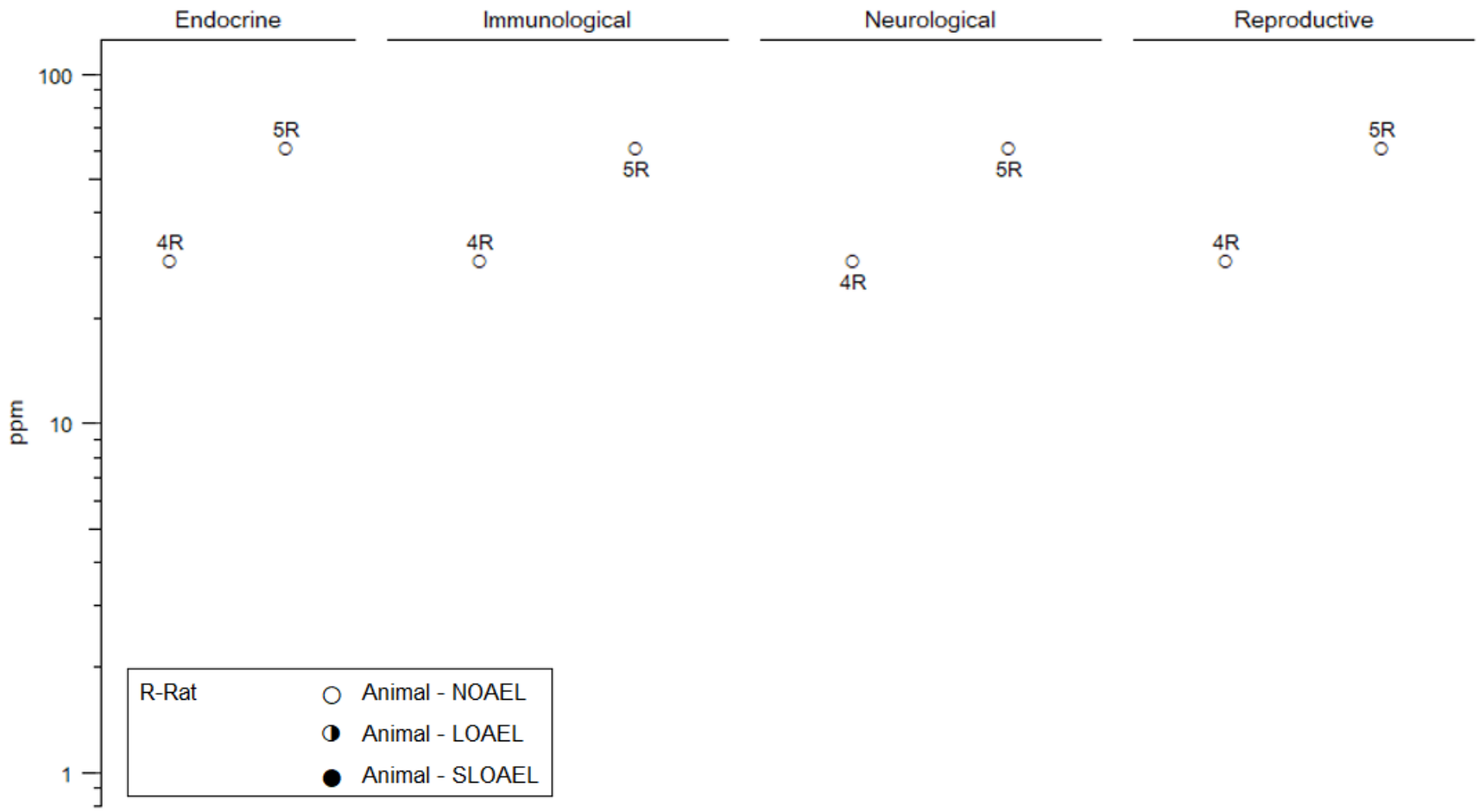


Table 2-2. Levels of Significant Exposure to Nitrophenols – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE									
Abu-Qare et al. 2000									**4-nitrophenol**
1	Rat (Sprague-Dawley) 7–21 F	Once GD 14, 15, 16, 17, or 18 (GW)	0, 100	BW, FI, WI, HE, BI, OW, DX	Bd wt	100			
					Hemato	100			
					Neuro	100			
					Repro	100			
					Develop	100			
Branch et al. 1983b									**4-nitrophenol**
2	Rat (Albino) 25 M, 25 F	Once (G)	70, 110, 171, 268, 420	LE, CS	Death			171 F 268 M	3/5 females died at 171 mg/kg; 4/5 males died at 268 mg/kg (LD_{50} = 230 mg/kg/)
					Resp	70 F 171 M		171 F 268 M	Dyspnea prior to death
					Neuro	110		268	Convulsions and prostration prior to death
EPA 1992a									**4-nitrophenol**
3	Rat (Sprague-Dawley) 20 F	10 days GDs 6–16 (G)	0, 1.4, 13.8, 27.6	LE, BW, GN, RX, DX	Bd wt	13.8	27.6		12% decrease in maternal body weight
					Repro	27.6			
					Develop	27.6			
Kavlock 1990									**4-nitrophenol**
4	Rat (Sprague-Dawley) 12 F	Once GD 11 (G)	0, 333, 667, 1,000	LE, CS, BW, DX	Death			667	3/13 died
					Bd wt	1,000			
					Develop	1,000			

Table 2-2. Levels of Significant Exposure to Nitrophenols – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Koizumi et al. 2001									**4-nitrophenol**
5	Rat (Sprague-Dawley) 5 M, 5 F	14 days (G)	0, 3, 12.5, 50, 200	LE, CS, BW, HE	Bd wt	200			
					Hemato	200			
Laughlin et al. 1983									**2- nitrophenol**
6	Rat (Sprague-Dawley) 5 F	10 days GDs 6–15 (GO)	0, 50, 125, 250, 500, 1,000	LE, CS, BW, RX	Bd wt	1,000			
					Repro	500		1,000	Post implantation loss
Li et al. 2017; Tang et al. 2016									**4-nitrophenol**
7	Rat (Wistar) 9 M	Once (G)	0, 200	BW, BI, OW, HP	Bd wt	200			
					Gastro		200		Necrosis and desquamation of the mucosal epithelium of small intestine; loss of goblet cells
					Hepatic		200		Disordered hepatocytes; detached central vein of the hepatic lobule
					Renal	200			
					Endocr	200			
					Immuno	200			
					Repro	200			
[Histology evaluated in liver and small intestine only.]									
Li et al. 2017; Tang et al. 2016									**4-nitrophenol**
8	Rat (Wistar) 12 M	3 days (G)	0, 200	BW, BI, OW, HP	Bd wt			200	25% decrease in body weight
					Gastro		200		Necrosis and desquamation of the mucosal epithelium of small intestine; loss of goblet cells
					Hepatic		200		Disordered hepatocytes, widened hepatic sinusoid

Table 2-2. Levels of Significant Exposure to Nitrophenols – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Renal	200			
					Endocr	200			
					Immuno	200			
					Repro	200			
[Histology evaluated in liver and small intestine only.]									
Vernot et al. 1977									**4- nitrophenol**
9	Rat (Sprague-Dawley) NS M	Once (NS)	Not reported	LE	Death			620	LD_{50}
Vernot et al. 1977									**2- nitrophenol**
10	Rat (Sprague-Dawley) NS M	Once (NS)	Not reported	LE	Death			2,830	LD_{50}
Vernot et al. 1977									**3-nitrophenol**
11	Rat (Sprague-Dawley) NS M	Once (NS)	Not reported	LE	Death			930	LD_{50}
Plasterer et al. 1985									**4-nitrophenol**
12	Mouse (CD1) 10 F	8 days GDs 7–14 (GO)	0, 400	LE, CS, BW CS, RX, DX	Death			400	19% decrease in maternal survival
					Bd wt		400		18% decrease in maternal body weight gain
					Repro	400			
					Develop	400			
Plasterer et al. 1985									**4-nitrophenol**
13	Mouse (CD1) 10 F	8 days (GO)	0, 62.5, 125, 250, 500, 1,000	LE, BW	Death			625.7	LD_{50}
					Bd wt	1,000			

Table 2-2. Levels of Significant Exposure to Nitrophenols – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Vernot et al. 1977									**2-nitrophenol**
14	Mouse (CF-1) NS	Once (NS)	Not reported	LE	Death			1,300	LD_{50}
Vernot et al. 1977									**4-nitrophenol**
15	Mouse (CF-1) NS	Once (NS)	Not reported	LE	Death			470	LD_{50}
Vernot et al. 1977									**3-nitrophenol**
16	Mouse (CF-1) NS	Once (NS)	Not reported	LE	Death			1,410	LD_{50}
INTERMEDIATE EXPOSURE									
Hazleton 1989									**4-nitrophenol**
17	Rat (Sprague-Dawley) 20 M, 20 F	13 weeks 7 days/week (GW)	0, 25, 70, 140	LE, CS, FI, BW, BC, OP, OW, GN, HP	Death			140	15/20 males and 6/20 females died
					Bd wt	140			
					Resp	70		140	Dyspnea and wheezing (prior to death)
					Cardio	140			
					Gastro	140			
					Hemato	140			
					Musc/skel	140			
					Hepatic	140			
					Renal	140			
					Dermal	140			
					Ocular	140			
					Endocr	140			
					Immuno	140			
					Neuro	70		140	Prostration (prior to death)
					Repro	140			

Table 2-2. Levels of Significant Exposure to Nitrophenols – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Koizumi et al. 2001									**4-nitrophenol**
18	Rat (Sprague-Dawley) 12 M, 12 F	18 days PNDs 4–21 (G)	0, 80, 110, 160	DX	Develop	160			
Koizumi et al. 2001									**4-nitrophenol**
19	Rat (Sprague-Dawley) 6 M, 6 F	18 days PNDs 4–21 (G)	0, 110, 160, 230, 320	LE, CS	Death			320 F	6/6 females died
								230 M	3/6 males died
					Neuro	160		230	Convulsions
Koizumi et al. 2001									**4-nitrophenol**
20	Rat (Sprague-Dawley) 12 M, 12 F	28 days (G)	0, 60, 160, 400, 1,000	LE, CS, BW, FI, BC, HE, UR, GN, OW, HP	Death			1,000	10/12 males and 10/12 females died
					Bd wt	1,000			
					Resp	400		1,000	Oligopnea
					Cardio	1,000			
					Gastro	1,000			
					Hepatic	1,000			
					Renal	160	400		Eosinophilic bodies in proximal renal tubular cells
					Endocr	1,000			
					Immuno	1,000			

Table 2-2. Levels of Significant Exposure to Nitrophenols – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Neuro	400		1,000	Tonic convulsions, decreased locomotor activity, prostration
					Repro	1,000			

[a]The number corresponds to entries in Figure 2-3; differences in levels of health effects between male and females are not indicated in Figure 2-3. Where such differences exist, only the levels of effect for the most sensitive sex are presented.

BC = blood chemistry; Bd wt or BW = body weight; BI = biochemical indices; Cardio = cardiovascular; CS = clinical signs; Develop = developmental; DX = developmental toxicity; Endocr = endocrine; F = female(s); FI = food intake; (G) = gavage, neat or vehicle other than water or oil; Gastro = gastrointestinal; GD = gestation day; GN = gross necropsy; (GO) = gavage with oil vehicle; (GW) = gavage with water vehicle; HE = hematology; Hemato = hematological; HP = histopathology; Immuno = immunological; LD_{50} = median lethal dose; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); Musc/skel = musculoskeletal; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; OP = ophthalmology; OW = organ weight; PND = postnatal day; Repro = reproductive; Resp = respiratory; RX = reproductive toxicity; UR = urinalysis; WI = water intake

Figure 2-3. Levels of Significant Exposure to Nitrophenols – Oral
Acute (≤14 days)

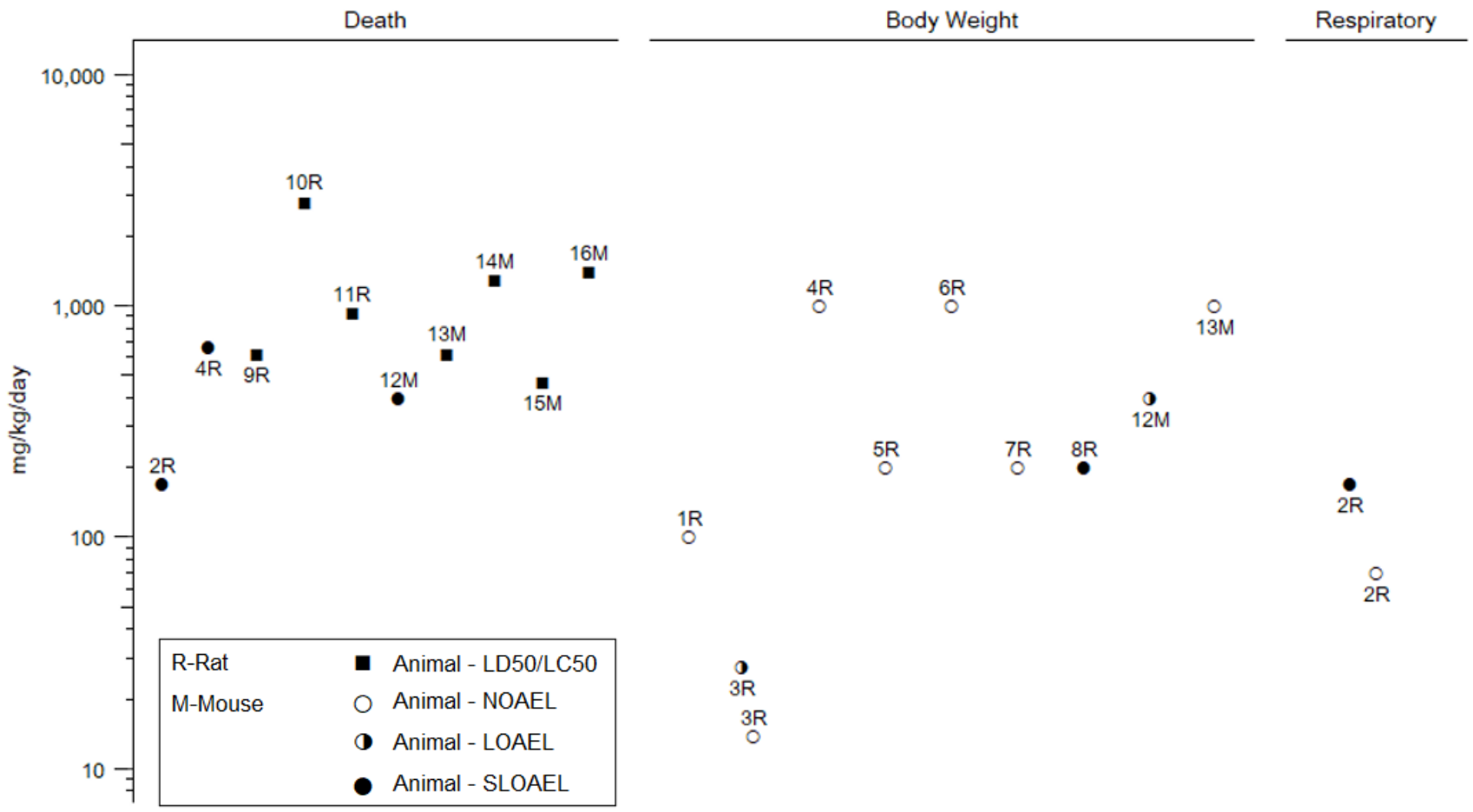


Figure 2-3. Levels of Significant Exposure to Nitrophenols – Oral
Acute (≤14 days)

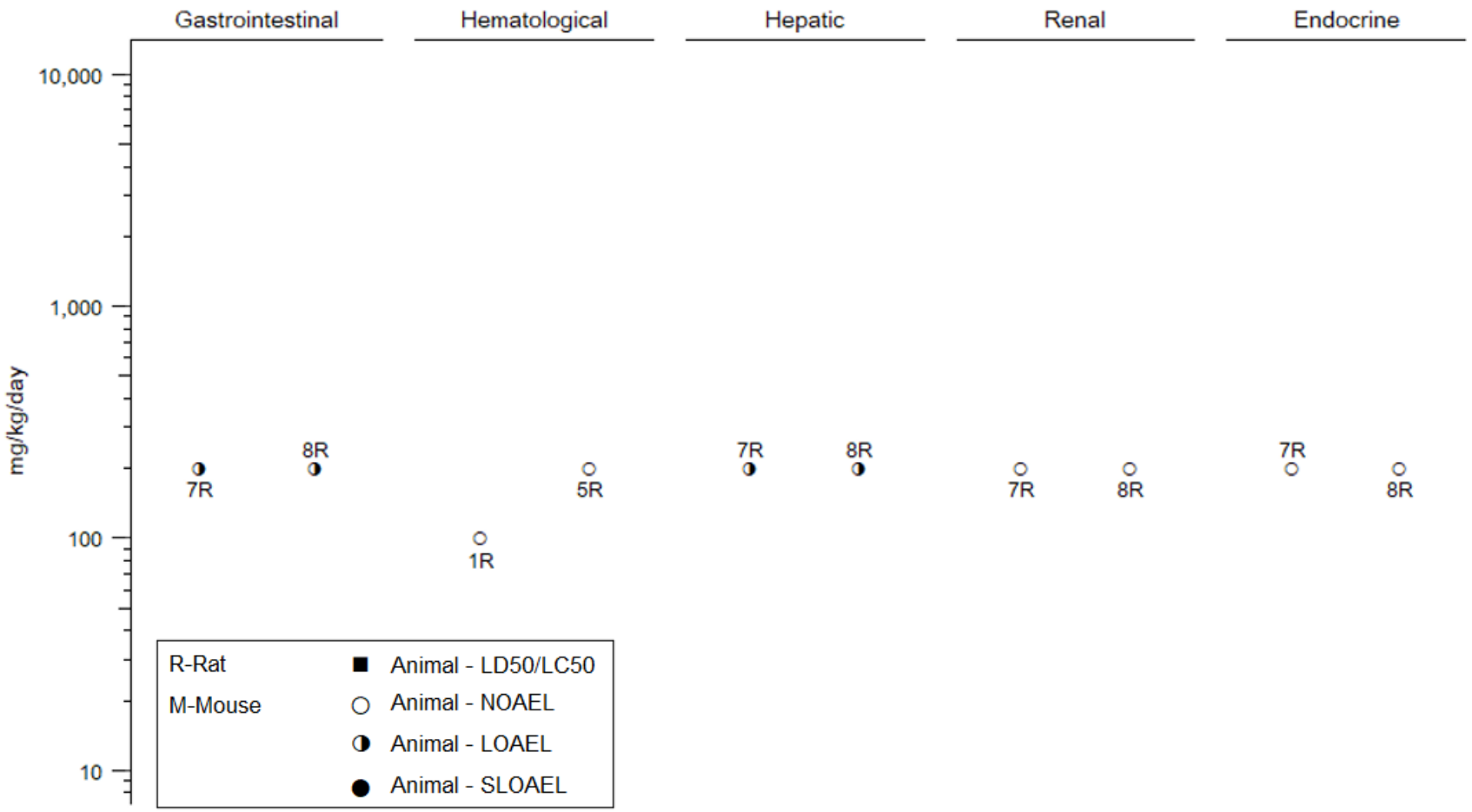


Figure 2-3. Levels of Significant Exposure to Nitrophenols – Oral
Acute (≤14 days)

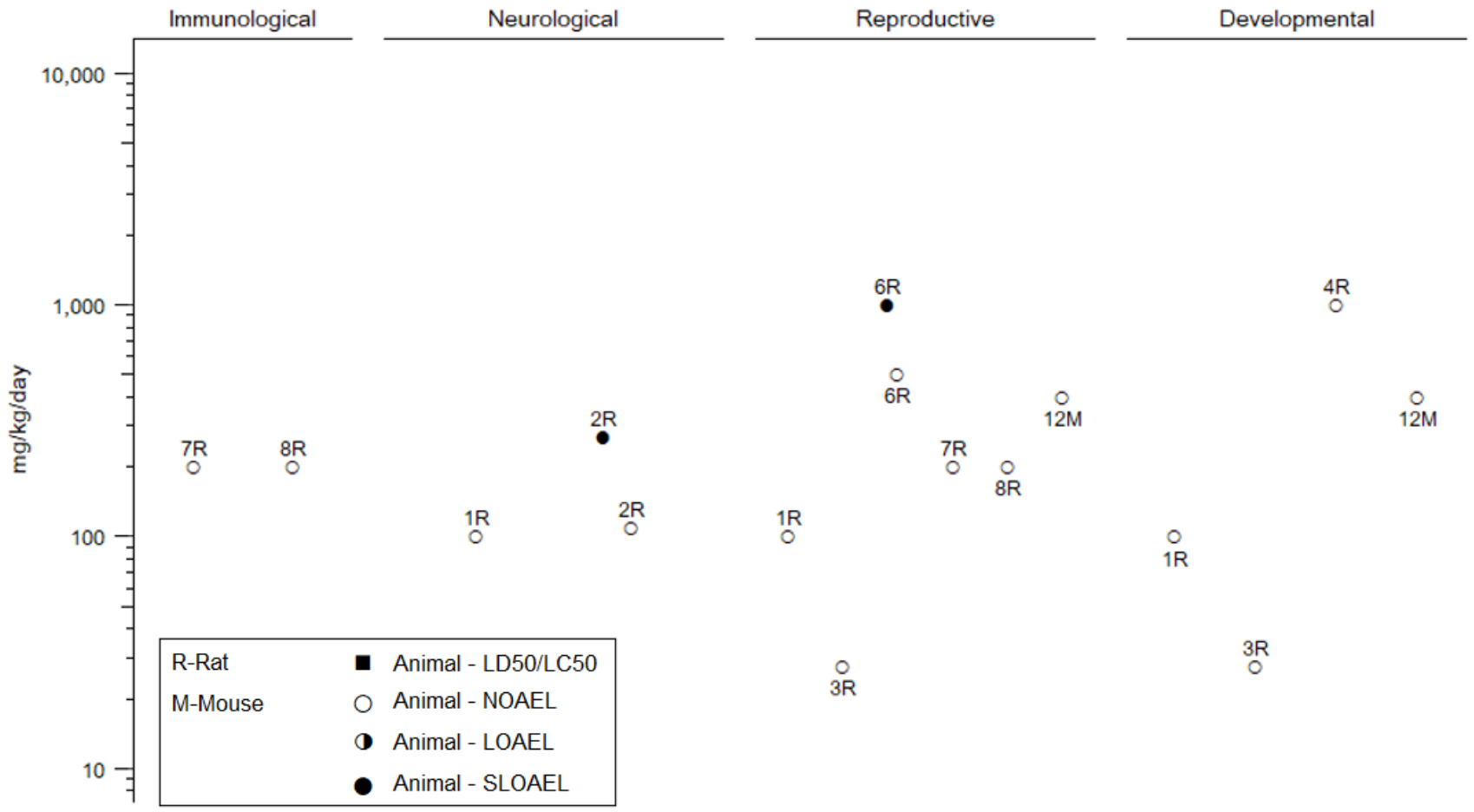


Figure 2-3. Levels of Significant Exposure to Nitrophenols – Oral
Intermediate (15-364 days)

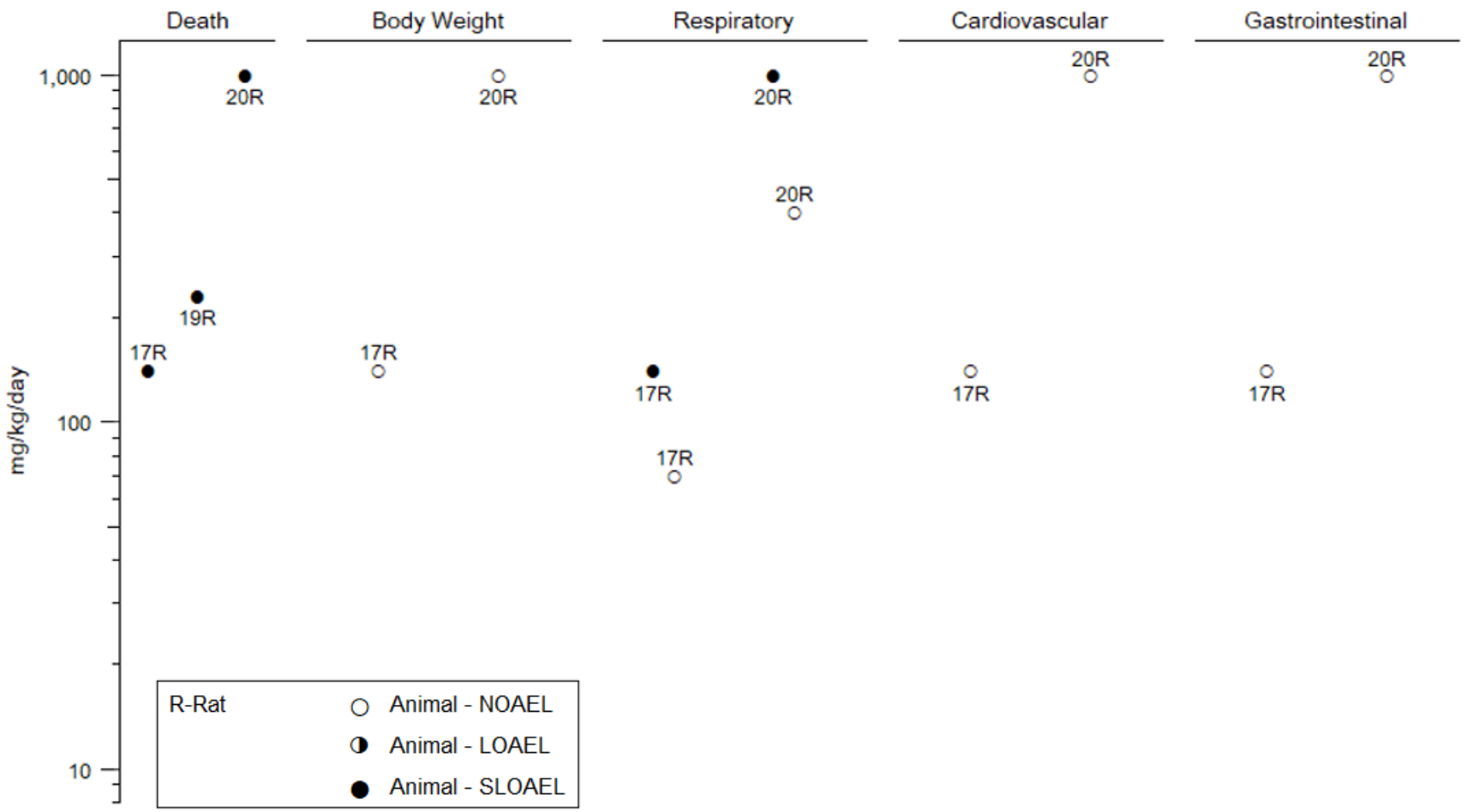


Figure 2-3. Levels of Significant Exposure to Nitrophenols – Oral
Intermediate (15-364 days)

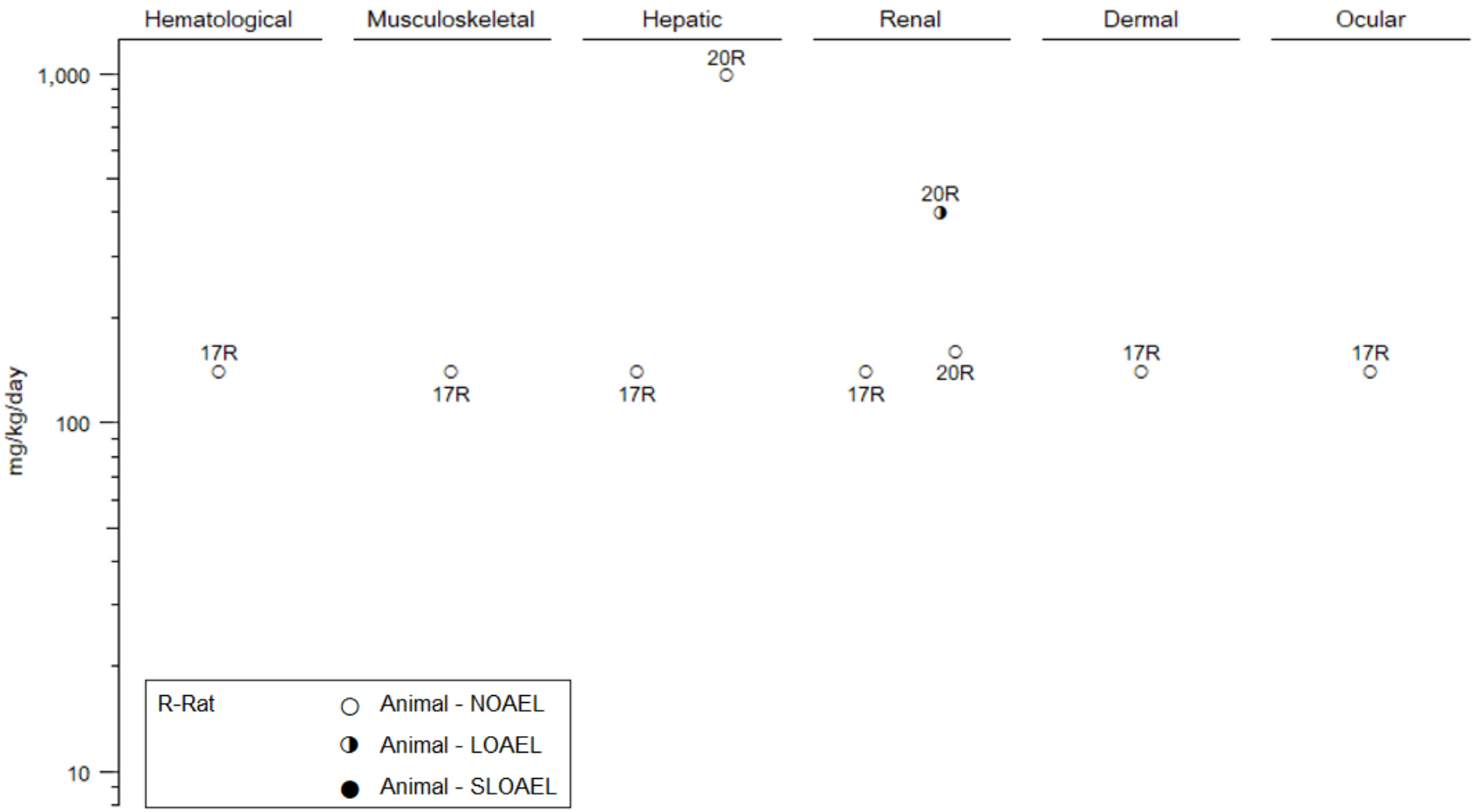


Figure 2-3. Levels of Significant Exposure to Nitrophenols – Oral
Intermediate (15-364 days)

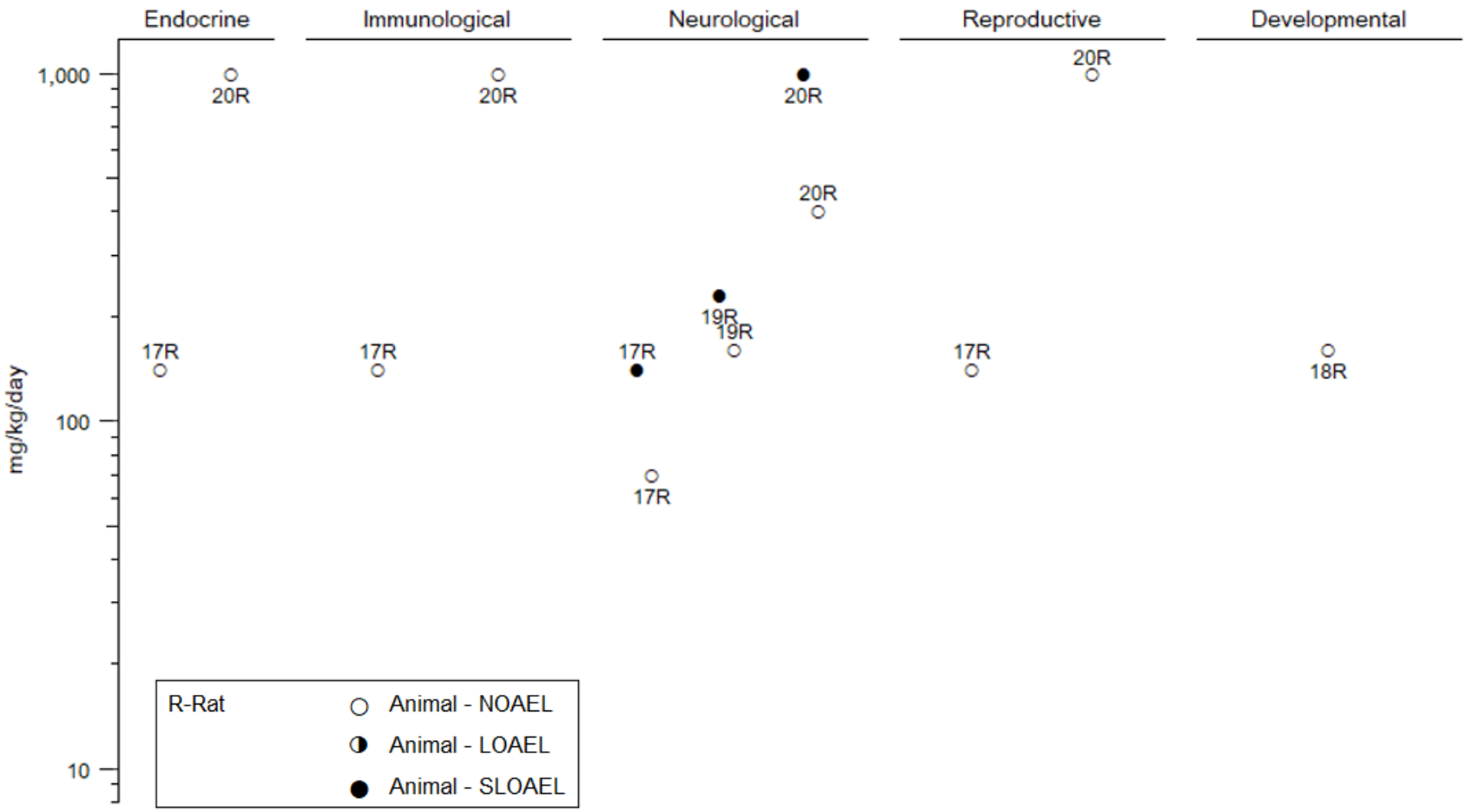


Table 2-3. Levels of Significant Exposure to Nitrophenols – Dermal

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE								
Branch et al. 1983a								**4-nitrophenol**
Rabbit (New Zealand white) 5 M, 5 F	24 hours (occluded conditions)	5,000 mg/kg in saline	LE, CS, GN	Dermal		5,000 mg/kg		Erythema and edema
EPA 1992a								**4-nitrophenol**
Rabbit (New Zealand white) 6 NS	Once (conjunctival sac)	100 mg (solid)	CS	Ocular			100 mg	Severe irritation and corneal opacity; inflammation and visible destruction of iris
Monsanto 1983a								**4-nitrophenol**
Rabbit (New Zealand white) 3 M, 3 F	Once (conjunctival sac)	70 mg (solid)	CS	Ocular			70 mg	Corneal cloudiness, corneal neovascularization, blistering of conjunctival tissue
Monsanto 1983b								**4-nitrophenol**
Rabbit (New Zealand white) 3 M, 3 F	24 hours (occluded conditions)	184 mg/kg in saline	CS, GN	Dermal		184 mg/kg		Skin scabbing and scarring
Monsanto 1984								**4-nitrophenol**
Rabbit (New Zealand white) 3 M, 3 F	4 hours (occluded conditions)	0, 148 mg/kg in saline	CS, GN	Dermal		148 mg/kg		Erythema and edema
INTERMEDIATE EXPOSURE								
U.S. Army 1985								**4-nitrophenol**
Rat (Sprague-Dawley) F0: 12 M, 24 F F1: 13 M, 26 F	2 generations 20–24 weeks per generation 5 days/week	0, 50, 100, 250 mg/kg/day in ethanol	LE, CS, BW, OW, HP, RX, DX	Bd wt	250 mg/kg/day			
				Cardio	250 mg/kg/day			
				Hepatic	250 mg/kg/day			
				Renal	250 mg/kg/day			

Table 2-3. Levels of Significant Exposure to Nitrophenols – Dermal

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
				Dermal		50 mg/kg/day		Skin irritation (erythema, scaling, scabbing, cracking) and histopathological changes in the skin (chronic inflammation, acanthosis, eschar, sebaceous hypertrophy) in F0 and F1 rats
				Neuro	250 mg/kg/day			
				Repro	250 mg/kg/day			
				Develop	250 mg/kg/day			
CHRONIC EXPOSURE								
NTP 1993								**4-nitrophenol**
Mouse (Swiss-Webster) 60 M, 60 F	78 weeks 3 days/week	0, 40, 80, 160 mg/kg/day in acetone	LE, CS, BW, GN, HP	Bd wt	160 mg/kg/day			
				Resp	160 mg/kg/day			
				Cardio	160 mg/kg/day			
				Gastro	160 mg/kg/day			
				Musc/skel	160 mg/kg/day			
				Hepatic	160 mg/kg/day			
				Renal	160 mg/kg/day			
				Dermal	160 mg/kg/day			
				Ocular	160 mg/kg/day			
				Endocr	160 mg/kg/day			
				Immuno	160 mg/kg/day			
				Neuro	160 mg/kg/day			
				Repro	160 mg/kg/day			

Bd wt or BW = body weight; Cardio = cardiovascular; CS = clinical signs; Develop = developmental; DX = developmental toxicity; Endocr = endocrine; F = female(s); Gastro = gastrointestinal; GN = gross necropsy; HP = histopathology; Immuno = immunological; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); Musc/skel = musculoskeletal; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; OW = organ weight; Repro = reproductive; Resp = respiratory; RX = reproductive toxicity

2.2 DEATH

No studies were identified regarding death in humans after exposure to 2-, 3-, or 4-nitrophenol. In animals, mortality was evaluated following inhalation exposure to 2- or 4-nitrophenol; oral exposure to 2-, 3-, or 4-nitrophenol; and dermal exposure to 2- or 4-nitrophenol.

No exposure-related mortalities were observed in rats exposed to 4-nitrophenol following exposure to concentrations up to 4,059 mg/m^3 for 4 hours (Smith et al. 1988) or intermittent exposure to concentrations up to 2,133 mg/m^3 for 2 weeks (Smith et al. 1988) or 29.18 mg/m^3 for 4 weeks (Hazleton 1983). Similarly, no exposure-related deaths were observed in rats intermittently exposed to 2-nitrophenol concentrations up to 61.5 mg/m^3 for 4 weeks (Hazleton 1984).

In acute oral lethality studies, reported oral median lethal dose (LD_{50}) values were 2,830 mg/kg for rats and 1,300 mg/kg for mice exposed to 2-nitrophenol (Vernot et al. 1977), 930 mg/kg for rats and 1,410 mg/kg for mice exposed to 3-nitrophenol (Vernot et al. 1977), and 202–620 mg/kg for rats and 470–625.7 mg/kg for mice exposed to 4-nitrophenol (Branch et al. 1983b; Plasterer et al. 1985; Vernot et al. 1977). The cause of death was not reported in acute lethality studies; however, Branch et al. (1983b) reported dyspnea, convulsions, and/or prostration prior to death. In a 14-day gavage study, no exposure-related deaths were reported in rats exposed to 4-nitrophenol doses up to 200 mg/kg/day for 14 days (Koizumi et al. 2001).

In pregnant rodents, 3/13 maternal rats died following a single exposure to 667 mg/kg on gestational day (GD) 11 (Kavlock 1990) and a 19% decreased in maternal survival was observed in mice exposed to 400 mg/kg/day on GDs 7–14 (Plasterer et al. 1985). No maternal deaths were reported in rats exposed to 4-nitrophenol at doses up to 27.6 mg/kg/day on GDs 6–16 (EPA 1992a) or 2-nitrophenol at doses up to 1,000 mg/kg/day on GDs 6–15 (Laughlin et al. 1983).

Increased mortality was also reported in rats following intermediate-duration oral exposure to 4-nitrophenol. In adult rats, 10/12 males and 10/12 females died following gavage exposure to 1,000 mg/kg/day for up to 28 days (Koizumi et al. 2001) and 15/20 males and 6/20 females died following gavage exposure to 140 mg/kg/day for up to 13 weeks (Hazleton 1989). Clinical signs observed prior to death included slow, shallow, or irregular breathing and neurological effects (convulsions, decreased activity, and/or prostration). In neonatal mice exposed to 4-nitrophenol on postnatal days (PNDs) 4–21 via gavage, decreased survival was observed at 230 mg/kg/day in male rat

pups (3/6 died) and 320 mg/kg/day in female rat pups (6/6 died); convulsions were observed prior to death (Koizumi et al. 2001).

No exposure-related mortalities were observed in animals following dermal exposure to nitrophenols. In an acute dermal lethality study, all rabbits exposed to 4-nitrophenol at a dose of 5,000 mg/kg in saline under occluded conditions for 24 hours survived (Branch et al. 1983a). In dermal studies in mice, decreased survival was not observed following exposure to 2- or 4-nitrophenol diluted in dioxane to a dose of 138 mg/kg/day applied twice weekly for 12 weeks (Boutwell and Bosch 1959) or doses up to 160 mg/kg/day diluted in acetone 3 days/week for 78 weeks (NTP 1993). Similarly, no exposure-related deaths were observed in F0 or F1 rats exposed to 4-nitrophenol doses up to 250 mg/kg/day diluted in ethanol over two generations (5 days/week; 20–24 weeks per generation) (U.S. Army 1985).

2.3 BODY WEIGHT

No studies were identified regarding body weight in humans after exposure to 2-, 3-, or 4-nitrophenol. In animals, body weights were evaluated following inhalation exposure to 2- or 4-nitrophenol, oral exposure to 2- or 4-nitrophenol, and dermal exposure to 4-nitrophenol. Based on a systematic evaluation of the literature, body weight effects are not classifiable as a health effect of oral exposure to 4-nitrophenol. The full results of the systematic review are presented in Appendix C.

Decreased body weight gains of unspecified magnitudes were reported in rats following exposure to 4-nitrophenol at concentrations ≥1,304 mg/m^3 for 4 hours or intermittent exposure to ≥294 mg/m^3 for 2 weeks (Smith et al. 1988). In a second 2-week inhalation study with 4-nitrophenol, Smith et al. (1988) observed lower than expected body weight gains in both control and exposed rats (up to 112 mg/m^3). The study authors attributed the low body weight gain to stress associated with handling. Due to lack of quantitative data reported as well as potential stress-related body weight effects, NOAEL and LOAEL calls for body weight could not be determined for this study. In intermediate-duration inhalation studies, no exposure-related changes in body weight were observed in rats intermittently exposed to 2-nitrophenol at concentrations up to 61.5 mg/m^3 (Hazleton 1984) or 4-nitrophenol at concentrations up to 29.18 mg/m^3 (Hazleton 1983).

Evidence for body weight effects following acute-duration oral exposure to nitrophenols is mixed. No body weight effects were noted in rats exposed once to 4-nitrophenol via gavage at doses up to 1,000 mg/kg (Abu-Qare et al. 2000; Kavlock 1990; Li et al. 2017; Tang et al. 2016). One study reported

a transient 25% decrease in body weights of male rats exposed to 200 mg/kg/day of 4-nitrophenol via gavage for 3 days (body weights were comparable to control after a 3-day recovery period) (Li et al. 2017; Tang et al. 2016). However, Koizumi et al. (2001) did not observe exposure-related changes in body weights in male or female rats exposed to 200 mg/kg/day of 4-nitrophenol via gavage for 14 days. In pregnant rats, a 12% decrease in maternal body weights was observed in dams exposed to 27.6 mg/kg/day of 4-nitrophenol via gavage on GDs 6–16 (EPA 1992a). However, no exposure-related changes in maternal body weights were observed in rat dams exposed to 2-nitrophenol via gavage at doses up to 1,000 mg/kg/day on GDs 6–15. In mice, an 18% decrease in maternal body weight gain was observed following exposure to 400 mg/kg/day of 4-nitrophenol via gavage for 8 days on GDs 7–14; however, no exposure-related changes in body weight were observed in nonpregnant mice similarly exposed for 8 days to doses up to 1,000 mg/kg/day (Plasterer et al. 1985).

Intermediate-duration exposure to 4-nitrophenol showed no body weight effects in rats following gavage exposure to doses up to 1,000 mg/kg/day for 28 days (Koizumi et al. 2001) or 140 mg/kg/day for 13 weeks (Hazleton 1989).

In a 2-generation dermal study in rats, no body weight effects were reported in F0 or F1 rats exposed intermittently to 4-nitrophenol doses up to 250 mg/kg/day for 20–24 weeks per generation (U.S. Army 1985). Similarly, no body weight effects were observed in Swiss-Webster mice exposed intermittently to dermal applications of 4-nitrophenol at doses up to 160 mg/kg/day for 78 weeks (NTP 1993).

2.4 RESPIRATORY

No studies were identified regarding respiratory effects in humans after exposure to 2-, 3-, or 4-nitrophenol. In animals, respiratory toxicity was evaluated in a single inhalation study of exposure to 2-nitrophenol and inhalation, oral, and dermal studies of exposure to 4-nitrophenol. The upper respiratory tract (nasal tissue) appears to be a sensitive target of inhalation exposure to 2-nitrophenol in rats; however, since data are limited to a single study, a systematic review could not be conducted for respiratory effects following inhalation exposure to 2-nitrophenol. Respiratory effects were only noted following 4-nitrophenol exposure to oral doses associated with mortality.

In the only inhalation study evaluating 2-nitrophenol, rats intermittently exposed for 4 weeks showed squamous metaplasia of the nasal epithelium of 10/10 males and 9/10 females exposed to 32.5 mg/m^3 and 10/10 males and 10/10 females at 61.5 mg/m^3 (Hazleton 1984). Incidence of this lesions was 1/sex in

control animals and 0/10 males and 1/10 females at 5 mg/m^3. No exposure-related changes in lung weight or histology were observed at concentrations up to 61.4 mg/m^3, and no clinical signs of respiratory distress were noted.

In inhalation studies evaluating 4-nitrophenol, no clinical signs of respiratory distress or adverse changes in lung weight or histology were observed in rats intermittently exposed to concentrations up to 2,133 mg/m^3 for 2 weeks (Smith et al. 1988) or 29.18 mg/m^3 for 4 weeks (Hazleton 1983). Additionally, no exposure-related lesions were observed in nasal tissues of rats intermittently exposed to 29.18 mg/m^3 for 4 weeks (Hazleton 1983).

As discussed in Section 2.2 (Death), clinical signs of respiratory distress were often reported prior to death following exposure to lethal oral doses of 4-nitrophenol. Dyspnea was reported in rats exposed once to gavage doses ≥171 mg/kg (Branch et al. 1983b). In intermediate-duration gavage studies, Koizumi et al. (2001) reported oligpnea (shallow or slow breathing) in rats exposed to 1,000 mg/kg/day for up to 28 days and Hazleton (1989) reported dyspnea and wheezing prior to death in rats exposed to 140 mg/kg/day for up to 13 weeks. No clinical signs of respiratory distress were noted at nonlethal doses, and no exposure related changes in lung weight or histology were noted in the intermediate-duration gavage studies (not evaluated in the acute-duration gavage study).

In a chronic-duration dermal study, no histopathological findings were observed in the nose or lungs of mice following exposure to 4-nitrophenol for 78 weeks (3 days/week) at doses up to 160 mg/kg/day (NTP, 1993).

Intraperitoneal injection of nitrophenols in rats has shown a potential to alter respiration (Cameron 1958; Grant 1959). Rats were injected with 667 mg/kg of 2-nitrophenol, 250 mg/kg of 3-nitrophenol, 78 mg/kg of 4-nitrophenol, or saline control. Following injection, respiration rates were increased by 24% in the 3-nitrophenol group and 31% in the 2-nitrophenol group, compared to baseline; 4-nitrophenol respiration rate increase was comparable to saline control (2%) (Grant 1959). Oxygen consumption was decreased by 3-nitrophenol only, and 4-nitrophenol increased rate of carbon dioxide output (Cameron 1958).

2.5 CARDIOVASCULAR

No studies were identified regarding cardiovascular effects in humans after exposure to 2-, 3-, or 4-nitrophenol. In animals, no studies evaluated cardiovascular function; however, a limited number of

studies evaluated heart weight and/or histology following inhalation exposure to 2-nitrophenol and inhalation, oral, or dermal exposure to 4-nitrophenol. Based on available data, the heart does not appear to be a sensitive toxicity target of nitrophenols in animals.

No exposure-related changes in heart weight or histology were observed in rats after intermittent exposure to 2-nitrophenol concentrations up to 61.5 mg/m^3 (Hazleton 1984). In inhalation studies evaluating 4-nitrophenol, no exposure-related changes in heart weight or histology were observed in rats following intermittent exposure to concentrations up to 2,133 mg/m^3 (Smith et al. 1988) or 29.18 mg/m^3 for 4 weeks (Hazleton 1983).

Oral and dermal studies also did not observe exposure-related changes in heart weight or histology in rats exposed to 4-nitrophenol at doses up to 1,000 mg/kg/day via gavage for 28 days (Koizumi et al. 2001), 140 mg/kg/day via gavage for 13 weeks (Hazleton 1989), or 250 mg/kg/day via dermal application for 20–24 weeks (U.S. Army 1985). In mice, no exposure-related changes in heart weight or histology were observed following dermal exposure to 4-nitrophenol at doses up to 160 mg/kg/day for 78 weeks (NTP 1993).

2.6 GASTROINTESTINAL

No studies were identified regarding gastrointestinal effects in humans after exposure to 2-, 3-, or 4-nitrophenol. In animals, a limited number of studies evaluated the gastrointestinal system following inhalation exposure to 2-nitrophenol and inhalation, oral, or dermal exposure to 4-nitrophenol.

Based on limited data, the gastrointestinal system does not appear to be a sensitive toxicity target of nitrophenols following inhalation exposure. No histopathological changes to the gastrointestinal system were observed in rats after intermediate-duration inhalation exposure to 2-nitrophenol at concentrations up to 61.5 mg/m^3 (Hazleton 1984). Similarly, inhalation exposure to 4-nitrophenol as not associated with histopathological changes in the gastrointestinal system in rats following acute-duration exposure to concentrations up to 2,133 mg/m^3 (Smith et al. 1988) or intermediate-duration exposure concentrations up to 29.18 mg/m^3 (Hazleton 1983).

There is limited evidence suggesting possible gastrointestinal effects after acute oral exposure to 4-nitrophenol. Tang et al. (2016) qualitatively described damage to the small intestine of male Wistar rats following gavage exposure to 200 mg/kg/day for 1 or 3 days, including loss of mucosal goblet cells and

necrosis and desquamation of intestinal epithelial cells. This finding did not persist after a 3-day recovery period; no other tissues of the gastrointestinal tract were evaluated. However, in longer-duration gavage studies, no histopathological changes were noted in the gastrointestinal tract of Sprague-Dawley rats at doses up to 1,000 mg/kg/day for 28 days (Koizumi et al. 2001) or up to 140 mg/kg/day for 13 weeks (Hazleton 1989). The reason for this inconsistency with acute data is unclear; however, differences in strain susceptibility may have contributed to conflicting findings.

In the only dermal study evaluating the gastrointestinal system, no exposure-related lesions were observed in mice intermittently exposed to doses up to 160 mg/kg/day for 78 weeks (NTP 1993).

2.7 HEMATOLOGICAL

No studies were identified regarding hematological effects in humans after exposure to 2-, 3-, or 4-nitrophenol. In animals, a limited number of studies evaluated hematological indices following inhalation exposure to 2- or 4-nitrophenol and oral exposure to 4-nitrophenol. Based on a systematic evaluation of the literature, hematological effects are not classifiable as health effects following inhalation exposure to 4-nitrophenol. The full results of the systematic review are presented in Appendix C.

Acute inhalation studies indicate that exposure to 4-nitrophenol may be associated with methemoglobinemia. In a 2-week study with 4-nitrophenol, methemoglobin levels were increased in male rats exposed to 294 mg/m^3 (0.87%) and 2,133 mg/m^3 (1.53%), compared to the control value of 0.2% (Smith et al. 1988). The study authors also noted qualitatively that increased methemoglobinemia was accompanied by the darker urine and proteinuria. When Smith et al. (1988) repeated the experiment with lower concentrations, methemoglobin levels were increased at 112 mg/m^3 (1.5%) compared to control (0.5%); methemoglobin levels at 26 mg/m^3 (0.3%) were comparable to control. After a 14-day recovery period, methemoglobin levels remained elevated at 2,133 mg/m^3 only. In a 4-hour acute lethality study, methemoglobin levels were measured in two rats exposed to 1,304 mg/m^3 (Smith et al. 1988). At the end of the 14-day observation period, methemoglobin levels were reported as “normal;” however, limited conclusions can be drawn from this due to lack of control animals, small animal numbers, and measurement only at the end of the observation period.

There is no clear evidence for methemoglobinemia in rats following intermediate-duration exposure to nitrophenols. In a 4-week inhalation study in rats exposed to 2-nitrophenol, elevated methemoglobin levels (2.32% in males and 4.08% in females) were only observed at the lowest exposure level (5 mg/m^3)

at the interim blood draw on day 15; control values on day 15 were 1.00% in males and 1.99% in females (Hazleton 1984). At the end of the 4-week exposure, methemoglobin levels in rats were comparable to control at concentrations up to 61.5 mg/m^3. A similar non-monotonic trend was observed in male rats exposed to 4-nitrophenol for 4 weeks, which showed increased methemoglobin levels (2.23%) at the mid-exposure levels of 5.27 mg/m^3, compared to control (0.77%), but not at the high-exposure level of 29.18 mg/m^3 (1.11%); methemoglobinemia was not observed in female rats at concentrations up to 29.18 mg/m^3 (Hazleton, 1983). Additionally, Hazleton (1983) tested rats in three separate "squads," and methemoglobin levels varied widely between squads. Due to lack of an exposure-response relationship in these studies, findings are considered spurious and non-adverse.

No adverse effects in other hematological parameters were noted in rats following inhalation exposure to 4-nitrophenol at acute-duration concentrations up to 2,133 mg/m^3 (Smith et al. 1988) or intermediate-duration concentrations up to 29.18 mg/m^3 (Hazleton, 1983). Similarly, no adverse effects in other hematological parameters were observed in rats exposed to 2-nitrophenol at inhalation concentrations up to 61.5 mg/m^3 (Hazleton 1984).

Data pertaining to hematological effects following oral exposure to 4-nitrophenol are limited but do not report any adverse changes in hematological indices in rats following a single gavage exposure to 100 mg/kg (Abu-Qare et al. 2000), gavage exposure to 200 mg/kg/day for 14 days (Koizumi et al. 2001), or gavage exposure to doses up to 140 mg/kg/day for 13 weeks (Hazleton 1989).

2.8 MUSCULOSKELETAL

No studies were identified regarding musculoskeletal effects in humans after exposure to 2-, 3-, or 4-nitrophenol. In animals, a limited number of studies evaluated the musculoskeletal system following inhalation exposure to 2-nitrophenol and inhalation, oral, and dermal exposure to 4-nitrophenol. Based on available data, the musculoskeletal system does not appear to be a toxicity target of nitrophenols in animals.

No histopathological changes in skeletal muscle or bone were observed in rats following a 4-week exposure to 2-nitrophenol at concentrations up to 61.5 mg/m^3 (Hazleton 1984) or 4-nitrophenol at concentrations up to 29.18 mg/m^3 (Hazleton 1983). Similarly, no histopathological changes in skeletal muscle or bone were observed in rats exposed to 4-nitrophenol via gavage doses up to 140 mg/kg/day for 13 weeks (Hazleton 1989) or dermal doses up to 160 mg/kg/day for 78 weeks (NTP 1993).

2.9 HEPATIC

No studies were identified regarding hepatotoxicity in humans after exposure to 2-, 3-, or 4-nitrophenol. In animals, the hepatic system was evaluated following inhalation exposure to 2-nitrophenol and inhalation, oral, and dermal exposure to 4-nitrophenol.

In inhalation studies, no adverse, exposure-related changes in liver clinical chemistry, liver weight, or histology were observed in rats following a 4-week exposure to 2-nitrophenol at concentrations up to 61.5 mg/m^3 (Hazleton 1984) or 4-nitrophenol at concentrations up to 29.18 mg/m^3 (Hazleton 1983).

There is limited evidence suggesting possible hepatic effects after acute-duration oral exposure to 4-nitrophenol. Li et al. (2017) qualitatively reported disordered hepatocytes and detachment of the central vein of the hepatic lobule in male Wistar rats following a single gavage exposure to 200 mg/kg. Similarly, disordered hepatocytes and a widened hepatic were qualitatively reported in male rats exposed to 200 mg/kg/day via gavage for 3 days (Li et al. 2017). Absolute and relative liver weights were decreased by 34 and 12%, respectively, after the 3-day exposure to 200 mg/kg/day (Li et al. 2017; Tang et al. 2016). Organ weight decreases and histopathological changes were transient, showing reversal following a 3-day recovery period. Li et al. (2017) proposed that hepatic effects were mediated via the aryl hydrocarbon receptor (AhR) signaling pathway. In support, a 36% increase in AhR levels were observed in the liver of Sprague-Dawley rats exposed to 100 mg/kg/day via subcutaneous injection for 28 days (Chen et al. 2016). The injection study also indicated that 4-nitrophenol exposure induces oxidative stress in the liver, based on elevated levels of superoxide dismutase and catalase. Other effects noted following exposure to 100 mg/kg/day via subcutaneous injection include histopathological changes (inflammatory cell infiltration, hepatocyte degeneration, and hepatic sinusoid damage) and mild elevations of alanine aminotransferase (ALT; 28%), aspartate aminotransferase (AST; 56%), and total bilirubin (56%). No changes in liver weight were observed.

In contrast to acute oral studies, no adverse effects on liver clinical chemistry, weight, or histology were observed in Sprague-Dawley rats exposed to 4-nitrophenol at gavage doses up to 1,000 mg/kg/day for 28 days (Koizumi et al. 2001) or up to 140 mg/kg/day for 13 weeks (Hazleton 1989). The reason for this inconsistency with acute data is unclear; however, differences in strain susceptibility may have contributed to conflicting findings,

In dermal studies, 4-nitrophenol exposure was not associated with adverse changes in liver weight or histology in rats at doses up to 250 mg/kg/day for 20–24 weeks (U.S. Army 1985) or in mice at doses up to 160 mg/kg/day for 78 weeks (NTP 1993).

2.10 RENAL

No studies were identified regarding renal effects in humans after exposure to 2-, 3-, or 4-nitrophenol. In animals, the renal system was evaluated following inhalation, oral, and dermal exposure to 4-nitrophenol and inhalation exposure to 2-nitrophenol. Based on available data, the renal system does not appear to be a sensitive toxicity target of nitrophenols in animals following inhalation or dermal exposure; findings following oral exposure are mixed.

No exposure-related changes in kidney serum biochemistry, weight, or histology were observed in rats intermittently exposed to 4-nitrophenol concentrations up to 2,133 mg/m^3 for 2 weeks (Smith et al. 1988), 4-nitrophenol concentrations up to 29.18 mg/m^3 for 4 weeks (Hazleton 1983), or 2-nitrophenol concentrations up to 61.5 mg/m^3 for 4 weeks (Hazleton 1984). A 38% decrease in urine volume was reported in rats exposed to 2,133 mg/m^3 for 2 weeks (Smith et al. 1988). The biological relevance of this finding in the absence of biochemical or histopathological changes in unclear. It could be secondary to decreased water intake since rats were lethargic at this exposure concentration; however, water consumption was not measured.

One acute oral study reported a 14% increase in relative kidney gland weight in rats exposed to 200 mg/kg/day via gavage for 3 days; however, this finding was considered secondary to a 25% decrease in body weight and therefore not adverse (Li et al. 2017; Tang et al. 2016). In support, both body weight and relative kidney weights were comparable to control after a 3-day recovery period. The same study authors did not observe an exposure-related change in kidney gland weight following a single exposure to 200 mg/kg. This study did not evaluate renal clinical chemistry or kidney histology following exposure, and no other acute-duration oral studies evaluated renal endpoints.

One intermediate-duration oral study reported eosinophilic bodies in the proximal renal tubular cells in Sprague-Dawley male rats, but not female rats, exposed to 4-nitrophenol at gavage doses ≥400 mg/kg/day for 28 days (Koizumi et al. 2001). The study authors concluded that the male-rat specific change in the kidney is due to α2u-globulin formation, which is not relevant to humans. However, human relevance cannot be ruled out based on the available analysis, which did not evaluate kidneys for α2u-globulin

accumulation or report hyaline droplet formation or other aspects of the established pathological sequence associated with α2u-globulin nephropathy (e.g., single cell necrosis, sloughing of epithelial cells into the proximal tubule, formation of granular casts, linear mineralization of the papilla, or tubule hyperplasia or regeneration; as established by EPA [1991]). Koizumi et al. (2001) did not observe any exposure-related changes in renal clinical chemistry or kidney weight following exposure to doses up to 1,000 mg/kg/day. In another intermediate-duration oral study evaluating 4-nitrophenol, no exposure-related changes in kidney serum biochemistry, weight, or histology were observed in male or female Sprague-Dawley rats at gavage doses up to 140 mg/kg/day for 13 weeks (Hazleton 1989).

In a 2-generation dermal studies, no exposure-related changed in kidney weight or histology were observed in F0 or F1 rats exposed to 4-nitrophenol at doses up to 250 mg/kg/day for 20–24 weeks per generation (U.S. Army 1985). Similarly, no exposure-related renal lesions were observed mice exposed to 4-nitrophenol at dermal doses up to 160 mg/kg/day for 78 weeks (NTP 1993).

2.11 DERMAL

No studies were identified regarding dermal effects in humans after exposure to 2-, 3-, or 4-nitrophenol. In animals, dermal effects were evaluated following inhalation exposure to 2-nitrophenol and inhalation, oral, and dermal exposure to 4-nitrophenol.

The skin is not a target of nitrophenol toxicity following inhalation or oral exposure. No dermatological or histopathological skin changes were observed in rats after intermittent exposure to 2-nitrophenol concentrations up to 61.5 mg/m^3 for 4 weeks (Hazleton 1984) or intermittent exposure to 4-nitrophenol concentrations up to 2,133 mg/m^3 for 2 weeks (Smith et al. 1988) or 29.18 mg/m^3 for 4 weeks (Hazleton 1983). Similarly, no dermatological or histopathological skin changes were observed in rats exposed to 4-nitrophenol via gavage for 13 weeks (Hazleton 1989).

Acute dermal exposure to 4-nitrophenol in rabbits is associated with skin irritation. Erythema and edema were reported in rabbits exposed to 148 mg/kg for 4 hours or 5,000 mg/kg for 24 hours (Branch et al. 1983a; Monsanto 1984); additional effects noted at 5,000 mg/kg included a dark brown discoloration of the dermal tissue, sloughing and scarring of the skin, hardening of the skin of the exposed area, and epidermal desquamation. Another study reported skin scabbing and scarring in rabbits exposed to 184 mg/kg for 24 hours (Monsanto 1983b).

In rats, repeated dermal application of ≥50 mg/kg/day in a 2-generation study (20–24 weeks, 5 days/week) resulted in skin irritation (erythema, scaling, scabbing, cracking) and histopathological changes in the skin (chronic inflammation, acanthosis, eschar, sebaceous hypertrophy) in F0 and F1 rats (U.S. Army 1985). However, no dermal effects were observed in mice following dermal application of 4-nitrophenol for 78 weeks (3 days/week) at doses up to 160 mg/kg/day (NTP 1993).

2.12 OCULAR

No studies were identified regarding ocular effects in humans after exposure to 2-, 3-, or 4-nitrophenol. In animals, ocular effects were evaluated following inhalation, oral, and direct ocular exposure to 4-nitrophenol and inhalation exposure to 2-nitrophenol. Based on a systematic evaluation of the literature, ocular effects are a suspected health effect of exposure to 4-nitrophenol. The full results of the systematic review are presented in Appendix C.

Inhalation exposure to 4-nitrophenol has been associated with ocular effects in rats. Transient corneal opacity was observed in 4/6 rats following a single 4-hour exposure to 4,059 mg/m^3; the effect persisted in one rat throughout a 14-day observation period (Smith et al. 1988). No clinical evidence of ocular effects or histopathological changes in the eye were observed after a 4-hour exposure to 1,304 mg/m^3 or repeated exposure (6 hours/day, 5 days/week) for 2 weeks at concentrations up to 2,133 mg/m^3 (Smith et al. 1988). Intermittent exposure for 4 weeks resulted in an increased incidence of unilateral and bilateral diffused anterior capsular cataracts in male rats at 29.18 mg/m^3 (6/15), compared to 1/15 control male rats (Hazleton 1983). While 6/15 female rats at 29.18 mg/m^3 also had cataracts, incidence was not significantly increased over control female incidence (4/15). Cataracts are likely to have been caused by direct ocular contact with 4-nitrophenol dust; however, a systemic effect cannot be totally excluded in the absence of mechanistic data.

No exposure-related changes ophthalmology or eye histology were observed in rats intermittently exposed to 2-nitrophenol via inhalation at concentrations up to 61.5 mg/m^3 (Hazleton 1984) or in rats exposed to 4-nitrophenol at gavage doses up to 140 mg/kg/day for 13 weeks (Hazleton 1989). No histopathological changes in the eye were observed in mice following 4-nitrophenol exposure to dermal doses up to 160 mg/kg/day for 78 weeks (NTP 1993).

Severe conjunctival irritation and blistering, moderate-to-severe corneal cloudiness, corneal neovascularization, and inflammation and visible destruction of the iris were observed in rabbits

following ocular instillation of 4-nitrophenol (as a granular solid) directly into the conjunctival sac at doses of 70–100 mg/kg (EPA 1992b; Monsanto 1983a). Findings were not reversible in most animals during the post-observation period of 7 days (EPA 1992b) or 31 days (Monsanto 1983a). EPA (1992b) classified 4-nitrophenol as a corrosive substance based on these results.

2.13 ENDOCRINE

No studies were identified regarding endocrine system effects in humans after exposure to 2-, 3-, or 4-nitrophenol. In animals, a limited number of studies evaluated the endocrine system following inhalation exposure to 2-nitrophenol and inhalation, oral, and dermal exposure to 4-nitrophenol. Based on available data, the endocrine system does not appear to be a sensitive toxicity target of nitrophenols in animals.

No histopathological changes were noted in the thyroid gland in rats intermittently exposed to 4-nitrophenol at inhalation concentrations up to 2,133 mg/m^3 for 2 weeks (Smith et al. 1988). In 4-week inhalation studies in rats, no exposure-related changes in organ weight or histology of the adrenal glands, thyroid, pituitary gland, or pancreas were observed following intermittent exposure to 2-nitrophenol at concentrations up to 61.5 mg/m^3 (Hazleton 1984) or 4-nitrophenol at concentrations up to 29.18 mg/m^3 (Hazleton 1983).

One acute oral study reported a 41% increase in relative adrenal gland weight in rats exposed to 200 mg/kg/day via gavage for 3 days; however, this finding was considered secondary to a 25% decrease in body weight and therefore not adverse (Li et al. 2017; Tang et al. 2016). In support, both body weight and relative adrenal weights were comparable to control after a 3-day recovery period. The same study authors did not observe an exposure-related change in adrenal gland weight following a single exposure to 200 mg/kg. In intermediate-duration oral studies, no exposure-related changes in organ weight or histology of the adrenal glands, thyroid, pituitary gland, or pancreas were observed in rats following gavage exposure to 4-nitrophenol at doses up to 1,000 mg/kg/day for 28 days (Koizumi et al. 2001) or 140 mg/kg/day for 13 weeks (Hazleton 1989).

In a chronic-duration dermal study, no exposure-related histopathological lesions were observed in the adrenal glands, thyroid, parathyroid, pituitary gland, or pancreas of mice following dermal application of doses up to 160 mg/kg/day for 78 weeks (NTP 1993).

2.14 IMMUNOLOGICAL

No studies were identified regarding immunotoxicity in humans after exposure to 2-, 3-, or 4-nitrophenol. In animals, a limited number of studies evaluated immune system organs following inhalation, oral, and dermal exposure to 4-nitrophenol and inhalation exposure to 2-nitrophenol. Based on available data, the immune system does not appear to be a sensitive toxicity target of nitrophenols in animals; however, none of the identified animal studies evaluated functional immune endpoints.

Absolute spleen weight was reportedly decreased in rats intermittently exposed to 4-nitrophenoal at an inhalation concentration of 2,133 mg/m^3 for 2 weeks; however, the toxicological relevance is uncertain due to unspecified magnitude of change and no associated histopathological changes (Smith et al. 1988). For other immune organs, no exposure-related changes were noted in thymus weight or histology or bone marrow histology at concentrations up to 2,133 mg/m^3 for 2 weeks (Smith et al. 1988). In 4-week inhalation studies in rats, no exposure-related changes were observed for spleen or thymus weight or spleen, thymus, bone marrow, or lymph node histology following intermittent exposure to 2-nitrophenol at concentrations up to 61.5 mg/m^3 (Hazleton 1984) or 4-nitrophenol at concentrations up to 29.18 mg/m^3 (Hazleton 1983).

In an acute-duration oral study, no exposure-related changes in spleen weight were observed following exposure to 4-nitrophenol at 200 mg/kg/day via gavage for 1 or 3 days; histology was not evaluated (Tang et al. 2016). In intermediate-duration oral studies, no exposure-related changes in spleen or thymus weight or spleen, thymus, bone marrow, or lymph node histology were observed in rats following gavage exposure to 4-nitrophenol at doses up to 1,000 mg/kg/day for 28 days (Koizumi et al. 2001) or 140 mg/kg/day for 13 weeks (Hazleton 1989).

In a chronic-duration dermal study, no exposure-related histopathological lesions were observed in the spleen, thymus, bone marrow, or lymph nodes of mice following dermal application of doses up to 160 mg/kg/day for 78 weeks (NTP 1993).

2.15 NEUROLOGICAL

No studies were identified regarding neurotoxicity in humans after exposure to 2-, 3-, or 4-nitrophenol. In animals, neurological effects were evaluated following inhalation, oral, and dermal exposure to 4-nitrophenol and inhalation exposure to 2-nitrophenol.

In an acute-duration inhalation study, lethargy was "sporadically" observed in rats during the second week of exposure to 4-nitrophenol at a concentration of 2,133 mg/m^3 4-nitrophenol (5 days/week); no clinical signs of neurotoxicity were observed at concentrations ≤294 mg/m^3 (Smith et al. 1988). No histopathological changes in the brain were observed. In 4-week inhalation studies in rats, no exposure-related changes in brain weight or histology were observed following intermittent exposure to 2-nitrophenol at concentrations up to 61.5 mg/m^3 (Hazleton 1984) or 4-nitrophenol at concentrations up to 29.18 mg/m^3 (Hazleton 1983).

As discussed in Section 2.2 (Death), clinical signs of neurotoxicity were often reported prior to death following exposure to lethal oral doses of 4-nitrophenol. Convulsions and prostration were observed following single gavage exposures to ≥268 mg/kg (Branch et al. 1983b). In intermediate-duration gavage studies, neurological effects noted prior to death included convulsions in neonatal rats exposed to ≥230 mg/kg/day on PNDs 4–21 (Koizumi et al. 2001); decreased locomotor activity, convulsions, and prostration in rats exposed to 1,000 mg/kg/day for up to 28 days (Koizumi et al. 2001); and prostration prior to death in rats exposed to 140 mg/kg/day for up to 13 weeks (Hazleton 1989). No clinical signs of neurotoxicity were noted at non-lethal doses in acute- or intermediate-duration oral studies.

No exposure-related changes in brain weight were noted in rats following a single gavage exposure to 100 mg/kg (Abu-Qare et al. 2000) and no exposure-related changes in brain weight or histology were observed in rats exposed to gavage doses up to 1,000 mg/kg/day for 28 days (Koizumi et al. 2001) or 140 mg/kg/day for 13 weeks (Hazleton 1989)

In dermal studies evaluating 4-nitrophenol, no exposure-related clinical signs of neurotoxicity were observed in adult F0 or F1 rats exposed to concentrations up to 250 mg/kg/day over two generations (20–24 weeks per generation) or in mice exposed to concentrations up to 160 mg/kg/day for 78 weeks (NTP 1993; U.S. Army 1985). A 15% decrease in relative brain weight was reported in adult F1 males at 250 mg/kg/day in the 2-generation study; however, this is considered secondary to a concurrent 11% increase in F1 male body weight (U.S. Army 1985). Brain weights in adult F0 males and females and adult F1 females were comparable to control at doses up to 250 mg/kg/day. No exposure-related changes in brain weight or histology were observed in the chronic-duration study in mice at doses up to 160 mg/kg/day (NTP 1993).

2.16 REPRODUCTIVE

No studies were identified regarding reproductive toxicity in humans after exposure to 2-, 3-, or 4-nitrophenol. In animals, the organs of the reproductive system were evaluated following inhalation and oral exposure to 2-nitrophenol and inhalation, oral, and dermal exposure to 4-nitrophenol. Female reproductive function was evaluated in oral and dermal studies, while male reproductive function was only evaluated in a dermal study. Available studies do not indicate that the reproductive system is a sensitive target of nitrophenol toxicity.

The only study identified evaluating both male and female reproductive function following exposure to 4-nitrophenol was a 2-generation dermal study in rats, which found no evidence of impaired reproductive function at doses up to 250 mg/kg/day (U.S. Army 1985). No exposure-related changes were observed in mating, fertility, gestation, or litter indices. Additionally, no exposure-related changes were observed in reproductive organ weight or histology.

Acute oral studies evaluated potential reproductive effects in rodent dams exposed to 2- or 4-nitrophenol during gestation. A 1.9-fold increase in post implantation loss was observed in rat dams exposed to 1,000 mg/kg/day of 2-nitrophenol via gavage from GDs 6–15 (Laughlin et al. 1983). Observed mean post implantation loss was 2.3±2.2 at 1,000 mg/kg/day, compared to 1.2±0.8 in concurrent controls. While this finding is not statistically significant due to high standard deviation and small animal number, the study authors concluded that observed post implantation losses may be biologically relevant since values were outside the upper range for historical controls. No changes in post implantation losses were observed at doses up to 500 mg/kg/day. In acute-duration gestational exposure studies evaluating 4-nitrophenol, no exposure-related changes in corpora lutea, implantations, implantation loss or resorption, or number of viable fetuses was observed at doses up to 100 mg/kg/day in rats (Abu-Qare et al. 2000; EPA 1992a) or 400 mg/kg/day in mice (Plasterer et al. 1985).

Other studies that evaluated weight and/or histology of male and female reproductive organs, but not reproductive function, did not identify the reproductive system as a toxicity target of nitrophenols. No exposure-related changes in testes weight or testes or epididymides histology were observed in in rats intermittently exposed to 4-nitrophenol at inhalation concentrations up to 2,133 mg/m^3 for 2 weeks (Smith et al. 1988). In 4-week inhalation studies in rats, no exposure-related changes in the weight or histology of male or female reproductive organs were observed following intermittent exposure to 2-nitrophenol at concentrations up to 61.5 mg/m^3 (Hazleton 1984) or 4-nitrophenol at concentrations up to 29.18 mg/m^3

(Hazleton 1983). Similarly, no exposure-related changes in male or female reproductive organ weight or histology were observed in rats exposed to 4-nitrophenol at gavage doses up to 1,000 mg/kg/day for 28 days (Koizumi et al. 2001) or 140 mg/kg/day for 13 weeks (Hazleton 1989). One acute oral study also reported a lack of exposure-related changes in testes weight in rats exposed to a 4-nitrophenol dose of 200 mg/kg/day for 1 or 3 days (Tang et al. 2016). Mice exposed to 4-nitrophenol at dermal doses up to 160 mg/kg/day for 78 weeks also showed no evidence of histopathological changes in male or female reproductive organs (NTP 1993).

Although inhalation, oral, and dermal exposure data do not indicate that the reproductive system is a sensitive target of nitrophenol toxicity, 4-nitrophenol has been shown to alter reproductive endpoints after parenteral exposure in male rodents. Reported effects include increased serum testosterone, decreased serum estradiol, and hyperplasia of Leydig cells in the testes of rats following daily subcutaneous injections of 10 mg/kg/day for 4 weeks (Zhang et al. 2013); decreased serum testosterone and sperm count in rats following daily subcutaneous injections of 100 mg/kg/day for 4 weeks (Zhang et al. 2015); and severe damage to the seminiferous tubules in mice exposed to 4-nitrophenol via weekly intraperitoneal injections of 50 mg/kg/day for 6 weeks (Mi et al. 2013). These changes were associated with altered expression of estrogen receptors (ERs; increased ERα and decreased ERβ) in rats (Zhang et al. 2013) and elevated markers of oxidative stress in rats and mice (Mi et al. 2013; Zhang et al. 2015). Markers of oxidative stress were also elevated in rat testes following a single intratesticular injection of 3 mg/kg of 4-nitrophenol (Zhang et al. 2016). In cultured testicular somatic cells from mice, no evidence of oxidative stress was observed following exposure to 4-nitrophenol; however, decreased cell proliferation, increased apoptosis, and altered cell cycles were observed (Wei et al. 2021). Given the lack of corroborating evidence of these observed reproductive outcomes in studies using the oral, inhalation, and dermal routes of exposure, the human relevance of male reproductive toxicity following parenteral exposure are unclear.

2.17 DEVELOPMENTAL

No studies were identified regarding developmental toxicity in humans after exposure to 2-, 3-, or 4-nitrophenol. In animals, a limited number of studies evaluated developmental effects following oral and dermal exposure to 4-nitrophenol.

The available literature on acute oral exposure to 4-nitrophenol has not identified any associations with developmental effects following gestational exposure. The only comprehensive teratology study

identified did not observe exposure-related changes in litter parameters, fetal body weight, or fetal variations or malformations were observed in rats following maternal exposure to doses up to 27.6 mg/kg/day from GDs 6–16 (EPA 1992a). Other developmental studies did not observe exposure-related effects on offspring weight or gross examination in rats following single maternal exposures up to 1,000 mg/kg (Abu-Qare et al. 2000; Kavlock 1990) or in mice following maternal exposure to doses up to 400 mg/kg/day on GDs 7–14 (Plasterer et al. 1985). While Kavlock (1990) classified 4-nitrophenol as an active developmental toxicant based on a >10% reduction in litter biomass following maternal exposure to gavage doses ≥667 mg/kg on GD 11, the reported statistical analysis in this study do not support this conclusion.

One oral study evaluated growth and development in rats following neonatal exposure to 4-nitrophenol at gavage doses up to 160 mg/kg/day on PNDs 4–21 (Koizumi et al. 2001). Some rats were sacrificed immediately after exposure, while others were maintained (without further exposure) until 12 weeks of age to evaluate sexual development. No exposure-related changes in general behavior, body weight, reflex ontogeny, developmental landmarks, hematology, clinical chemistry, gross necropsy, organ weight or histology, or timing of puberty (preputial separation or vaginal opening) were observed. In a dose-range-finding study using the same dosing schedule, increased mortality and convulsions were observed during the neonatal exposure period at ≥230 mg/kg/day (Koizumi et al. 2001).

No developmental effects in F1 or F2 offspring were observed in a 2-generation dermal study in rats at doses of 4-nitrophenol up to 250 mg/kg/day for 20–24 weeks per generation (U.S. Army 1985). Survivability from birth to weaning was effectively 100% for rat pups in all dosage groups in both the F1 and F2 generations, and all F2 pups that had not been directly dosed with 4-nitrophenol were normal in appearance, behavior, and growth (U.S. Army 1985).

Although oral and dermal exposure data do not indicate that the developing rodent is a sensitive target of nitrophenol toxicity, subcutaneous exposure to 4-nitrophenol has been shown to alter reproductive development in female rats and exhibit anti-androgenic and estrogenic activities in male and female rats following exposure prior to puberty. A single subcutaneous injection of 4-nitrophenol at 10 mg/kg in female neonatal rats on PND 0 resulted in an increase in the ratio of primordial and primary follicles in female rats at PNDs 14 and 21, an increase in serum estradiol and luteinizing hormone (LH) at PND 14 (but not PND 7 or PND 21), a decrease in ERβ expression in the ovaries on PND 7 and PND 14, and a 2–3-day delay in vaginal opening (Zhang et al. 2017). In prepubertal ovariectomized rats, exposure to ≥10 mg/kg/day via subcutaneous injections on PNDs 25–31 increased uterine weights; no changes in

serum follicle-stimulating hormone (FSH) or LH were observed at doses up to 100 mg/kg/day (Li et al. 2006). In prepubertal, testosterone-supplemented, castrated male rats, exposure to 0.1 mg/kg/day via subcutaneous injections on PNDs 28–31 resulted in an increase in serum LH and FSH levels and a decrease in weights of androgen-dependent accessory sex glands (seminal vesicles, ventral prostate, glans penis, levator ani plus bulbocavernosus muscles). Given the lack of corroborating evidence for altered reproductive development in oral and dermal studies, the human relevance of developmental reproductive toxicity following subcutaneous injection are unclear.

2.18 CANCER

No studies were identified regarding cancer in humans after exposure to 2-, 3-, or 4-nitrophenol. Animal studies evaluating potential carcinogenicity of nitrophenols are limited to dermal studies evaluating rodents exposed to 2- or 4-nitrophenol.

There is only one study of complete carcinogenicity of 4-nitrophenol (NTP 1993). In this study, a comprehensive histopathological examination did not show any exposure-related increases in malignant or benign neoplasms in mice at dermal doses up to 160 mg/kg/day, 3 times/week for 78 weeks. When benign and malignant neoplasms was combined, the overall incidence was elevated in male mice exposed to 40 mg/kg/day (33/59) and 80 mg/kg/day (33/60), compared to control (20/56); however, the overall incidence of benign and malignant neoplasms combined at 160 mg/kg/day was comparable to control (20/57). NTP (1993) concluded that there was no evidence of carcinogenic activity in male or female Swiss-Webster mice exposed dermally to 4-nitrophenol doses up to 160 mg/kg/day.

A 2-generation study in rats indicated that exposure to 4-nitrophenol at doses up to 250 mg/kg/day for 20–24 weeks per generation did not result in an increase in grossly identified neoplasms; however, a comprehensive histopathological examination was not conducted (U.S. Army 1985).

In a series of initiation-promotion dermal studies, a 20% solution of 2- or 4-nitrophenol dissolved in dioxane was applied to the shaved skin of mice twice weekly for 12 weeks to evaluate potential tumor-promoting activity (Boutwell and Bosch 1959). No skin tumors were observed; however, the utility of this study is limited due to lack of a dioxane-only control and lack of evaluation following exposure to an initiating compound.

IRIS (2002), IARC (2022), and NTP (2021) have not evaluated the potential for 2-, 3-, or 4-nitrophenol to cause carcinogenicity in humans.

2.19 GENOTOXICITY

Available data generally indicate that 2-, 3-, and 4-nitrophenol are not mutagenic. Findings for clastogenicity and deoxyribonucleic acid (DNA) damage are mixed but suggest that nitrophenols may be clastogenic or interact directly with DNA under certain conditions.

2-Nitrophenol is not mutagenic in *Salmonella typhimurium* in the presence or absence of metabolic activation (Chiu et al. 1978; Dellarco and Prival 1989; Shimizu and Yano 1986; Suzuki et al. 1983) or in *Escherichia coli* in the absence of metabolic activation (Szybalski 1958). 2-Nitrophenol did not induce DNA damage in *Bacillus subtilis* (Shimizu and Yano 1986). However, in the *umu* test in *S. typhimurium,* one study reported that 2-nitrophenol was DNA damaging (Degirmenci et al. 2000) but a second study did not find evidence of DNA damage (Bonnefoy et al. 2012). No data were available regarding genotoxic properties of 2-nitrophenol in eukaryotic organisms. Results of *in vitro* genetic testing for 2-nitrophenol are presented in Table 2-4.

Table 2-4. Genotoxicity of 2-Nitrophenol *In Vitro*

Species (test system)	Endpoint	Results activation		Reference
		With	Without	
Prokaryotic organisms				
Salmonella typhimurium strains TA98, TA100	Gene mutation	NT	–	Chiu et al. 1978
S. typhimurium strains TA98, TA100	Gene mutation	–	–	Dellarco and Prival 1989
S. typhimurium strains TA98, TA1538, TA1537, TA100, TA1535	Gene mutation	–	–	Shimizu and Yano 1986
S. typhimurium strains TA98, TA100	Gene mutation	–	–	Suzuki et al. 1983
Escherichia coli strain sd-4-73	Gene mutation	NT	–	Szybalski 1958
S. typhimurium strain TA1535/pSK1002	DNA damage	–	–	Bonnefoy et al. 2012

Table 2-4. Genotoxicity of 2-Nitrophenol *In Vitro*

Species (test system)	Endpoint	Results activation		Reference
		With	Without	
S. typhimurium strain TA1535/pSK1002	DNA damage		+[a]	Degirmenci et al. 2000
Bacillus subtilis strains H17, M45	DNA damage	NT	–	Shimizu and Yano 1986

[a]Test was conducted with and without metabolic activation; however, the study authors did not indicate under which condition(s) 2-nitrophenol was positive for DNA damage.

+ = positive result; – = negative result; DNA = deoxyribonucleic acid; NT = not tested

3-Nitrophenol is not mutagenic in *S. typhimurium* in the presence or absence of metabolic activation (Haworth et al. 1983; Shimizu and Yano 1986; Suzuki et al. 1983) or in *E. coli* in the absence of metabolic activation (Szybalski 1958). 3-Nitrophenol induced DNA damage in *B. subtilis* (Shimizu and Yano 1986) and *S. typhimurium* (Degirmenci et al. 2000). No data were available regarding genotoxic properties of 3-nitrophenol in eukaryotic organisms. Results of *in vitro* genetic testing for 3-nitrophenol are presented in Table 2-5.

Table 2-5. Genotoxicity of 3-Nitrophenol *In Vitro*

Species (test system)	Endpoint	Results activation		Reference
		With	Without	
Prokaryotic organisms				
Salmonella typhimurium strains TA1535, 1537, TA98, TA100	Gene mutation	–	–	Haworth et al. 1983
S. typhimurium strains TA98, TA1538, TA1537, TA100, TA1535	Gene mutation	–	–	Shimizu and Yano 1986
S. typhimurium strains TA98, TA100	Gene mutation	–	–	Suzuki et al. 1983
Escherichia coli strain sd-4-73	Gene mutation	NT	–	Szybalski 1958
Bacillus subtilis strains H17, M45	DNA damage	NT	+	Shimizu and Yano 1986
S. typhimurium strain TA1535/pSK1002	DNA damage		+[a]	Degirmenci et al. 2000

[a]Test was conducted with and without metabolic activation; however, the study authors did not indicate under which condition(s) 3-nitrophenol was positive for DNA damage.

+ = positive result; – = negative result; DNA = deoxyribonucleic acid; NT = not tested

Results of *in vitro* and in vivo genetic testing for 4-nitrophenol are presented in Tables 2-6 and 2-7, respectively.

Table 2-6. Genotoxicity of 4-Nitrophenol *In Vitro*

Species (test system)	Endpoint	Results activation		Reference
		With	Without	
Prokaryotic organisms				
Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98, TA100	Gene mutation	–	(+) TA1535 – TA1537, TA1538, TA98, TA100	EPA 1990b
Salmonella typhimurium strains TA98, TA100	Gene mutation	–	–	Dellarco and Prival 1989
S. typhimurium strains TA1535, 1537, TA98, TA100	Gene mutation	–	–	Haworth et al. 1983
S. typhimurium strains TA100, TA1535, TA1537, TA98	Gene mutation	–	–	NTP 1993
S. typhimurium strains G46, TA1535, TA1000, C3076, TA1537, D3052, TA1538, TA98	Gene mutation	–	–	Probst et al. 1981
S. typhimurium strains TA98, TA1538, TA1537, TA100, TA1535	Gene mutation	–	–	Shimizu and Yano 1986
Salmonella typhimurium strains TA98, TA100)	Gene mutation	–	–	Suzuki et al. 1983
Escherichia coli strains WP2, WP2 uvrA	Gene mutation	–	–	Probst et al. 1981
Escherichia coli strain sd-4-73	Gene mutation	–	–	Szybalski 1958
E. coli strain K12 envA uvrB	Prophage induction	–	NT	Ho and Ho 1981
S. typhimurium strains TA1538, TA1978	DNA repair	NT	–	Rashid and Mumma 1986
E. coli K12 and WP2 strains	DNA repair	NT	–	Rashid and Mumma 1986
Bacillus subtilis strains H17, M45	DNA damage	NT	+	Shimizu and Yano 1986
Proteus mirabilis strains PG273, PG713	DNA damage	NT	(+)	Adler et al. 1976
Mammalian organisms				
Mouse L5178Y lymphoma TK +/– cells	Gene mutation	–	NT	Amacher and Turner 1982
Mouse L5178Y lymphoma TK +/– cells	Gene mutation	–	–	Oberly et al. 1984
Mouse L5178Y lymphoma TK +/– cells	Gene mutation	–	–	EPA 1990c

Table 2-6. Genotoxicity of 4-Nitrophenol *In Vitro*

Species (test system)	Endpoint	Results activation		Reference
		With	Without	
Chinese hamster ovary cells	Chromosomal aberrations	–	+	EPA 1990a
Chinese hamster ovary cells	Chromosomal aberrations	+	–	NTP 1993
Chinese hamster ovary cells	Sister chromatid exchanges	–	–	NTP 1993
Rat primary hepatocytes	Unscheduled DNA synthesis	NT	–	Probst et al. 1981
Chinese hamster ovary cells	Inhibition of DNA synthesis	NT	+	Garrett and Lewtas 1983
Chinese hamster ovary cells	DNA damage	–	–	Hartmann and Speit 1997

+ = positive result; – = negative result; (+) = weakly positive result; DNA = deoxyribonucleic acid; NT = not tested

Table 2-7. Genotoxicity of 4-Nitrophenol *In Vivo*

Species (test system)	Endpoint	Results	Reference
Mouse (s.c.)	Host-mediated mutations	–	Buselmaier et al. 1973
Drosophila melanogaster (inhalation)	Sex-linked recessive lethal mutations	–	NTP 1993
D. melanogaster (oral)	Sex-linked recessive lethal mutations	–	NTP 1993

– = negative results; s.c. = subcutaneous injection

In almost all *in vitro* studies identified, 4-nitrophenol was not mutagenic in the presence or absence of metabolic activation in *S. typhimurium* (Dellarco and Prival 1989; Haworth et al. 1983; NTP 1993; Probst et al. 1981; Shimizu and Yano 1986; Suzuki et al. 1983), in the absence of metabolic activation in *E. coli* (Szybalski 1958), or in the presence or absence of metabolic activation in mouse lymphoma cells (Amacher and Turner 1982; EPA 1990c; Oberly et al. 1984). One study reported weak mutagenic activity (2.7-fold increase in revertants) in *S. typhimurium* strain TA1535 in the presence of metabolic activation only; all other strains were negative (EPA 1990b). 4-Nitrophenol did not induce prophage in *E. coli* (Ho and Ho 1981). *In vivo*, 4-nitrophenol did not induce host-mediated mutations in mice following subcutaneous injection (Buselmaier et al. 1973) or sex-linked recessive mutations in *Drosophila melanogaster* following inhalation or dietary exposure (NTP 1993).

Findings regarding clastogenicity following *in vitro* exposure to 4-nitrophenol are mixed. Two studies reported increased chromosomal aberrations in Chinese hamster ovary (CHO) cells following exposure to 4-nitrophenol; however, EPA (1990a) reported induction without metabolic activation (but not with metabolic activation) and NTP (1993) reported induction with metabolic activation (but not without metabolic activation). Both studies utilized rat S9 as the metabolic activation system. No induction of sister chromatid exchanges was observed in CHO cells exposed to 4-nitrophenol (NTP 1993).

Findings regarding DNA damage and repair in bacteria and mammalian cells following *in vitro* exposure to 4-nitrophenol are also mixed. Shimizu and Yano (1986) reported induced DNA damage when tested in *B. subtilis* by the rec assay, and Adler et al. (1976) reported a weak (1.35-fold) increase in DNA damage in repair-deficient *Proteus mirabilis* strain, compared to wild-type strain. However, DNA repair was not induced in *S. typhimurium* or *E. coli* (Rashid and Mumma 1986). In mammalian cells, 4-nitrophenol did not induce unscheduled DNA synthesis in rat primary hepatocytes (Probst et al. 1981) or DNA damage in CHO cells (Hartmann and Speit 1997). However, Garrett and Lewtas (1983) reported a 97% inhibition of DNA synthesis in CHO cells exposed to 4-nitrophenol in the absence of cytotoxicity.

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

3.1 TOXICOKINETICS

Information on the toxicokinetics for nitrophenols is available from several animal studies and mostly focuses on 4-nitrophenol.

- Absorption of 4-nitrophenol following both dermal and oral exposure is rapid. For oral exposure, limited data indicate that the extent of oral absorption is 36%. The extent of dermal absorption appears to be species-dependent, ranging from 11% in dogs to ~70% in rats and pigs. No inhalation data are available.

- Upon absorption, 4-nitrophenol is widely distributed in the body after oral exposure. The highest distribution is to the gastrointestinal tract. 4-Nitrophenol is also found in the kidneys, liver, plasma, placenta, and maternal brain within 30 minutes of exposure. The levels steadily decrease across all tissues over a period of 24 hours. Dermal application of 4-nitrophenol in animals results in very minimal body burden of 4-nitrophenol. No inhalation data are available.

- Both 2- and 4-nitrophenol undergo metabolic transformation by hepatic and extrahepatic phase I and phase II metabolism. Phase I reactions mediated by cytochrome P450 include oxidation to form nitroquinone and 4-nitrocatechol, and reduction to yield 2- and 4-aminophenol for 2- and 4-nitrophenol, respectively. The resulting metabolites and the parent compounds undergo phase II biotransformation reactions, which include conjugation with glucuronic acid to form glucuronides, inorganic sulfates to form sulfates, and for 4-nitrophenol, glutathione to form mercapturic acid derivatives.

- 4-Nitrophenol is excreted rapidly in the urine following oral or dermal exposure, with very small amounts excreted in the feces; elimination half-life values were approximately 4 hours. Following oral exposure, the administered dose was excreted as 4% glucuronides, 8% sulfates, 11% hot-acid hydrolysates, 16% non-conjugated compounds, and 61% water-soluble metabolites. Characterization of metabolites following dermal exposure is limited but indicates that >50% of the excreted dose is the conjugate form.

3.1.1 Absorption

No studies were identified regarding the rate and extent of absorption in humans following exposure to nitrophenols via any route. In animals, available data on the rate and extent of absorption are limited to 4-nitrophenol following oral or dermal exposure.

4-Nitrophenol is rapidly absorbed in animals after oral exposure. Abu-Qare et al. (2000) observed that 36% of a single gavage dose of 4-nitrophenol in Sprague-Dawley rats was absorbed in the gastrointestinal tract after 30 minutes. The study authors attributed this absorption of an oral dose of 4-nitrophenol in the

gastrointestinal tract to the lipid solubility of the chemical's non-ionized form (Abu-Qare et al. 2000). Abu-Qare et al. (2000) also showed that metabolites detected in urine can be used as a proxy measure for absorption of 4-nitrophenol after oral exposure in animals. Other oral studies that measured metabolites in the excreta indicated absorption of 4-nitrophenol (Robinson et al. 1951a; Williams 1938). Single oral doses between 182 and 264 mg/kg resulted in detection of sulfate-conjugates of 4-nitrophenols in the urine of rabbits (Williams 1938). Robinson et al. (1951b) reported the excretion of nitro compounds and conjugates in the urine of rabbits after gavage doses of 2-nitrophenol (200–330 mg/kg), 3-nitrophenol (150–200 mg/kg), and 4-nitrophenol (150–200 mg/kg). Lawford et al. (1954) showed that in a monkey, oral absorption of 4-nitrophenol was rapid, since peak blood concentrations of the compound were achieved within minutes after a gavage dose of 20 mg/kg.

Dermal application of 4-nitrophenol in animals showed species-dependent absorption. In rabbits and dogs, 35 and 11%, respectively, of the total dose of ^{14}C-labeled 4-nitrophenol was recovered in the urine over a 7-day period following dermal exposure (U.S. Army 1983). The calculated absorption rate, determined by quantifying the radiolabeled 4-nitrophenol in the urine over 2 days, was 16% of the dose/day for 2 days in rabbits and 3% of the dose/day for 2 days in dogs. Thus, absorption was more extensive and more rapid in rabbits than in dogs. Unabsorbed 4-nitrophenol accounted for 53 and 86% of the applied dose in the rabbits and dogs, respectively (U.S. Army 1983). In rats, ~70% of an applied dose of ^{14}C-4-nitrophenol was recovered in the urine and feces within 120 hours of dermal exposure; nearly 30% of unabsorbed 4-nitrophenol was washed off of the skin 24 hours after dermal application (Hughes and Hall 1997).

In another study, 4-nitrophenol was topically applied to the shaved abdomen of female weanling pigs at a concentration of 300 µg (150 µg cold 4-nitrophenol + 150 µg ^{14}C4-nitrophenol) in 100 µL ethanol vehicle over a 7.5-cm^2 area, yielding a final concentration of 40 µg/cm^2 (Qiao et al. 2000). The skin was non-occlusively covered and 4-nitrophenol was left in place for 96 hours. Approximately 71% of the applied dose was absorbed. The reported topical bioavailability was 57%, the mean absorption time was 27.05 hours, and the absorption half-life was 18.75 hours (Qiao et al. 2000). Following a single dermal dose of 160 mg/kg 4-nitrophenol in male and female mice, the estimated absolute bioavailability was 21% in male mice and 19% in female mice, with a maximum plasma concentration occurring 1 hour after dosing for males and 2 hours after dosing for females (Eichenbaum et al. 2009).

3.1.2 Distribution

No studies were identified that quantitatively described distribution in humans following exposure to nitrophenols via any route. In animals, available data on the distribution are limited to 4-nitrophenol following oral or dermal exposure.

One study in rats evaluated measured tissue concentrations at various time points after a single oral dose of 100 mg/kg ^{14}C-labeled 4-nitrophenol in pregnant Sprague-Dawley rats (Abu-Qare et al. 2000). This study found that >50% of the radioactivity was recovered in the gastrointestinal tract 30 minutes after exposure, and that the highest tissue concentration of radioactivity 30 minutes after exposure was the kidney, followed by the liver with about half the concentration of the kidney, followed by the plasma with about a third the concentration of the kidney (Abu-Qare et al. 2000). Abu-Qare et al. (2000) also observed distribution of 4-nitrophenol into the tissue of the fetus, suggesting that 4-nitrophenol crosses the placental barrier after oral exposure in rats.

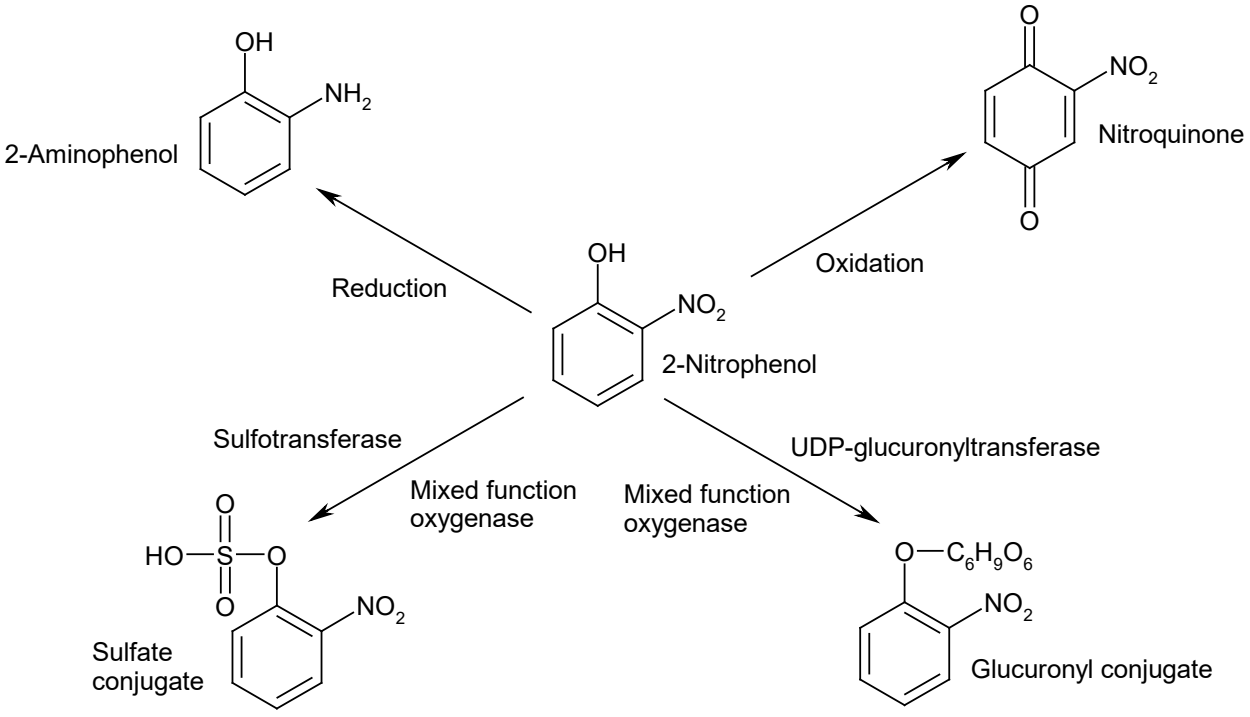
Studies indicate that 4-nitrophenol is minimally distributed in animals after dermal exposure. Following a dermal application of ^{14}C-4-nitrophenol, the body burden of 4-nitrophenol in rats measured 120 hours post-exposure was minimal (0.4%), with the majority of 4- nitrophenol being excreted via urine (63%) and feces (3%) during this time period (Hughes and Hall 1997). Similarly, only 2% of 4-nitrophenol was detected in the body of weanling piglets 96 hours after dermal exposure (Qiao et al. 2000).

Evidence suggests that there is also minimal body burden following intravenous or intraperitoneal exposure. Following intravenous exposure, <0.04% 4-nitrophenol remained in the body of female weanling piglets 96 hours after dosing (Qiao et al. 2000). Intravenous injection of ^{14}C-labeled 4-nitrophenol to rabbits (0.12 mg/kg) or dogs (0.06 mg/kg) resulted in undetectable levels of radioactivity in all major tissues and organs 7 days after treatment (U.S. Army 1983). Similarly, the body burden of 4-nitrophenol in rats after intraperitoneal administration was approximately 0.4% after 120 hours of exposure (Hughes and Hall 1997). Eichenbaum et al. (2009) reported a drastic drop in plasma concentration of 4-nitrophenol just 15 minutes after daily intravenous administration in male and female mice for 2 days; the study authors suggested that this is evidence of extensive distribution of 4-nitrophenol outside the plasma.

3.1.3 Metabolism

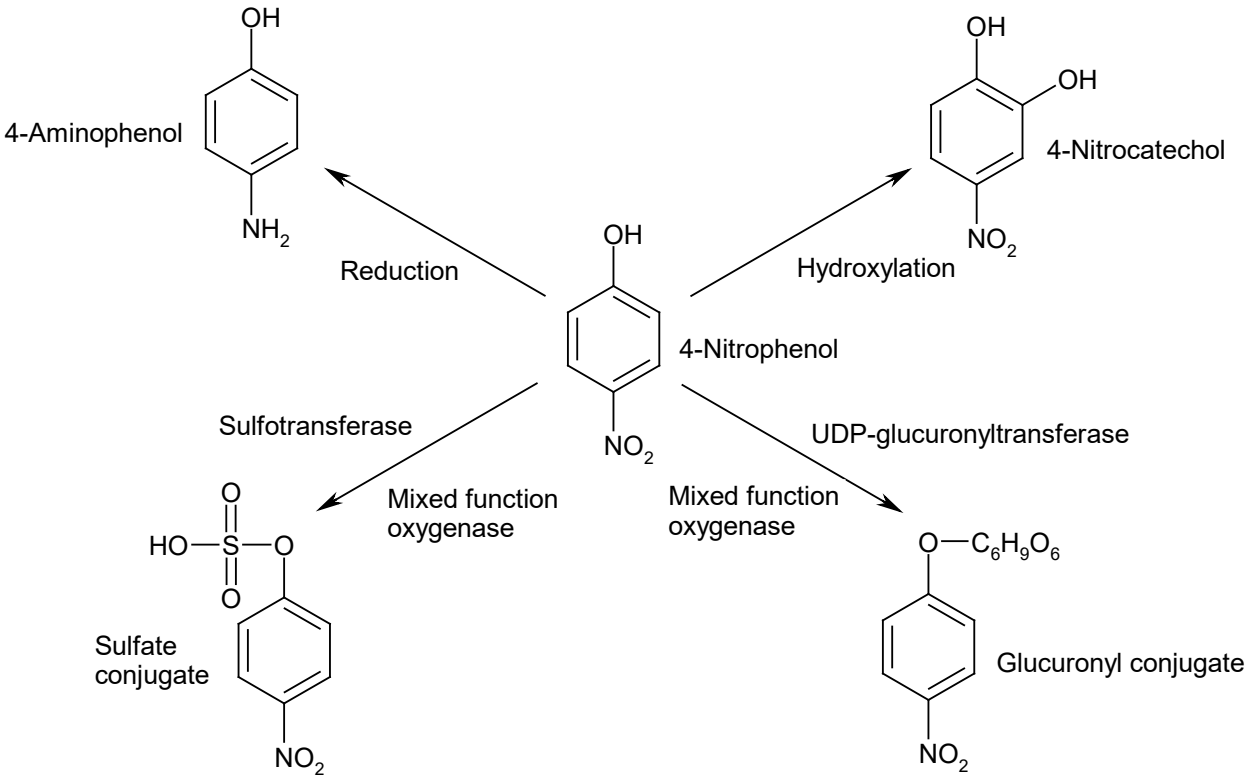
4-Nitrophenol is readily metabolized in the body. The primary metabolic pathway for 4-nitrophenol is conjugation with the formation of glucuronide or sulfate conjugates. Metabolism also occurs through reduction or oxidation. Figures 3-1 and 3-2 depict the metabolism pathway for 2- and 4- nitrophenol after oral administration in rats, respectively, as adapted from Robinson et al. (1951a). A metabolic pathway figure for the metabolism of 3-nitrophenol has not been identified but is expected to be similar to 2- and 4-nitrophenol. As metabolic information on nitrophenols comes exclusively from animal studies, some differences may be anticipated regarding how this information generalizes to metabolism pathways in humans.

Figure 3-1. Proposed Metabolic Pathway of 2-Nitrophenol Following Oral Administration in Rats



Source: Robinson et al. 1951a

Figure 3-2. Proposed Metabolic Pathway of 4-Nitrophenol Following Oral Administration in Rats



Source: Robinson et al. 1951a

No studies regarding metabolism in humans following exposure to nitrophenols were identified. Studies regarding metabolism in animals include a few studies evaluating 2-, 3-, and 4-nitrophenols after oral exposure and 4-nitrophenol after dermal exposure.

4-Nitrophenol is rapidly metabolized in animals after oral exposure. Robinson et al. (1951a) studied the metabolism of orally administered 2-, 3-, and 4-nitrophenol (200–330 mg/kg) in rabbits. In these rabbits, conjugation was almost complete, with 70% of the dose excreted in urine being in the form of nitrophenol glucuronides (Robinson et al. 1951a). Eighty percent of the nitro group of the nitrophenols was excreted in urine and unchanged; the rest underwent reduction ranging from 6 to 14% of the dose. Oxidation accounted for <1% of the dose. Figure 3-1 shows that 2-nitrophenol undergoes phase I metabolism by oxidation to form nitroquinone and reduction to form 2-aminophenol. The two metabolites and the parent compound undergo phase II metabolism through conjugation with glucuronic acid to from glucuronides and inorganic sulfates to form sulfates (Robinson et al. 1951a). Figure 3-2 shows that 4-nitrophenol undergoes metabolic transformation by hepatic and extrahepatic phase I and phase II metabolism

(Machida et al. 1982). Phase I reactions mediated by cytochrome P450 include oxidation to form 4-nitrocatechol and reduction to yield 4-aminophenol (Machida et al. 1982). The two polar metabolites and the parent compound undergo phase II biotransformation reaction, which includes conjugation with glucuronic acid to form glucuronides, sulfuric acid to form sulfates, and glutathione to form mercapturic acid derivatives (Machida et al. 1982). 4-Nitrophenol hydroxylation to 4-nitrocatechol is mediated by the CYP2E1 enzyme (Abu-Qare et al. 2000).

4-Nitrophenol is rapidly metabolized in dogs, rabbits, and pigs after dermal exposure. 4-Nitrophenol is metabolized by conjugation with glucuronic (60–80%) and sulfonic acid (10–20%) and reduction to aminophenols (10%); <1% of the dose is excreted unchanged as 4-nitrophenol (U.S. Army 1983). While the acid conjugates are excreted rapidly, reduction to aminophenols may take 48 hours (U.S. Army 1983). The observed absence of labeled ^{14}C-4-nitrophenol in tissue specimens after topical exposure in dogs and rabbits supports an efficient metabolic clearance (U.S. Army 1983). Qiao et al. (2000) reported a metabolic half-life of 27.15 hours in pigs for the formation of 4-nitrophenol-glucuronide from 4-nitrophenol, with a metabolic rate constant of 0.037 L/hour (Qiao et al. 2000).

Parenteral exposure to 4-nitrophenol showed rapid metabolism in animals. Intravenous administration of 4-nitrophenol showed that the glucuronide and sulfate conjugates could be detected in the plasma within 1 minute after the injection of doses between 1.6 and 8.0 mg/kg (Machida et al. 1982). Machida et al. (1982) also demonstrated that rat liver homogenates had the greatest amount of glucuronidation activity, followed by the kidney, lung, and small intestine homogenates, in decreasing order. Sulfation, however, was detected almost exclusively in the liver. No differences in conjugation mechanisms for 4-nitrophenol between male and female rats have been reported (Meerman et al. 1987).

3.1.4 Excretion

No studies regarding excretion in humans following exposure to nitrophenol were identified. Studies in animals are limited to studies evaluating excretion following oral or dermal exposure to 4-nitrophenol. Although the information is limited, bioaccumulation of 2-, 3-, and 4-nitrophenol in organisms is not expected to occur due to the rapid excretion of the more polar metabolites.

4-Nitrophenol is rapidly excreted in animals after oral exposure. 4-Nitrophenol was rapidly excreted after a single oral dose of 100 mg/kg in rats, with more than half of the dose excreted through urine and feces after only 4 hours, and >95% of the dose having been excreted after 96 hours (Abu-Qare et al. 2000).

This dose of 4-nitrophenol was excreted as 4% glucuronides, 8% sulfates, 11% hot-acid hydrolysates, 16% non-conjugated compounds, and 61% water-soluble metabolites (Abu-Qare et al. 2000). Single oral doses between 182 and 264 mg/kg in another study resulted in detection of sulfate-conjugates of 4-nitrophenol in the urine (Williams 1938). Robinson et al. (1951b) reported the excretion of nitro compounds and conjugates in the urine of rabbits after gavage doses of 2-nitrophenol (200–330 mg/kg), 3-nitrophenol (150–200 mg/kg), and 4-nitrophenol (150–200 mg/kg).

Excretion of ^{14}C-labeled 4-nitrophenol following dermal exposure was rapid in animals. In rabbits, 78% of the absorbed dose was recovered in urine obtained within 1 day of exposure and virtually complete elimination within 3 days (U.S. Army 1983). In dogs, 61% of the absorbed dose was recovered in urine obtained within 2 days of exposure, with virtually complete elimination within 5 days (U.S. Army 1983). Fecal elimination accounted for <1% of the applied dose in both species. In mice, the calculated elimination half-life values for 4-nitrophenol were 4.31 and 4.92 hours for male and female mice, respectively (Eichenbaum et al. 2009). In female weanling pigs, almost all of the administered 4-nitrophenol was recovered in the urine 96 hours following dermal administration (Qiao et al. 2000). More than half of the amount measured in urine was the conjugate form. As seen in rabbits and dogs, <1% of the dermal dose was recovered in the feces of pigs (Qiao et al. 2000).

Additional information regarding excretion can be found in intravenous injection studies. Within the first day after exposure in rabbits and dogs, 78 and 92%, respectively, of intravenously administered 4-nitrophenol was excreted (U.S. Army 1983). These results suggest a rapid excretion of 4-nitrophenol after intravenous exposure with little to no accumulation in the body. In mice, 4-nitrophenol was rapidly eliminated following a single intravenous dose of 25 mg/kg, with estimated half-life values of 1.09 and 0.687 hours in male and females, respectively (Eichenbaum et al. 2009). In female weanling pigs, approximately 90% of an intravenous dose was excreted in urine in the first 12 hours, with excretion half-lives for 4-nitrophenol and the conjugate of 0.84 and 0.86 hours, respectively (Qiao et al. 2000). The conjugate form comprised two-thirds of the total amount in urine and 4-nitrophenol comprised the other one-third (Qiao et al. 2000). As seen with dermal exposure, <1% of the administered dose was recovered in the feces (Qiao et al. 2000).

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 have been published for nitrophenols.

3.1.6 Animal-to-Human Extrapolations

The metabolism of nitrophenols has not been studied in humans. The lack of this information precludes a non-speculative attempt to discuss potential interspecies differences or similarities in the toxicity of nitrophenols, as well as a determination of which animal species is the most appropriate model for humans. Extrapolations of nitrophenols oral toxicity data from animals to humans should consider the type of exposure because some of the differences in toxic and carcinogenic responses in animal studies can be explained based on saturation of the detoxification/excretion mechanism due to bolus (gavage) administration.

While it is unclear if methemoglobinemia is a health effect associated with 4-nitrophenol exposure based on no data in humans and low evidence in animals (see Appendix C for details), it is noted that humans could be more sensitive to this potential effect since it is estimated that rats have 2–5 times as much methemoglobin reductase activity, which controls the amount of methemoglobin in blood, compared to humans (Bloom and Brandt 1999).

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. Susceptibility to health effects from exposure to hazardous substances may differ between children and adults, 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 nitrophenols are discussed in Section 5.7, Populations with Potentially High Exposures.

Human populations that have experienced health effects from exposure to 2-, 3-, or 4-nitrophenol have not been identified, as little research has been conducted on this subject. Based on results from a study of ethanol-treated rats, it is possible that individuals who consume ethanol may have slower rates of clearance of 4-nitrophenol due to the presence of ethanol causing rapid metabolization of 4-nitrophenol into 4-nitrocatechol, which competes with 4-nitrophenol for the formation of sulfate and glucuronide conjugates (Reinke and Moyer 1985). This subpopulation, if exposed to 4-nitrophenol, may be considered potentially susceptible (Reinke and Moyer 1985).

While there is low evidence of hematological effects in animal studies following exposure to nitrophenols, a few studies report methemoglobinemia. The underlying cause for methemoglobinemia is the oxidation of ferrous (Fe^{2+}) to ferric (Fe^{3+}) iron within the hemoglobin molecule creating the dysfunctional methemoglobin molecule (Price 2011). Cells have an innate mechanism to protect themselves from oxidative stress with the help of systems like cytochrome b reductase, nicotinamide adenine dinucleotide (NADH) methemoglobin reductase, nicotinamide adenine dinucleotide phosphate (NADPH) methemoglobin reductase, reduced glutathione, and ascorbic acid (Price 2011). Depletion of the reducing power of these systems could potentially lead to methemoglobinemia. Xenobiotics and pharmaceuticals that have nitrites or nitrates in them can potentially act as powerful oxidizing agents, as they actively convert ferric to ferrous ions resulting in oxidative stress, which can give rise to methemoglobinemia (Price 2011).

Methemoglobinemia can be hereditary or acquired. Hereditary reasons include a rare dominant disorder where glutamate replaces valine in position 67 on the beta chain of the hemoglobin molecule (Price 2011). This permanently increases the methemoglobin levels to 15–30% (Price 2011). People affected are cyanotic but do not exhibit any other symptoms (Stucke et al. 2006). Cytochrome b_5 reductase deficiency is another hereditary disorder that gives rise to methemoglobinemia. This is caused by an

enzymatic lesion associated with the glycolysis pathway in red blood cells and is associated with cyanosis from birth (Percy and Lappin 2008). In addition to being a genetic disorder, this enzyme does not fully activate until 4 months after birth even in genetically normal infants, leaving them more susceptible to oxidative stress and subsequently to methemoglobinemia than adults (Price 2011). Newborn infants utilize fetal hemoglobin until they are 2–4 months old and have reduced oxygen-carrying capacity (Schechter 2008). Infants also have low levels of NADPH, which continuously reduces methemoglobin. Therefore, infants (as well as individuals congenitally deficient in this enzyme), and potentially pregnant women and their fetuses, may represent unusually susceptible subpopulations, as there is some evidence to suggest that 4-nitrophenol crosses the placental barrier (Abu-Qare et al. 2000; Naoum 2012). However, more research is needed to determine if children are especially susceptible to the health effects of exposure to nitrophenols.

External factors including medications and exposure to xenobiotics also cause methemoglobinemia. Angina and other cardiac-related incidents that are commonly treated using nitrite-based medications cause methemoglobinemia and are reported as a complication of the therapeutic use of these drugs (Bojar et al. 1987; Marshall and Ecklund 1980). Self-administration of local anesthetic drugs like benzocaine have also been known to cause this condition, and especially in children (Nappe et al. 2015).

Dapsone, a commonly used anti-inflammatory for treating infections has severe side effects including methemoglobinemia; it is recommended that patients use pulse oximeter to monitor blood oxygen levels regularly (Ashurst et al. 2010; Mahmood et al. 2019; Toker et al. 2015). Drugs to treat malaria (quinines) also cause methemoglobinemia (Kudale et al. 2014). For methemoglobinemia due to drug exposure, traditional first-line therapy is generally infusion of methylene blue.

Exposure to xenobiotics like aniline, chlorobenzene, fires, organic nitrites, and nitrites and nitrates from well water and food, respectively, are all implicated in causing acquired methemoglobinemia. As discussed in Section 2.7, exposure to 4-nitrophenol by inhalation for 6 hours/day, 5 days/week for 2 weeks caused an in increase in methemoglobin by 665% after 10 days at 2,470 mg/m^3. After 14 days of recovery, erythrocytes, hemoglobin, and methemoglobin continued to be elevated by 7, 7.5, and 250%, respectively. One rat showed cyanosis after the first exposure. At a lower dose of 130 mg/m^3, the rats showed a 200% increase in methemoglobin compared to control after 10 exposures and returned to normal after a 14-day recovery period. These results suggest that inhalation exposure to 4-nitrophenol could exacerbate any increase in methemoglobin that would occur in the subpopulations described above that have existing hereditary or acquired methemoglobinemia.

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 nitrophenols 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 nitrophenols 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 nitrophenols 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 identified regarding levels of 2-, 3-, or 4-nitrophenol in human tissues, fluids, or excreta that were associated with exposure to nitrophenols. While the presence of 4-nitrophenol in the urine may be due to exposure to 4-nitrophenol itself, it may also be the result of exposure to other chemicals such as methyl parathion and nitrobenzene, of which 4-nitrophenol is a metabolite (Barr et al. 2002; EPA 2009a; Li and Kannan 2018; Li et al. 2019), confounding its use as a specific reliable biomarker of exposure.

Due to the rapid excretion of 2- and 4-nitrophenol conjugates in the urine, their use as biomarkers of exposure may be limited to recent exposures only. Based on the current body of literature, it is not known if urinary excretion of 2- or 4-nitrophenol (or their conjugates) can be associated quantitatively with exposure to these chemicals. National Health and Nutrition Examination Survey (NHANES) data identifies the levels of 4-nitrophenol in urine; however, this could be due to exposure to 4-nitrophenol itself or to a chemical that is metabolized to 4-nitrophenol.

Hair has been used as a biomarker of exposure to 4-nitrophenol that captures cumulative exposure over a longer period, but these levels could also be due to exposure to 4-nitrophenol or those for which 4-nitrophenol is a metabolite, and more research is needed to understand the correlation of hair measurements with serum or urine concentrations of 4-nitrophenol (Béranger et al. 2018).

As discussed in Section 3.1.3, the pathways to metabolize 2- or 4-nitrophenol have only been identified in rats. 2-Nitrophenol is metabolized to 2-aminophenol, nitroquinone, sulfate conjugates, and glucuronyl conjugate. 4-Nitrophenol is metabolized to 4-aminophenol, 4-nitrocatechol, sulfate conjugates, and glucuronyl conjugates. All of the identified metabolites could be potentially used to detect exposure to 2-and 4-nitrophenol; however, none of them have been used as such in the literature. Additionally, while identification of metabolites of 2- or 4-nitrophenol in human tissues, fluids, or excreta could reflect exposure to nitrophenols specifically, it could also reflect exposure to alternate parent compounds that metabolize via the same pathways (e.g., nitrobenzene, methyl parathion). There is no literature on metabolism of 3-nitrophenol or biomarkers that could be potentially used to indicate exposure.

3.3.2 Biomarkers of Effect

No biomarkers of effect that are specific to nitrophenols have been identified. Ocular effects, including cataracts, are suspected health effects of nitrophenol exposure; however, these findings are not unique to

nitrophenols. Evidence for other potential health effects, including methemoglobinemia and decreased body weight, is low and can also be observed following exposure to several different chemicals. More research is needed in this area to identify biomarkers of effect after exposure to nitrophenols.

3.4 INTERACTIONS WITH OTHER CHEMICALS

No studies were identified regarding interactions of 2-, 3-, and 4-nitrophenol with other chemicals *in vitro* or regarding interactions of 2-, 3-nitrophenol with other chemicals *in vivo*. There are *in vivo* studies that detail the interactions of 4-nitrophenol with other chemicals.

In ethanol-treated rats, 4-nitrophenol is rapidly metabolized to 4-nitrocatechol, which competes with 4-nitrophenol for the formation of sulfate and glucuronide conjugates (Reinke and Moyer 1985). This reduction in the conjugation of 4-nitrophenol may lead to the formation of amino derivatives.

The interaction between arginine, a feed additive, with antioxidant activities and parenteral (subcutaneous injections) exposure of 4-nitrophenol was investigated in Sprague-Dawley rats (Xu et al. 2016). The study showed that the changes in body weight and liver weight caused by 4-nitrophenol were significantly attenuated when treated with arginine orally (Xu et al. 2016). Additionally, the follicular deformation, irregularities in the granulosa arrangement and the increase in oxidative stress in female rat ovaries caused by parenteral exposure to 4-nitrophenol was ameliorated by arginine (Xu et al. 2016). Arginine is a known precursor to nitric oxide (Stuehr 2004) and nitric oxide is involved in the intracellular signaling to modulate folliculogenesis and atresia, steroidogenesis, prostaglandin biosynthesis, ovulation, luteolysis, and oocyte maturation (Hattori and Tabata 2006). A human study concluded that oral arginine supplementation resulted in some improvement in ovarian response, endometrial receptivity, and pregnancy rate in patients with follicular deficiencies (Battaglia et al. 1999). Based on this evidence, arginine may be able to mitigate potential effects of exposure to 4-nitrophenol in the ovarian tissues.

Another animal study, which subjected male ICR mice to parenteral (intraperitoneal injections) exposure to 4-nitrophenol, provides evidence that quercetin, a flavonoid, mitigates the effects of 4-nitrophenol on male reproduction (Mi et al. 2013). Quercetin is a polyphenolic compound that is present in foods of plant origin. The antioxidant properties of these flavonoids are crucial in the inhibitory role that they play in reducing reactive oxygen species (Hollman et al. 1996). The authors hypothesized that 4-nitrophenol produces toxicity in the reproductive system by causing lipid peroxidation and production of free radicals (Mi et al. 2013). This in turn causes increased oxidative stress and mitochondrial dysfunction resulting in

cell apoptosis (Mi et al. 2013). The study authors also implicated the role of endoplasmic reticulum in the response to reproductive toxicity (Mi et al. 2013). The disruption of protein folding in endoplasmic reticulum altered the homeostasis, thus changing the downstream signaling cascades (Wu and Kaufman 2006). 4-Nitrophenol causes oxidative stress in the target organ system; quercetin, with its antioxidant properties, helps assuage this condition. In the study by Mi et al. (2013), quercetin supplementation is shown to repair the damage to seminiferous tubule epithelium and restore the damaged antioxidant status to normal levels by acting on multiple endpoints including Bcl-x1, XBP-1, and HO-1. Quercetin is an antioxidant that has shown the potential to attenuate the possible reproductive effects of 4-nitrophenol (Mi et al. 2013).

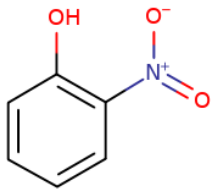
Chen et al. (2016) used phytosterol, a combination of plant sterols and stanols that are known to have antioxidant properties, to study its protective effects against 4-nitrophenol-induced effects in the liver using male Sprague-Dawley rats. In this study, oral phytosterol mitigated the hepatotoxicity caused by parenteral (subcutaneous injection) 4-nitrophenol suggesting that phytosterol has protective effects. This study continued to provide evidence to the mechanism through which 4-nitrophenol impaired normal physiology (i.e., it generated reactive oxygen species, increased oxidative stress, which led to peroxidation of lipids, and eventually led to membrane damage) (Chen et al. 2016).

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Nitrophenols (also referred to as mononitrophenols) exist in three isomeric forms: 2-nitrophenol (or ortho- or o-), 3-nitrophenol (or meta- or m-), and 4-nitrophenol (or para- or p-). All three of these nitrophenols are manmade. Table 4-1 lists common synonyms, trade names, and other pertinent identification information for 2-nitrophenol, Table 4-2 lists this information for 3-nitrophenol, and Table 4-3 lists this information for 4-nitrophenol.

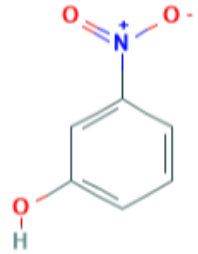
Table 4-1. Chemical Identity of 2-Nitrophenol

Characteristic	Information
Chemical Name	2-Nitrophenol
Synonym(s) and Registered trade name(s)	O-Hydroxynitrobenzene; 2-Hydroxynitrobenzene; o-Nitrophenol; Phenol, o-nitro-; Phenol, 2-nitro
Chemical formula	$C_6H_5NO_3$
Chemical structure	
CAS registry number	88-75-5

CAS = Chemical Abstracts Service

Source: NLM 2022a

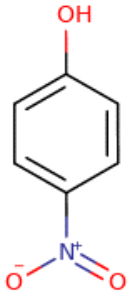
Table 4-2. Chemical Identity of 3-Nitrophenol

Characteristic	Information
Chemical Name	3-Nitrophenol
Synonym(s) and Registered trade name(s)	M-Hydroxynitrobenzene; 3-Hydroxynitrobenzene; m-Nitrophenol; Phenol, m-nitro-; Phenol, 3-nitro-;
Chemical formula	$C_6H_5NO_3$
Chemical structure	
CAS registry number	554-84-7

CAS = Chemical Abstracts Service

Source: NLM 2022b

Table 4-3. Chemical Identity of 4-Nitrophenol

Characteristic	Information
Chemical Name	4-Nitrophenol
Synonym(s) and Registered trade name(s)	P-Hydroxynitrobenzene; 4-Hydroxynitrobenzene; Niphen; P-Nitrophenol; Paranitrophenol; Phenol, p-nitro-; Phenol, 4-nitro-; PNP
Chemical formula	$C_6H_5NO_3$
Chemical structure	
CAS registry number	100-02-7

CAS = Chemical Abstracts Service

Source: NLM 2022c

4.2 PHYSICAL AND CHEMICAL PROPERTIES

2-Nitrophenol is a light yellow, aromatic solid; 3- and 4-nitrophenol are colorless to pale yellow solids. The nitrophenols are expected to be highly soluble in water. They also have low vapor pressures, and therefore, low potential for long range atmospheric transport (Harrison et al. 2005). Tables 4-4, 4-5, and 4-6. List important physical and chemical properties of 2-, 3-, and 4-nitrophenol, respectively.

Table 4-4. Physical and Chemical Properties of 2-Nitrophenol

Property	Information	Reference
Molecular weight	139.109	NLM 2022a
Color	Light yellow	O'Neil 2006
Physical state	Crystalline solid	NLM 2022a
Melting point	44–45°C	O'Neil 2006
Boiling point	216°C	Haynes et al. 2015
Density:	1.29 g/cm^3 at 40°C	Haynes et al. 2015
Odor	Aromatic	O'Neil 2006
Odor threshold: Water Air	 10 mg/L 8x10^{-11} moles/m^3	 Verschueren1983 Fazzalari 1978
Taste threshold	0.001 mg/L	Verschueren1983
Solubility: Water Organic solvent(s)	 2,100 mg/L at 20°C 2,500 mg/L at 25°C 10,800 mg/L at 100°C Very soluble in ethanol, ether, acetone, benzene, pyridine, chlorine; freely soluble in carbon sulfide, alkali hydroxides	 Verschueren 1983 Yalkowsky et al. 2010 Verschueren 1983 Budavari 1996; Haynes et al. 2015
Partition coefficients: Log K_{ow} Log K_{oc}	 1.79 1.76–2.04	 Hansch et al. 1995 Gawlik et al. 1998; Tülp et al. 2009
Vapor pressure At 20°C	0.113 mm Hg at 25°C	NLM 2022a
Henry's law constant	1.3x10^{-5} at 20°C 1.63x10^{-5} at 25°C	Tremp et al. 1993 Harrison et al. 2002
Disassociation constant (pKa)	7.23	NLM 2022a
Autoignition temperature	550°C	NLM 2022a
Flashpoint	108°C	NLM 2022a
Flammability limits	No data	NLM 2022a
Conversion factors ppm (v/v) to mg/m^3 in air at 20°C mg/m^3 to ppm (v/v) in air at 20°C	 1 ppm=5.783 mg/m^3 1 mg/m^3=0.173 ppm	NLM 2022a
Explosive limits	No data	NLM 2022a

Table 4-5. Physical and Chemical Properties of 3-Nitrophenol

Property	Information	Reference
Molecular weight	139.11 g/mol	NLM 2022b
Color	Colorless to pale yellow	NLM 2022b
Physical state	Crystalline solid	NLM 2022b
Melting point	96.8°C	NLM 2022b
Boiling point	194°C	NLM 2022b
Density: At 20°C/4°C	 1.485	 O'Neil 2006
Odor	Aromatic to sweetish	Sittig 1981
Odor threshold: Water Air	 0.6 m/L 3.0 mg/m^3	 Verschueren 1983
Taste threshold	No data	
Solubility: Water Organic solvent(s)	 13,550 mg/L at 25°C 133,000 mg/L at 90°C Very soluble in acetone, ether, ethanol, benzene	 Yalkowsky et al. 2010 Verschueren 1983 Haynes et al. 2015
Partition coefficients: Log K_{ow} Log K_{oc}	 2.00 1.68	 Hansch et al. 1995 Borisover and Graber 1997
Vapor pressure	5.85x10^{-5} mm Hg at 25°C	Bannan et al. 2017
Henry's law constant	2.00x10^{-9} atm-m^3/mole at 25°C	NLM 2022b
Dissociation constant	8.36	NLM 2022b
Autoignition temperature	400°C	NLM 2022b
Flashpoint	>100°C	NLM 2022b
Flammability limits	No data	NLM 2022b
Conversion factors ppm (v/v) to mg/m^3 in air at 20°C mg/m^3 to ppm (v/v) in air at 20°C	 1 mg/m^3=0.18 ppm 1 ppm=5.69 mg/m^3	 NLM 2022b
Explosive limits	No data	NLM 2022b

Table 4-6. Physical and Chemical Properties of 4-Nitrophenol

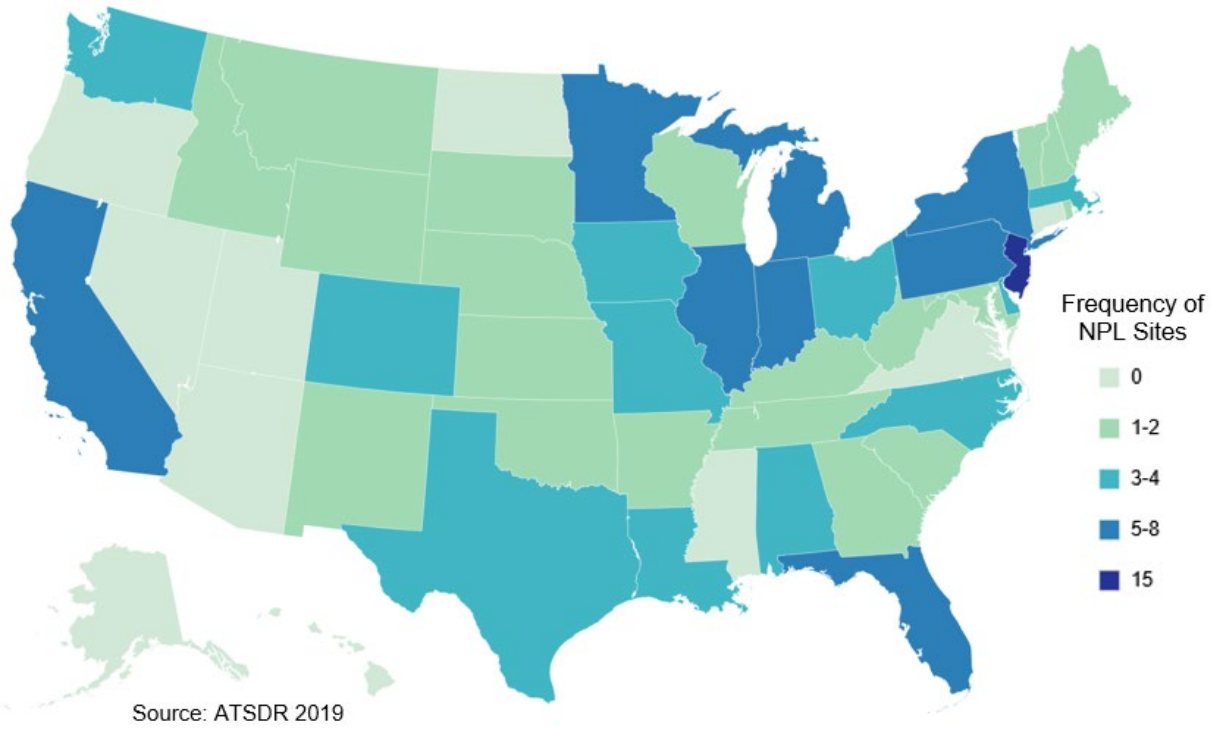
Property	Information	Reference
Molecular weight	139.11	O'Neil 2006
Color	Colorless to slightly yellow	O'Neil 2006
Physical state	Solid	NLM 2022c
Melting point	113–114°C	O'Neil 2006
Boiling point	279°C	Lewis 2007
Density: At 20°C	1.479 g/cm^3	Lewis 2007
Odor	Odorless	O'Neil 2006
Odor threshold: Water Air	 2.5 mg/L 2.3 mg/m^3	 Verschueren1983
Taste threshold	43.4 mg/L	NLM 2022c
Solubility: Water Organic solvent(s)	 10,000 mg/L at 15°C 15,600 mg/L at 25°C Very soluble in ethanol, ether, and acetone; freely soluble in alcohol, chloroform; soluble in solution of fixed alkali hydroxides and carbonates	 Verschueren1983 Yalkowsky et al. 2010 Haynes et al. 2015; O'Neil 2006
Partition coefficients: Log K_{ow} Log K_{oc}	 1.91 2.37	 Hansch et al. 1995 Schüürmann et al. 2006
Vapor pressure	1.2x10^{-5} mm Hg at 25°C	Bannan et al. 2017
Henry's law constant	1.28x10^{-8} atm-m^3/mol at 20°C	Tremp et al. 1993
Dissociation constant	7.15	NLM 2022c
Autoignition temperature	490°C	NLM 2022c
Flashpoint	169°C	NLM 2022c
Flammability limits	No data	NLM 2022c
Conversion factors ppm (v/v) to mg/m^3 in air at 20°C mg/m^3 to ppm (v/v) in air at 20°C	 1 mg/m^3=0.173 ppm 1 ppm=5.783 mg/m^3	NLM 2022c
Explosive limits	No data	NLM 2022c

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Nitrophenols have been identified in at least 135 of the 1,867 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2019). However, the number of sites in which nitrophenols have 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 2-Nitrophenol, 3-Nitrophenol, and/or 4-Nitrophenol Contamination



- Nitrophenols are used as intermediates to produce dyes, pigments, pharmaceuticals, rubber chemicals, lumber preservatives, photographic chemicals, pesticides, and fungicides.

- There is no evidence of nitrophenols being released from natural sources. Releases to the environment are primarily from manufacturing and processing industries as well as vehicle exhaust.

- Photolysis, settling, and wet deposition are important fate processes of nitrophenols in air. Nitrophenols are expected to biodegrade in both water and soil.

- Monitoring data for nitrophenols in U.S. air are limited. Levels in water and soil vary widely.
- The general population may be exposed to nitrophenols via inhalation of ambient air or the ingestion of contaminated drinking water.
- Populations with potentially high exposure include workers involved in the manufacture or use of nitrophenols, applicators of certain pesticides that metabolize to 4-nitrophenol, and people who live near landfill sites or agricultural areas that contain pesticides that metabolize to 4-nitrophenol.

There are no known natural sources of nitrophenols in the environment. Nitrophenols can be formed in the air following atmospheric photochemical reactions of several aromatic compounds formed from anthropogenic sources. They are also formed in vehicular exhausts following the thermal reaction of fuel with oxides of nitrogen. 4-Nitrophenol is also formed as a metabolite of certain organophosphate insecticides, including methyl parathion (Li and Kannan 2018; Li et al. 2019). Methyl parathion can be degraded to 4-nitrohenol by hydrolysis or photocatalysis. 2-, 3-, and 4-nitrophenol can also be formed in the atmosphere following photochemical reactions of nitrobenzene, aromatic hydrocarbons, and bromobenzene (Nojima et al. 1976, 1980; Rippen et al. 1987). In the air, both photolysis and physical removal processes such as gravitational settling of aerosols and wet deposition by rain and snow will probably determine the fate of nitrophenols. The atmospheric half-lives of these compounds are estimated to be 3–18 days (NLM 2022a, 2022b, 2022c). In water, both photolysis and biodegradation will be important fate processes. Photolysis will be more important in near-surface water, where attenuation of sunlight is usually minimal. The half-life of these nitrophenols may range between one and eight days in fresh water and may range between 13 and 139 days in sea water. In soils, biodegradation may be the most important fate process for these nitrophenols. In top-soil, the half-life of 4-nitrophenol may be about one to three days under aerobic conditions and around 14 days under anaerobic conditions. In subsoils, the half-life of 4-nitrophenol may be about 40 days under aerobic conditions and even slower under anaerobic conditions. The half-life of 2-nitrophenol may be about 12 days under aerobic conditions (Bourquin 1984; Bourquin et al. 1982; EPA 1985a; Kincannon and Lin 1985; Løkke 1985). The products of biodegradation have also been studied with pure cultures of microorganisms. Catechol, beta-keto adipic acid, and nitrite have been identified as products of aerobic biodegradation of 2-nitrophenol (Zeyer and Kearney 1984) and 4-nitrocatechol, hydroquinone, gamma-hydroxymuconic semialdehyde, and nitrite from 4-nitrophenol (Spain et al. 1979). In addition, 2- and 4-aminophenol have been isolated from anaerobic biodegradation of 2- and 4-nitrophenol, respectively (Adhya et al. 1981; Villanueva 1961). Studies have found that the rate of disappearance of nitrophenols, both in water and soil, may not be first-order, and evaluation of a biodegradation half-life may not be meaningful (Hoover et al. 1986; Jones and Alexander 1986, 1988; Scow et al. 1986; Scow et al. 1989; Zaidi et al. 1988, 1989).

Monitoring data for nitrophenols in any environmental medium were limited, and recent data are lacking for most mediums. The average concentration of 2-nitrophenol in the gas phase during seven rainfalls in Portland, Oregon in 1984 was 0.024 µg/m^3. The corresponding concentration in rainwater was 0.059 µg/L (Leuenberger et al. 1985). Nitrophenols have been identified in effluents from several industries at a median concentration of less than 10 µg/L (Staples et al. 1985). 4-Nitrophenol was detected in the potable water supply of Ames, Iowa at a concentration of 0.2 mg/L. The source of the compound was likely the contamination of well water from coal gas plant wastes (EPA 1980). Nitrophenols have been detected in 131 NPL waste sites (ATSDR 2019). The frequency of these sites within the United States can be seen in Figure 5-1. No report on the detection of any nitrophenols in any food was found in the literature. The NHANES measured 4-nitrophenol in 90% of urine samples of the general population, with a geometric mean value of 0.64 µg/L (CDC 2020). Although no experimental data are available, it is likely that people who manufacture or use nitrophenols, people who consume contaminated drinking water from groundwaters adjacent to methyl and ethyl parathion-treated farmlands, and people who live near landfill sites containing pesticides that metabolize to nitrophenols are potentially exposed to doses higher than the background level. Farmworkers have been shown to have significantly higher mean creatinine-adjusted concentrations of urinary 4-nitrophenol than the general population (López-Gálvez et al. 2018). Children playing in and around contaminated soil may also be exposed to higher levels of nitrophenols. However, urinary levels of 4-nitrophenol may be due to exposure to methyl parathion and related pesticides (that metabolize to 4-nitrophenol), rather than direct exposure to nitrophenols.

5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.2.1 Production

Facilities in the United States that produce, process, or use 2- and 4-nitrophenol are presented in Tables 5-1 and 5-2, respectively. 2-Nitrophenol is produced either by the catalytic hydrolysis of 2-nitrochlorobenzene with NaOH or by the reaction of dilute HNO_3 on phenol with subsequent steam distillation for separation from 4-nitrophenol (EPA 1985a; Lewis 2007). 4-Nitrophenol is produced either by the catalytic hydrolysis of 4-nitrochlorobenzene or by the reaction of dilute HNO_3 on phenol and subsequent steam distillation to separate the 4- from the 2- isomer (EPA 1985a; Lewis 2007). 3-Nitrophenol is an impurity in 4-nitrophenol and is produced as a byproduct of synthesis or a degradation product (Wróbel et al. 2000).

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

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
LA	2	100,000	999,999	1, 2, 3, 5, 6, 13

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

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

Source: TRI21 2022 (Data are from 2021)

Table 5-2. Facilities that Produce, Process, or Use 4-Nitrophenol

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
LA	1	10,000	99,999	5, 13
OH	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. Used Processing
4. Sale/Distribution
5. Byproduct
6. Reactant
7. Formulation Component
8. Article Component
9. Repackaging
10. Chemical Processing Aid
11. Manufacture Aid
12. Ancillary
13. Manufacture Impurity
14. Process Impurity

Source: TRI21 2022 (Data are from 2021)

5.2.2 Import/Export

Syngenta Corporation in Greensboro, North Carolina reported receiving imports of 2-nitrophenol totaling 1,201,507 pounds in 2015 (EPA 2016). The U.S. International Trade Commission (US ITC) reported that 5,035 kg (Harmonized Tarriff Schedule [HTS] 29089920) of 4-nitrophenol were imported into the United States for consumption in 2021, with no domestic export data available (US ITC 2022).

5.2.3 Use

Nitrophenol isomers are primarily used as intermediates to produce dyes, pigments, pharmaceuticals, rubber chemicals, lumber preservatives, photographic chemicals, pesticides, and fungicides (EPA 1980; O'Neil 2006). Syngenta Corporation uses 2-nitrophenol to manufacture pesticides, fungicides, and other agricultural chemicals (EPA 2016). 3-Nitrophenol is used as an indicator and to synthesize some dyestuffs and drugs (Bingham et al. 2001; 2006). 4-Nitrophenol is used to darken leather and to manufacture drugs, fungicides, methyl and ethyl parathion insecticides, and dyes (Abdollahi and Mohammadirad 2014).

5.2.4 Disposal

Incineration under controlled conditions (to attain complete combustion) appears to be the best method of disposal for nitrophenols (OHM/TADS 1989). The waste containing nitrophenols can be incinerated with a rotary kiln incinerator at 820–1,600°C, with a residence time of hours. It can also be incinerated in a fluidized bed incinerator at 450–980°C, with a residence time of seconds for liquids and gases. The residence time is longer for solids. Incineration of large quantities may require scrubbers to control the emission of NO gases (EPA 1981b). Biological treatment with powdered activated carbon and activated sludge has been used for liquid wastes (Kincannon and Esfandi 1981). Oxidation by passing air at 275°C through the aqueous waste destroys 99.6% of 4-nitrophenol (Heimbuch and Wilhelmi 1985). A resin absorption (Ambelite XAD-7) method for the removal of 4-nitrophenol has been used for industrial wastewater. A guideline for maximum daily effluent discharge of 2.13 mg of total toxic organics (including both nitrophenols) per liter of wastewater was set for electroplating plants that discharge <10,000 gallons of wastewater per day (EPA 2020a). Similarly, the limitations for daily effluent discharge from electrical and electronic industries is set at 1.37 mg/L of total toxic organics (EPA 2020b).

5.3 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data 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).

5.3.1 Air

There were no releases of 2-nitrophenol to the atmosphere from domestic manufacturing and processing facilities required to report to the TRI in 2021 (TRI21 2022); see Table 5-3. There was an estimated release of <1 pound of 4-nitrophenol to the atmosphere from domestic manufacturing and processing facilities required to report to the TRI in 2021 (TRI21 2022); see Table 5-4.

Table 5-3. Releases to the Environment from Facilities that Produce, Process, or Use 2-Nitrophenol[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
LA	2	0	121	4,323	0	0	121	4,323	4,444
Total	2	0	121	4,323	0	0	121	4,323	4,444

[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, wastewater 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: TRI21 2022 (Data are from 2021)

Table 5-4. Releases to the Environment from Facilities that Produce, Process, or Use 4-Nitrophenol[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
LA	1	0	0	0	0	0	0	0	0
OH	1	0.034	0	0	0.19	0	0.224	0	0.224
Total	2	0.034	0	0	0.19	0	0.224	0	0.224

[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, wastewater 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: TRI21 2022 (Data are from 2021)

EPA's National Emission Inventory (NEI) database contains information regarding sources that emit criteria air pollutants (CAPs) and their precursors, and hazardous air pollutants (HAPs) for the 50 United States, Washington DC, Puerto Rico, and the U.S. Virgin Islands. Emissions are estimated from multiple sources, including state and local environmental agencies; the TRI database; computer models for on- and off-road emissions; and databases related to EPA's Maximum Achievable Control Technology (MACT) programs to reduce emissions of HAPs. 4-Nitrophenol emissions estimated from the 2017 inventory are summarized in Table 5-5.

Table 5-5. 4-Nitrophenol Emissions to the Air Based on 2017 National Emissions Inventory

Emission sector	Pounds emitted
Commercial cooking	32,489.83
Fuel combustion; commercial/institutional; biomass	3.18
Fuel combustion; commercial/institutional; other	0.002
Fuel combustion; electric generation; biomass	12.09

Table 5-5. 4-Nitrophenol Emissions to the Air Based on 2017 National Emissions Inventory

Emission sector	Pounds emitted
Fuel combustion; electric generation; coal	198.35
Fuel combustion; electric generation; natural gas	0.30
Fuel combustion; electric generation; oil	21.44
Fuel combustion; electric generation; other	0.02
Fuel combustion; industrial boilers; internal combustion engines; biomass	59.53
Fuel combustion; industrial boilers; internal combustion engines; coal	217.77
Fuel combustion; industrial boilers; internal combustion engines; natural gas	0.01
Fuel combustion; industrial boilers; internal combustion engines; oil	0.06
Fuel combustion; industrial boilers; internal combustion engines; other	40.91
Industrial processes; cement manufacture	0
Industrial processes; chemical manufacture	0
Industrial Processes - ferrous metals	109.80
Industrial processes; not elsewhere classified	3.61
Industrial processes; non-ferrous metals	0.45
Industrial processes; petroleum refineries	29.37
Industrial processes; pulp and paper	1.62
Industrial processes; storage and transfer	0.11
Miscellaneous non-industrial; not elsewhere classified	1,383.14
Solvent; industrial surface coating and solvent use	0.196
Waste disposal	1,803.45

Source: EPA 2017

There is no evidence of the formation of the nitrophenols from natural sources in the environment. The primary anthropogenic source of the nitrophenol isomers found in air is traffic activity. These nitrophenols are released from exhausts of both gasoline- and diesel-powered vehicles (Inomata et al. 2015, 2016; Lu et al. 2019; Nojima et al. 1983; Rubio et al. 2019). Since the efficiencies of the incinerator/thermal processes are <100%, a small amount of undegraded nitrophenols will be released into the air during these processes. Nitrophenols can also be formed in the air as a result of atmospheric photochemical reactions of nitrobenzene, aromatic hydrocarbons (e.g., benzene and toluene), and bromobenzene primarily formed from anthropogenic sources with nitrogen oxides present in the air (Nojima et al. 1976, 1980; Rippen et al. 1987). 4-Nitrophenol is a degradation product of some organophosphorus insecticides (Li and Kannan 2018; Li et al. 2019). Therefore, small amounts of 4-nitrophenol may be released in local windblown dusts in areas where these pesticides are used. Li et al. (2020) conducted a study of nitrated phenols and phenolic precursors in the atmosphere in urban Jinan, China. Coal combustion (45%) was the major source for 4-nitrophenol found in samples from winter,

whereas in the spring, vehicular exhaust (40%) was the major source. This trend also changed in the summer when secondary formation (41%) of 4-nitrophenol was the key source (Li et al. 2020). 2-Nitrophenol and 4-nitrophenol were not detected in the emissions from the burning of three types of firewood, but 4-nitrophenol was detected at an average concentration of 0.09±0.08 μg/m^3 in emissions from pellet stoves (Rubio et al. 2019).

5.3.2 Water

Estimated releases of 121 pounds (~0.055 metric tons) of 2-nitrophenol to surface water from 2 domestic manufacturing and processing facilities in 2021, accounted for about 2.7% of the estimated total environmental releases from facilities required to report to the TRI (TRI21 2022). This estimate includes releases to wastewater treatment and publicly owned treatment works (POTWs) (TRI21 2022); see Table 5-3. There were no releases of 4-nitrophenol to surface water from domestic manufacturing and processing facilities required to report to the TRI in 2021 (TRI21 2022); see Table 5-4.

Nitrophenols may form during water decontamination processes when nitrate and nitrite are present (Dzengel et al. 1999; Vione et al. 2001). Effluents from the textile industry may also release both 2- and 4-nitrophenol into surface water and publicly owned treatment works (POTWs) (EPA 1981a). In addition, 2- and 4-nitrophenol were found in treated wastewaters from the following industries: iron and steel manufacturing (nitrophenols formed during the coke making process); foundries (nitrophenols formed during the coke making process); pharmaceutical manufacturing; rubber processing; and electrical/electronic components production (EPA 1981b).

5.3.3 Soil

There were no releases of 2-nitrophenol to the soil. However, 4,323 pounds (~1.96 metric tons) of 2-nitrophenol, accounting for about 97% of the total environmental emissions, were released via underground injection (TRI21 2022); see Table 5-3. There was an estimated release of <1 pound of 4-nitrophenol to soil from domestic manufacturing and processing facilities required to report to the TRI in 2021 (TRI21 2022); see Table 5-4.

Manufacturing and processing industries are sources of nitrophenols in soils and may cause groundwater contamination near the disposal sites. The application of parathion formulations to foliage could be an additional source of 4-nitrophenol in soil. Atmospheric to terrestrial transfer, primarily through rainwater and snow, will be secondary sources of nitrophenols in water and soil (Harrison et al. 2005; Leuenberger et al. 1988). Deposition of vehicular exhaust on roadways is another source of nitrophenols in soil. No quantitative estimate of the amounts of 2- or 4-nitrophenol released into soil from the latter three sources is available.

5.4 ENVIRONMENTAL FATE

5.4.1 Transport and Partitioning

Air. The fate and distribution of 4-nitrophenol in different environmental compartments were assessed with a non-steady-state equilibrium model (Yoshida et al. 1983). The model predicted the following distribution: air, 0.0006%; water, 94.6%; soil, 0.95%; sediment, 4.44%; and biota, 0.00009%. Therefore, only a very small fraction of this compound released from various sources is expected to remain in the air. The atmospheric concentration of 2-nitrophenol is expected to be higher than 3- and 4-nitrophenol because it has a much higher Henry's law constant and vapor pressure than the other isomers. The partitioning of a chemical from the atmosphere to land and water depends on its physical state and physico-chemical properties such as the vapor pressure. In general, compounds with higher vapor pressures such as 2-nitrophenol tend to partition to the vapor phase, while substances with vapor pressures lower than $1x10^{-4}$ mm Hg tend to partition more to the particulate phase in the atmosphere. In a study of the phase distribution of nitrophenols in the ambient air of Rome, Italy, it was determined that 4-nitrophenol was predominantly detected in the particulate phase (82% particulate phase and 18% vapor phase), while 2-nitrophenol was predominantly in the vapor phase (Cecinato et al. 2005). The intra-media transport of the two compounds from their points of emission to locations farther away in the air will depend on the lifetime of the compounds in air. These compounds are likely to undergo atmospheric transport from polluted areas to less polluted or pristine areas (Rippen et al. 1987). However, there is no experimental evidence to confirm the long-range transport of these nitrophenols.

Water. Because of their significant water solubilities, partitioning of these chemicals from air to surface waters and land via wet deposition is expected to occur. The detection of both 2- and 4-nitrophenol in rainwater in a few studies (Harrison et al. 2005; Leuenberger et al. 1988; Rippen et al. 1987) supports this partitioning mechanism. Experimental volatilization rates for nitrophenols from water are unavailable.

The modeling data based on non-steady-state equilibrium predict that volatilization of 4-nitrophenol will be insignificant (Yoshida et al. 1983). The Henry's law constant values are $1.3x10^{-5}$ atm-m^3/mol at 20°C for 2-nitrophenol and $1.28x10^{-8}$ atm-m^3/mol at 20°C for 4-nitrophenol (Tremp et al. 1993), suggesting that only 2-nitrophenol may volatilize from water; however, the dissociation constant (pKa) values of the two compounds (7.23 for 2-nitrophenol and 7.15 for 4-nitrophenol) indicate that significant fractions of these nitrophenols will exist in partially anionic form in the environment (NLM 2022a, 2022b, 2022c). Since ionic species do not volatilize significantly from water, the ionization may further limit volatilization (NLM 2022a, 2022b, 2022c). The partitioning of nitrophenols between water and sediment is also expected to depend on the pH of the water. Under acidic conditions, the nitrophenols are expected to exist as the fully protonated species, which have a greater tendency to partition to the sediment compartment as opposed to the conjugate base (anionic form).

Sediment and Soil. Based on the vapor pressure and Henry's Law constants of these substances, volatilization of 3-, and 4-nitrophenol from soils is expected to be low. Since both the vapor pressure and Henry's Law constant of 2-nitrophenol are much larger than the other two isomers, 2-nitrophenol is expected to have greater volatilization potential; however, all three substances may partially exist in ionic form depending upon the pH of the soil, and the anionic species will not be volatile. In a laboratory study in which a test system was constructed to simulate a typical terrestrial ecosystem in terms of air flow (over soil), percolating water (through soil), and vegetation cover, the fate of nitrophenols was studied with radiolabeled compounds added to soil. Of the total radioactivity applied to soils, only 1.6% in the case of 4-nitrophenol and 45.3% in the case of 2-nitrophenol were recovered in the gas phase after 30 days that were not attributable to CO_2 formed from biodegradation or other mineralization processes. Although the portions of the gas phase that were not attributable to CO_2 were not identified (i.e., they could be the nitrophenols or their metabolites other than CO_2), this study indicates that volatilization from soil will be insignificant for 4-nitrophenol but may be possible for 2-nitrophenol. In the same terrestrial ecosystem study, 35.7 and 12.7% of the applied radioactivities were recovered in plants where 4-nitrophenol and 2-nitrophenol, respectively, were used (Figge et al. 1983). This indicates that a significant portion of nitrophenols (or their metabolites) may be transferred from soil to plant. However, this transfer may not indicate bioaccumulation in plants because of possible metabolism in plants.

The adsorption of the nitrophenols is also pH-dependent since anions tend to have higher mobility and greater leaching potential in soils as compared to the fully protonated neutral species. The measured log K_{oc} values for 2- and 4-nitrophenol in a clay loam soil of 5.1% organic matter content and a pH of 5.7 were 2.06 and 1.71, respectively (Boyd 1982). Other studies have reported log K_{oc} values in the range 2.18–2.42 for 4-nitrophenol (Hodson and Williams 1988). These K_{oc} values indicate that nitrophenols will not strongly adsorb to soils. Therefore, in the absence of significant degradation, nitrophenols may leach from soil and may be found in the leachate of landfills.

Other Media. The bioconcentration factor (BCF) (wet-weight basis) for 4-nitrophenol in a species of green algae (Chlorella fusca) was 30 (Geyer et al. 1984). In golden orfe fish (*Leuciscus idus melanotus*), the whole-body BCF after 3 days of exposure was 57 (Freitag et al. 1982). With ^{14}C radiolabeled test compound, the mean plateau whole-body ^{14}C BCF for 4-nitrophenol in the fathead minnow (*Pimephales oromelas*) was 180. Only 2.7% of the tissue contained the parent compound after 28 days of depuration, and the compound was eliminated with a mean depuration half-life of 150 hours. 4-Aminophenol was identified as a metabolite (Call et al. 1980). Other studies have estimated a BCF of 126 for 4-nitrophenol from its octanol/water partition coefficient and various regression equations (Isnard and Lambert 1988; Schueuermann and Klein 1988). Based on available BCFs, the bioconcentration potential of the nitrophenols is low, and evidence for biomagnification is lacking (Loehr and Krishnamoorthy 1988).

5.4.2 Transformation and Degradation

Air. The two processes that are likely to degrade nitrophenols in air are direct photolysis and reactions with atmospheric oxidants such as hydroxyl radicals in the air. Very few studies are available on photolysis of nitrophenols in the air. When 4-nitrophenol was coated on silica gel and irradiated with an ultraviolet (UV) lamp of wavelengths >290 nm in the presence of an air current, 39% of the starting material photomineralized to CO_2 after 17 hours (Freitag et al. 1982; Korte and Klein 1982). No experimental data on the vapor-phase photolysis of nitrophenols are available. The rate constant for the gas-phase reaction of 2-nitrophenol with OH radicals is 9.0×10^{-13} cm^3 -molecule/second at 21°C (Atkinson 1986) and 8.95×10^{-13} cm^3 -molecule/second at 27°C for 4-nitrophenol (Güsten et al. 1984). Assuming that a 24-hour average concentration of OH radicals in a normal atmosphere is 5×10^5 radicals/cm^3 (Atkinson 1986), the atmospheric half-life of 4-nitrophenol due to this reaction is an estimated 18 days

Water. Chemical oxidation reactions of 2- and 4-nitrophenol by singlet oxygen and alkyl peroxy radicals formed from sunlight-induced photochemical reactions in water are too slow to be significant (EPA 1985a; Scully and Hoigné 1987). OH radicals in water attack 2- and 4-nitrophenol at the 2- and 4-carbon positions, resulting in the formation of a variety of products including 1,4-benzoquinone, 1,4-dihydroxybenzene, and 4-nitrocatechol (4-nitro1,2-dihydroxybenzene) (Suarez et al. 1970). 4-Nitrophenol photo-reacts quite rapidly in water in the presence of nitrate or nitrite (EPA 1985a). This is not surprising, since nitrate and nitrite in water produce elevated concentrations of hydroxyl radicals when irradiated by sunlight. The irradiation of 4-nitrophenol in neutral or acidic aqueous solution in the presence of air at a wavelength of 365 nm produced primarily hydroquinone and HNO_2, together with small amounts of benzoquinone and 4-nitrocatechol (Hustert et al. 1981; Kotzias et al. 1986). Other studies have determined the photo-transformation quantum yield to be in the range $3.3x10^{-6}$–$8.3x10^{-6}$ at pH 9.0 (ECETOC 1984; Lemaire et al. 1985). From the quantum yield data, the half-life of 4-nitrophenol in near-surface water was an estimated 27.5 hours at pH 5.5 under sunlight conditions equivalent to noontime, summer conditions in Chicago (EPA 1985a). Hustert et al. (1981), determined the aquatic photolytic half-lives of 4-nitrophenol as 5.7 days at pH 5, 6.7 days at pH 7, and 13.7 days at pH 9. The phototransformation of 4-nitrophenol in snow and ice has shown the production of hydroquinone, benzoquinone, and 4-nitrosophenol (Klán and Holoubek 2002)

The biodegradability of nitrophenols in water has been studied extensively with pure cultures of microorganisms, mixed microorganisms, and standardized screening test methods (Blok et al. 1985; Boatman et al. 1986; Chambers et al. 1963; Freitag et al. 1982; Gerike and Fischer 1979; Jones and Alexander 1986; Kool 1984; Korte and Klein 1982; McCormick et al. 1976; Means and Anderson 1981; Neujahr et al. 1974; Patterson and Kodukala 1981; Pitter 1976; Rott et al. 1982; Sudhakar et al. 1976; Tabak et al. 1981; Wilderer 1981; Zaidi et al. 1988). Depending on test conditions, the results from these tests vary considerably, some predicting that 4-nitrophenol is not easily biodegradable and others predicting easy biodegradability. It has been established that the nitrophenols have a lag period before the onset of biodegradation (Haller 1978). Several studies have used natural waters to study the aerobic biodegradability of 4-nitrophenol and concluded that, after a few days of adaptation, it will rapidly biodegrade in many of these waters (Bourquin et al. 1982; Spain and Van Veld 1983; Spain et al. 1980, 1984). The half-life of biodegradation in natural water (parent compound disappearance) reported or estimated from experimental results are as follows: about 3.5 days in water from the Escambia River in Florida (Bourquin 1984; Bourquin et al. 1982) and a mean of 3.2 days for water collected from five ponds and one river in Georgia (Paris et al. 1983; Vaishnav and Korthals 1988). Ingerslev and Nyholm (2000) measured biodegradation of 4-nitrophenol using a shake flask method and found a 0–5-day lag period and

a 14–36-day half-life in river water with a bacterial count of 1,950–16,000 bacteria/mL. In lake water, the lag period was 0–7 days, and the half-life was 32–530 days with a bacterial count of 1,100–2,700. In coastal seawater, the lag time was 3 days, and the half-life was 21 days with a high bacterial count of 13,000 bacteria/mL. In offshore seawater, 4-nitrophenol had a lag period of 93–96 days and a half-life of 139 days with a low bacterial count of 100 bacteria/mL (Ingerslev and Nyholm 2000).

The rate and extent of degradation of 4-nitrophenol in natural water also depend on the initial concentration of the substance, nature and concentration of nutrients, activities of the organisms, and presence or absence of predators or inhibitors of degrader organisms (Hoover et al. 1986; Jones and Alexander 1988; Rubin and Alexander 1983; Rubin et al. 1982; Subba-Rao et al. 1982; Wiggins and Alexander 1988; Zaidi et al. 1989). Other studies have found that the rate of biodegradation of nitrophenols may follow complex kinetics, and the derivation of a half-life based on simple first-order kinetics in such cases would not be appropriate (Jones and Alexander 1986, 1988; Zaidi et al. 1988). Biodegradation studies of the two nitrophenols with digested sludge under methanogenic conditions have shown that the compounds are not easily biodegraded and that 4-nitrophenol at high concentration is inhibitory to methanogenic microorganisms (Battersby and Wilson 1989; Horowitz et al. 1982). The anaerobic biodegradation of 4-nitrophenol in bottom sediments of lakes and rivers is also a slow process (Siragusa and Delaune 1986). However, in anaerobic screening tests using digester sludge inocula, 4-nitrophenol completely disappeared in 1 week in one study (Boyd et al. 1983), and >75% mineralized in 56 days in another study (Shelton and Tiedje 1984). Under anaerobic experimental conditions in two flooded soils, >50% degradation of 2- and 4-nitrophenol was observed in 10 days (Sudhakar and Sethunathan 1978).

Sediment and Soil. Data regarding the chemical degradation of nitrophenols in soils are lacking. Oxides of manganese (+3/+4) undergo reductive dissolution by substituted phenols. However, nitrophenols are among the most resistant substituted phenols for this reaction, which will be quite slow at neutral and alkaline pHs. At low pHs, nitrophenols may degrade at an appreciable rate, forming dimeric and polymeric oxidation products, since the dissolution rate of one form of manganese oxide with 4-nitrophenol was $<10^{-9}$ mol/L-minute at a pH of 4.4 (Stone 1987). The significance of this reaction under environmental conditions where the concentration of nitrophenols will be expected to be much lower than that used (10^{-2} M) in the experiment of Stone (1987) is likely to be low. The photolytic reaction of nitrophenols will not be significant beyond the surface layer of soil because light attenuation will reduce the light intensity to insignificant levels. The most important fate determining process for nitrophenols in soils is expected to be biodegradation. Several studies support this conclusion. Several

pure cultures isolated from soils degraded nitrophenols (EPA 1985a). As in the case of water, adaptation of soil to 4-nitrophenol was a prerequisite for biodegradation; the presence of a critical number of degrader microorganisms was necessary for the initiation of biodegradation. However, unlike in natural water, the mineralization of low concentrations of 4-nitrophenol proceeds with little or no initial acclimation period (Scow et al. 1986). Addition of specific nutrients from pristine aquifers also resulted in more rapid adaptation (Aelion et al. 1987; Swindoll et al. 1988), and the rate of biodegradation was concentration-dependent (Scow et al. 1986). The biodegradation of 2-nitrophenol by soil microorganisms is comparatively slower than that of 4-nitrophenol (Alexander and Lustigman 1966; Figge et al. 1983). In a study designed to simulate biodegradation of chemicals under natural land disposal conditions, the half-life of 2-nitrophenol in sandy loam soil was estimated to be 12 days under aerobic conditions (Kincannon and Lin 1985). In topsoil, the half-life of 4-nitrophenol was about 1 day under aerobic conditions and 14 days under anaerobic conditions. Addition of certain nutrients reduced the anaerobic half-life of 4-nitrophenol. In subsoils, the half-life of 4-nitrophenol was 40 days under aerobic conditions and even slower under anaerobic conditions (Løkke 1985). From a laboratory microcosm study simulating coastal wetlands, the half-life of 4-nitrophenol was predicted to be 2–3 days (Portier 1985).

5.5 LEVELS IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to nitrophenols depends, in part, on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of nitrophenols 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 nitrophenols 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.

Table 5-6 shows the lowest limit of detections that are achieved by analytical analysis in environmental media. An overview summary of the range of concentrations detected in environmental media is presented in Table 5-7.

Table 5-6. Lowest Limit of Detection for Nitrophenols Based on Standards[a]

Media	Isomer	Detection limit	Reference
Municipal and industrial wastewater	2-Nitrophenol	0.45 µg/L	EPA 1984
	4-Nitrophenol	2.4 µg/L	EPA 1984
Drinking water	2-Nitrophenol	0.026 g/L	EPA 2000a
	4-Nitrophenol	0.18 g/L	EPA 2000a
Urine	4-Nitrophenol	0.10 µg/L	CDC 2020
Soil/sediment	2-Nitrophenol	660 µg/kg	EPA 1998
	4-Nitrophenol	330 µg/kg	EPA 1998
Groundwater	2-Nitrophenol	10 µg/L	EPA 1998
	4-Nitrophenol	50 µg/L	EPA 1998
Solid waste	3-Nitrophenol	Not reported	EPA 2007a

[a]Detection limits based on using appropriate preparation and analytics. These limits may not be possible in all situations.

Table 5-7. Summary of Environmental Levels of Nitrophenols

Media	Low	High	For more information
Outdoor air (ng/m^3)	0.01	17.8	Section 5.5.1
Indoor air (ng/m^3)	0.002	0.003	Section 5.5.1
Surface water (ppb)	0.011	88	Section 5.5.2
Ground water (ppb)	<0.2	250	Section 5.5.2
Drinking water (ppb)	<0.2	871.3	Section 5.5.2
Soil (ppb)	<0.8		Section 5.5.3

Detections of nitrophenols in air, water, and soil at NPL sites are summarized in Table 5-8.

Table 5-8. Nitrophenols 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
2-Nitrophenol					
Water (ppb)	10	12.3	5.50	4	4
Soil (ppb)	2,830	1,980	12.1	5	5
Air (ppbv)			No data		

Table 5-8. Nitrophenols 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
3-Nitrophenol[b]					
Water (ppb)			No data		
Soil (ppb)			No data		
Air (ppbv)			No data		
4-Nitrophenol					
Water (ppb)	16	27.4	11.3	9	7
Soil (ppb)	5,140	6,510	49.8	16	15
Air (ppbv)			No data		
Nitrophenol					
Water (ppb)			No data		
Soil (ppb)	1.60×10^6	43,800	432	2	2
Air (ppbv)			No data		

[a]Concentrations found in ATSDR site documents from 1981 to 2019 for 1,867 NPL sites (ATSDR 2019). Maximum concentrations were abstracted for types of environmental media for which exposure is likely. Pathways do not necessarily involve exposure or levels of concern.
[b]3-Nitrophenol was found at five NPL sites but no data on levels in water, soil, or air were reported.

5.5.1 Air

Monitoring data for nitrophenols in U.S. air are limited; therefore, monitoring data for these compounds in ambient air are presented from samples obtained both in the United States and other countries. In a study of phenols and nitrophenols in the air in the Strasbourg area of France, 3-nitrophenol was detected at mean concentrations of 0.1 ng/m^3 at urban sites, 0.2 ng/m^3 at suburban sites, and 0.01 ng/m^3 at rural sites (Delhomme et al. 2010). A study performed in 2003 of ambient air in Rome, Italy reported mean concentrations of 2-nitrophenol of 10.4 ng/m^3 in the gas phase and 3.5 ng/m^3 in the particulate phase; by contrast, 4-nitrophenol concentrations were 3.9 ng/m^3 in the gas phase and 17.8 ng/m^3 in the particulate phase (Cecinato et al. 2005). Earlier studies in Italy reported 4-nitrophenol concentrations of 0.94–0.163, 0.87, and 0.42 µg/m^3 in urban, semi-rural, and rural areas, respectively (Belloli et al. 2006). In Central Milano, summer concentrations of 4-nitrophenol were reported as 0.106–0.120 µg/m^3 while 2-nitrophenol concentrations were 0.130–0.177 µg/m^3. Analysis of tunnel air showed 2- and 4-nitrophenol concentrations to be 0.232–1.139 and 0.387–0.993 µg/m^3, respectively (Belloli et al. 2006). Concentrations of 2-nitrophenol (1.09–15.99ng/m^3) and 4-nitrophenol (1.29–3.77 ng/m^3) were detected in the air particulate matter collected in Birmingham, United Kingdom in samples collected in 2007 and

2008 (Özel et al. 2011). Air samples collected during 2010 and 2011 at the University of Santiago, Chile had atmospheric 2-nitrophenol concentrations of 8.3–106 ng/m^3 and 4-nitrophenol concentrations of 40–1,400 ng/m^3 (Rubio et al. 2012). Corresponding dew concentrations were not detected to 237 µg/L, not detected to 147 µg/L, and not detected to 629 µg/L for 2-, 3- and 4-nitrophenol, respectively. 4-Nitrophenol was found in ambient particulates from two sites in the Czech Republic (Kitanovski et al. 2020). Concentrations from 1990 to 2001 in air in other literature ranged from 0.8 to 350 ng/m^3 for 2-nitrophenol and from 1.2 to 300 ng/m^3 for 4-nitrophenol (Harrison et al. 2005). These measurements were mostly reported in Europe. Rudel et al. (2001) reported indoor air concentrations of 4-nitrophenol in four of seven samples at 0.002 to 0.003 µg/m^3, with detection of 0.17–6.82 µg/g dust in all the corresponding dust samples.

Concentrations taken from 1990 to 2001 of 2-nitrophenol in clouds were 0.2–0.3 and 0.059–1.4 µg/L in rain. Concentrations of 4-nitrophenol were 2.2–21 µg/L in clouds, 8.1–40.2 µg/L in fog, <0.01–16 µg/L in rain, and 0.008–0.013 µg/L in snow (Harrison et al. 2005). In the past, rainwater concentrations of 2-nitrophenol ranged from 0.024 to 1.4 µg/m^3. The average concentration of 2-nitrophenol in the gas phase during seven rainfalls in Portland, Oregon in 1984 was 0.024 µg/m^3. The corresponding concentration in rainwater was 0.059 µg/L (Leuenberger et al. 1985). The concentrations of 2-nitrophenol in air and rainwater at Dubendorf, Switzerland, in 1985 were 0.35 µg/m^3 (one rainfall) and 0.1–0.8 µg/L (several rainfalls), respectively (Leuenberger et al. 1988). 2-Nitrophenol was detected in rainwater at a concentration of 0.031 µg/L in Azusa, California, and at 0.1–1.4 µg/L in different locations in West Germany. 4-Nitrophenol was also detected in rainwater at concentrations of 2–24 µg/L in different locations in West Germany. Extremely high values of 4-nitrophenol (up to 50 µg/L) have been found in rainwater from a thunderstorm after a hot and sunny period (Rippen et al. 1987).

5.5.2 Water

Measurements of nitrophenols in water samples are well documented for the EPA's Water Quality Portal (WQP). These data are presented in Table 5-9 and summarized below.

Table 5-9. Summary of Concentrations of Nitrophenols (ppb) Measured in Surface and Groundwater Across the United States

Year range	Average	Maximum	Number of Samples	Percent detected
Surface water				
2-Nitrophenol				
2000–2004	0.26	0.88	104	53.8%
2005–2009	0.16	0.59	83	32.5%
2010–2014	0.40	1.12	329	10.3%
2015–2019	3.69	5.3	15	73.3%
2020–2022[a]		<0.3	96	0%
4-Nitrophenol				
2000–2004	1.60	4.54	146	71.9%
2005–2009	0.77	3.42	184	50.5%
2010–2014	0.96	9.25	208	37.5%
2015–2019	9.96	27	25	88%
2020–2022[a]	0.28	0.5	73	5.5%
Groundwater				
2-Nitrophenol				
2000–2004	0.25	0.57	158	6.3%
2005–2009	8.59	40	255	60.4%
2010–2014	4.77	5.0	76	56.6%
2015–2019	0.47	0.47	15	6.7%
2020–2022[a]	ND	ND	ND	ND
4-Nitrophenol				
2000–2004	20.11	49	140	3.6%
2005–2009	44.62	250	443	33.6%
2010–2014	20.0	20.0	47	87.2%
2015–2019		<0.2	14	0%
2020–2022[a]	ND	ND	ND	ND

[a]As of October 11, 2022.

ND = no data reported

Source: WQP 2022

According to the WQP database from 2000 to 2022, 2-nitrophenol has been detected in 19% of 627 samples of surface water samples at concentrations of <0.16–5.3 µg/L. The concentration of 4-nitrophenol ranged from <0.28 to 27 µg/L over the same period in 47% of 636 surface water samples at various locations in the United States. No data were reported for 3-nitrophenol (WQP 2022). Concentrations from 1990 to 2001 in surface waters in other literature ranged from 0.028 to 0.43 µg/L for

2-nitrophenol and from 0.011 to 88 µg/L for 4-nitrophenol (Harrison et al. 2005). These measurements were mostly reported in Europe.

According to the WQP database from 2000 to 2022, 2- and 4-nitrophenol have been detected in 41% (total samples 504) and 30% (total samples 644) of groundwater samples for the respective isomer at various locations in the United States. The concentration of 2-nitrophenol ranged from <0.25 to 40 µg/L and the concentration of 4-nitrophenol ranged from <0.2 to 250 µg/L in these samples (WQP 2022).

Nitrophenols (isomer unidentified) at a concentration of 5 mg/L were detected in oil shale retort water (Dobson et al. 1985). 4-Nitrophenol has been identified in effluent from a pesticide plant (EPA 1985a). Both 2- and 4-nitrophenol were detected in the final effluent from the wastewater of a petroleum industry refinery (Snider and Manning 1982). Nitrophenols have also been identified in primary and secondary effluents of municipal wastewater treatment plants. For example, both nitrophenols were identified in the secondary effluent from a wastewater treatment plant in Sauget, Illinois (Ellis et al. 1982), and 4-nitrophenol was detected in both primary and secondary effluent from a wastewater treatment plant in Los Angeles, California, in secondary effluent from a wastewater treatment plant in Orange County, California, and in primary effluent from a San Diego, California wastewater treatment plant (Young 1978).

4-Nitrophenol was found in stormwater runoffs from four (Long Island, New York; Washington, District of Columbia; Little Rock, Arkansas; and Eugene, Oregon) of 15 cities at concentrations ranging from 1 to 19 µg/L (Cole et al. 1984).

In the past, 4-nitrophenol was detected in the potable water supply of Ames, Iowa at a concentration of 0.2 mg/L. The source of the compound was speculated to be the contamination of well water from the wastes of a coal gas plant after the plant ceased operation around 1930 (EPA 1980). To assess drinking water contamination after the 2018 Camp Fire in California, water samples were collected from 10 homes in the burn area around Paradise, California. 2-Nitrophenol was detected in one home at 871.3 µg/L (Solomon et al. 2021).

5.5.3 Sediment and Soil

Nitrophenols have been detected in soil and sediment samples taken for EPA's WQP database from 2000 to 2022. These data are described below and summarized in Table 5-10.

Table 5-10. Summary of Concentrations of Nitrophenols (ppb) Measured in Soil and Sediment Across the United States

Year range	Average	Maximum	Number of samples	Percent detected
Soil				
2-Nitrophenol				
2000–2022[a]		<0.8	141	0%
4-Nitrophenol				
2000–2022[a]		<10	113	0%
Sediment				
2-Nitrophenol				
2000–2004	2,391	19,000	14	42.9%
2005–2009	230.4	444	71	9.9%
2010–2014	190.9	380	267	0.7%
2015–2019		<0.3	84	0%
2020–2022[a]	ND	ND	ND	ND
4-Nitrophenol				
2000–2004	5,725	34,000	14	42.9%
2005–2009	286.5	444	314	2.2%
2010–2014	69.2	130	270	0.7%
2015–2019	49.5	188	99	13.1%
2020–2022[a]	ND	ND	ND	ND

[a]As of October 11, 2022.

ND = no data reported

Source: WQP 2022

2-Nitrophenol and 4-nitrophenol were not detected in 141 (detection limit <0.8 µg/kg) and 113 (detection limit <10 µg/kg) soil samples, respectively from 2000 to 2022 (WQP 2022). 2-Nitrophenol and 4-nitrophenol were not detected in 92 soil samples collected from 2000 to 2022 from Superfund sites in the United States. Detection in sediment samples has steadily decreased since 2000. In 2000–2004, 2-nitrophenol and 4-nitrophenol were detected in 6 out of 14 samples (42.9%) at average concentrations of 2,391 and 5,725 µg/kg, respectively. The most recent sampling data (2015–2019) reported that 2-nitrophenol was below the detection limit of 0.3 µg/kg in all 84 samples and 4-nitrophenol was detected in 13 of 99 samples (13.1%) at an average concentration of 49.5 µg/kg. Superfund sites around the United States at a maximum concentration of 25 µg/kg. 3-Nitrophenol was found in one sample from Indiana Water Science Center in 2009 at a concentration of 200 µg/kg. 4-Nitrophenol was found in 12 of 2,448 sediment samples from Superfund sites at an average concentration of 105 µg/kg (WQP 2022).

In the past, the monitoring program conducted by EPA at Love Canal (Niagara Falls, New York) in 1980 qualitatively detected the presence of 2- and 4-nitrophenol in sediment/soil samples (Hauser and Bromberg 1982). The concentration range for 2-nitrophenol in a few unspecified municipal landfill leachates was reportedly 8.6–12.0 mg/L (Brown and Donnelly 1988). 2-Nitrophenol was detected at a concentration of 76 mg/L in one of 1,131 samples taken from drums, tanks, or other containers from 221 hazardous waste disposal sites in 41 states and one territory (EPA 1985b).

5.5.4 Other Media

No data in the literature demonstrated the presence of nitrophenols in foods. Nitrophenols were not included in the U.S. Food and Drug Administration (FDA) Total Diet Study (FDA 2006). The production of 4-nitrophenol from degradation or metabolism of several pesticides, including parathion (which is no longer used in the United States as of October 2003) (EPA 2000b) and methyl parathion, on plant leaves or in soil may result in the contamination of food crops following application of these pesticides. Hair samples were collected from adults (117) and children (40) living in Grande-Synthe, France in 2017; 4-nitrophenol concentrations results are presented in Table 5-11 (Iglesias-González et al. 2021). Perrone et al. (2014) found that 2- and 4-nitrophenol were present in both particulate matter and gas phase of automotive exhaust. 2-Nitrophenol was found at greater concentrations from diesel engine exhaust (0.32–2.34 µg/km) than gasoline engine exhaust (0.01 µg/km). 4-Nitrophenol showed similar results with concentrations of 0.48–5.04 µg/km for diesel engine exhaust and 0.41–1.30 µg/km for gasoline engine exhaust (Perrone et al. 2014).

Table 5-11. 2017 Hair Monitoring Data for 4-Nitrophenol in 117 Adults and 40 Children

	Positive detections (%)	25% Percentile (pg/mg)	50% Percentile (pg/mg)	75% Percentile (pg/mg)	95% Percentile (pg/mg)	Highest detected Value (pg/mg)
Adults	100	11.9	16.1	19.5	34.9	64.3
Children	100	12.6	17.9	30.4	59.2	310

Source: Iglesias-González et al. 2021

5.6 GENERAL POPULATION EXPOSURE

The general population may be exposed to nitrophenols through the inhalation of ambient air. Although limited air monitoring data are available, low levels (<1 μg/m^3) of 2-nitrophenol are expected to exist in the air. Nitrophenols have not been detected in foods. Whether this is due to a lack of effort directed at monitoring these compounds or because they are present at undetectable levels is not known. Therefore, exposure from food, although plausible, remains to be demonstrated with actual monitoring data. 4-Nitrophenol has been detected in human urine; however, this detection does not indicate direct exposure to this compound, as exposure to several pesticides can cause excretion of the compound in human urine. 4-Nitrophenol is also a metabolite of nitrobenzene (EPA 2009a). The geometric mean and percentiles of 4-nitrophenol detected in human urine from the National Health and Nutrition Examination Survey (NHANES) are presented in Table 5-12. Li and Kannan (2018) measured the concentrations of metabolites of organophosphate, insecticides, and herbicides from urine samples in eight countries, and the mean concentration of 4-nitrophenol in 35 samples from the United States was 1.6 ng/mL. An Environmental Influences on Child Health Outcomes (ECHO) Program study reported that 4-nitrophenol was 1 of 89 analytes measured in the urine of 171 pregnant women from the United States and Puerto Rico roughly spanning the years 2017–2020. 4-Nitrophenol was detected at 0.1–3.8 ng/mL in 69% (118) of the samples collected (Buckley et al. 2022).

Table 5-12. Geometric Mean and Selected Percentiles of Urinary 4-Nitrophenol (in μg/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

			Selected percentiles				
	Survey years	Geometric mean (95% CI)	50th	75th	90th	95th	Sample size
Total	2011–2012	0.64 (0.57–0.71)	0.63	1.17	2.17	3.31	2,350
	2013–2014	0.64 (0.60–0.69)	0.61	1.18	2.17	3.21	2,584
Age group							
6-11 years	2011–2012	0.61 (0.50–0.75)	0.60	1.21	2.08	2.78	394
	2013–2014	0.84 (0.72-0.98)	0.68	1.66	3.11	4.09	411
12–19 years	2011-2012	0.62 (0.51-0.74)	0.64	1.15	1.85	2.51	376
	2013–2014	0.66 (0.57–0.77)	0.68	1.23	1.82	2.71	415
20+ years	2011–2012	0.64 (0.57–0.72)	0.63	1.18	2.23	3.48	1,580
	2013–2014	0.62 (0.58–0.67)	0.57	1.14	2.07	3.21	1,758

Table 5-12. Geometric Mean and Selected Percentiles of Urinary 4-Nitrophenol (in µg/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles				Sample size
			50th	75th	90th	95th	
Sex							
Male	2011–2012	0.67 (0.61–0.74)	0.70	1.24	2.21	3.19	1,190
	2013–2014	0.67 (0.62–0.73)	0.65	1.17	2.02	3.03	1,306
Female	2011–2012	0.60 (0.52–0.70)	0.58	1.13	2.14	3.48	1,160
	2013–2014	0.62 (0.56–0.68)	0.58	1.19	2.32	3.40	1,278
Race/ethnicity							
Mexican American	2011–2012	0.62 (0.52–0.73)	0.68	1.18	1.84	2.51	285
	2013–2014	0.68 (0.58–0.80)	0.67	1.30	2.07	2.64	403
Non-Hispanic Black	2011–2012	0.70 (0.55–0.87)	0.72	1.37	2.34	3.47	642
	2013–2014	0.76 (0.69–0.84)	0.78	1.37	2.49	3.59	576
Non-Hispanic White	2011–2012	0.62 (0.54–0.71)	0.60	1.15	2.13	3.31	752
	2013–2014	0.60 (0.56–0.64)	0.57	1.10	2.03	3.16	986
All Hispanic	2011–2012	0.64 (0.58–0.72)	0.68	1.16	1.98	2.98	546
	2013–2014	0.69 (0.60–0.79)	0.67	1.29	2.17	2.82	637
Asians	2011–2012	0.72 (0.63–0.81)	0.62	1.54	2.84	3.87	325
	2013–2014	0.74 (0.62–0.89)	0.63	1.39	3.16	4.90	284

CI = confidence interval

Source: CDC 2020

A monitoring study of urine from 30 people and their dogs exposed to pesticides revealed the metabolite 4-nitrophenol in 100% of samples, with a geometric mean of 1.76 µg/L for humans and 2.91 µg/L for their dogs (Wise et al. 2022). Fenske et al. (2002) conducted a focus study on children of pesticide applicators, farm workers, agricultural, and a reference group. Children were ≤6 years old living in central Washington State. 4-Nitrophenol is a metabolite of the pesticides chlorpyrifos and parathion used in this area. 4-Nitrophenol was found in 6–8% of urine samples from each group (Fenske et al. 2002). Li et al. (2019) measured pesticide metabolite concentrations in Australian infants and toddlers. There was a significant increase in the concentration of urinary 4-nitrophenol with age, which may suggest that exposure increases because of increased activity and dietary intake (Li et al. 2019).

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Workers involved in the manufacture or use of nitrophenols and applicators of certain pesticides may be exposed to higher levels of nitrophenols than the general population. The geometric mean creatinine-adjusted concentration for urinary 4-nitrophenol (1.63 µg/g) in 20 migrant farmworkers in Sonora, Mexico was significantly higher than in the general United States population and Mexican American populations (López-Gálvez et al. 2018). Members of the general population who live near landfill sites that contain these compounds may be exposed at higher than background levels via inhalation. Another sector of the general population, those in agricultural areas that use methyl parathion and related pesticides (that metabolize to 4-nitrophenol) for crop protection, may be exposed to 4-nitrophenol at higher than background levels via the consumption of drinking water from contaminated groundwater and possibly via the consumption of foods. Since nitrophenols are released from car exhaust, potentially high exposures could also occur in populations living near heavy traffic, or people who work with or spend time around idling gasoline- or diesel-powered motor vehicles.

Children playing in and around soils containing certain pesticides may be exposed to nitrophenols. 4-Nitrophenol was detected in 96% of urine samples from children aged 2–5 years living in Washington State in 1998 in areas having potentially elevated organophosphorus pesticide exposure (Kissel et al. 2005). The mean concentration of urinary 4-nitrophenol was 11.6 µg/L. Roca et al. (2014) assessed exposure to pesticides in school children aged 6–11 years in agricultural and urban areas of Valencia, Spain with high pesticide use and high concentrations of contemporary pesticides in the air. 4-Nitrophenol was one of the most frequently detected compounds in urine samples, with a detection frequency of 53%. The geometric mean creatinine (Cre)-adjusted urinary level of 4-nitrophenol was 0.96 µg/g Cre. The median concentration of 4-nitrophenol was higher in the urine of children living in agricultural locations (1.11 µg/g Cre) than urban locations (0.4 µg/g Cre). 4-Nitrophenol was one of the most frequently detected biomarkers of pesticide exposure in the urine of lactating mothers in Valencia, Spain at an average concentration of 0.8 ng/mL and detection frequency of 84% (Fernández et al. 2020). Béranger et al. (2018) investigated prenatal exposure to pesticides by measuring pesticides and metabolites in hair strands in mothers living in agricultural areas of northeastern and southwestern France in 2011. 4-Nitrophenol was found at the second highest mean concentration (13.18 pg/mg) of the 140 pesticides and metabolites studied (Béranger et al. 2018).

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 nitrophenols 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 nitrophenols.

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 nitrophenols 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 nitrophenols. 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.

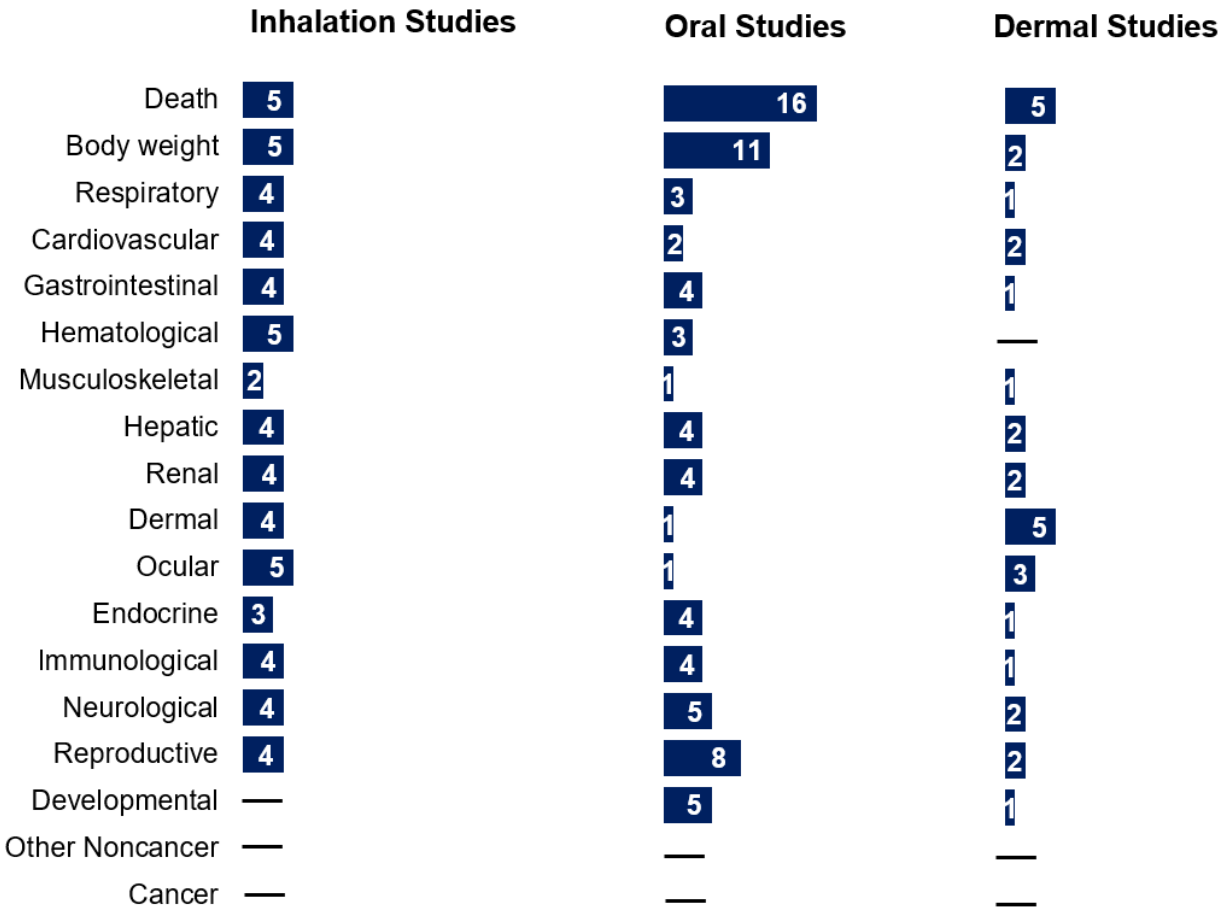
6.2 IDENTIFICATION OF DATA NEEDS

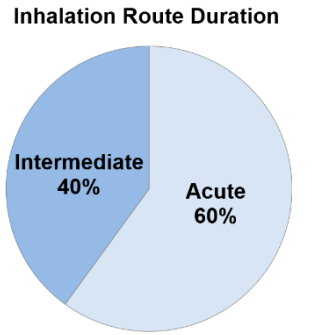
Missing information in Figure 6-1 should not be interpreted as a "data need." A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health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

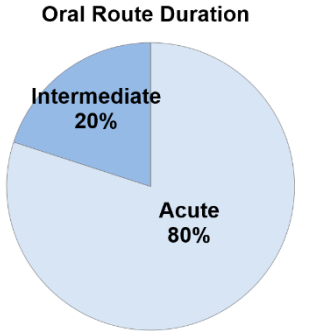
Figure 6-1. Summary of Existing Health Effects Studies on Exposure to Nitrophenols by Route and Endpoint *

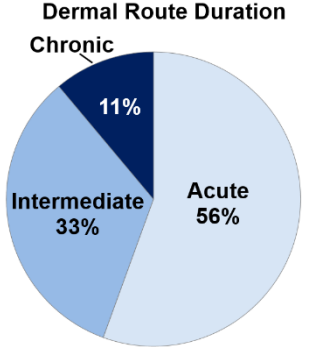
Potential reproductive, neurological, renal, hepatic, gastrointestinal, bodyweight, and cardiovascular effects were the most studied endpoints.

All available studies examined exposure in animals.









*Includes studies discussed in Chapter 2; the number of studies include those finding no effect. Figure 6-1 represents health effect studies only for 4-nitrophenol. Only one inhalation and one oral study were identified for 2-nitrophenol.

Acute-Duration MRLs. The available acute database was inadequate for deriving oral or inhalation MRLs for 2-, 3-, or 4-nitrophenol. No human data were available for any isomer via either route. No adequately conducted acute-duration animal inhalation studies were identified for 2- or 3-nitrophenol. Acute oral studies for 2-nitrophenol were limited to acute lethality studies and a gestational exposure study evaluating limited endpoints. Acute oral studies for 3-nitrophenol were limited to lethality studies. Available animal inhalation and oral data for 4-nitrophenol toxicity are considered inadequate for derivation of MRLs based on systematic review of the most sensitive endpoints, methemoglobinemia and body weight, respectively. Additional acute inhalation studies are needed to further investigate whether the hematological effects observed in rats can be corroborated and extrapolated across species. The additional data would add further confidence in this endpoint as a viable health effect for MRL development. Additional studies are needed to characterize health effects for lower-level oral doses of 4-nitrophenol. Studies are needed to characterize health effects following acute exposure to 2- and 3-nitrophenol.

Intermediate-Duration MRLs. The available intermediate-duration database was inadequate for deriving inhalation or oral MRLs for 2-, 3-, and 4-nitrophenol. No human data were available for any isomer via either route. No intermediate-duration inhalation data were available for 3-nitrophenol. For 2- and 4-nitrophenol, available studies were limited to a single 28-day study for each isomer. Additional intermediate inhalation studies on 2- and 4-nitrophenol are needed to corroborate the most sensitive endpoints of nasal lesions and cataracts, respectively. Additionally, mechanistic data underlying these effects would be useful, particularly studies designed to determine if cataracts are due to direct ocular contact with nitrophenol dust or systemic in origin. For oral exposure, no adequate intermediate-duration studies were identified for 2- or 3-nitrophenol. The intermediate oral database is also insufficient to derive an MRL for 4-nitrophenel, as the most sensitive effects (dyspnea, prostration) occurred at the lowest oral dose associated with lethality. As death is always considered a serious effect, an MRL is unable to be derived for health effects at this dose level (ATSDR 2018). Additional oral intermediate studies are needed to characterize health effects occurring at nonlethal doses. Studies are needed to characterize health effects following intermediate-duration oral exposure to 2- and 3-nitrophenol and intermediate-duration inhalation exposure to 3-nitrophenol.

Chronic-Duration MRLs. No adequately conducted chronic-duration human or animal studies were identified for 2-, 3-, or 4-nitrophenol; thus, the databases for each of these chemicals were inadequate for deriving chronic-duration MRLs.

Health Effects. There is a general lack of literature on the health effects of 2-, 3-, and 4-nitrophenol. The available literature suggests body weight, hematological, and ocular effects may be sensitive targets of toxicity after exposure to 4-nitrophenol, but no human studies have been published to date about either the toxicokinetics or the health effects of exposure to 2-, 3-, or 4-nitrophenol. This represents a very important data need, as epidemiologic evidence would strengthen the reliability of the available evidence from the existing animal study literature. Additional data are needed to investigate intermediate oral exposure in animals at low levels of 4-nitrophenol, as death was the most sensitive endpoint from the body of adequately conducted literature. There were many intraperitoneal studies that showed potential reproductive/endocrine effects in both male and female rats and mice; however, there were no studies using routes of exposure considered sufficient for MRL development, such as inhalation, oral, or dermal exposure. A data need exists for the study of reproductive/endocrine effects using these human-relevant routes of exposure at exposure levels relevant for human populations. A data need has also been identified to study the health effects of 3-nitrophenol in animals in all exposure routes and durations, as no current literature exists regarding the health effects of this chemical. Additional research on the relative potencies of 2-, 3-, and 4-nitrophenol would also add to the health effects literature.

Body weight. Based on systematic review, body weight effects following oral exposure are not classifiable as health effects following oral exposure to 4-nitrophenol due to no data in humans and low evidence from animal studies. Available oral studies of 4-nitrophenol have unexplained inconsistencies regarding decreased body weight following acute-duration exposure and no evidence of body weight effects following intermediate-duration exposure from a limited number of studies. Additional studies in multiple species evaluating 2-, 3-, and 4-nitrophenol would be useful to characterize whether body weight effects may be associated with nitrophenol exposure.

Hematological. Based on systematic review, hematological effects following inhalation exposure are not classifiable as health effects following oral exposure to 4-nitrophenol due to no data in humans and low evidence from animal studies. Two acute-duration inhalation experiments from a single report by Smith et al. (1988) suggest that methemoglobinemia may occur following exposure to 4-nitrophenol; however, these findings are not confirmed in intermediate-duration inhalation studies of 2- or 4-nitrophenol or oral exposure to 4-nitrophenol. Additional studies would help to identify the validity of the findings in the Smith et al. (1988) study. Mechanistic data supporting a mechanism by which nitrophenols could induce methemoglobinemia would also be useful.

Ocular. Based on systematic review, ocular effects are a suspected health effect of 4-nitrophenol due to no data in humans and a moderate level of evidence in animals. Ocular effects, including irritation, corneal opacity, and cataracts, have been observed following acute- and intermediate-duration inhalation exposure and direct eye contact with 4-nitrophenol. Mechanistic studies to determine whether ocular effects are due to direct ocular contact with nitrophenol dust or systemic in origin would be useful. Additional studies evaluating 2- and 3-nitrophenol would also be useful.

Epidemiology and Human Dosimetry Studies. No studies evaluating potential health effects in humans following exposure to nitrophenol were identified. Studies in humans that monitor exposure levels and health effects associated with nitrophenols would be useful.

Biomarkers of Exposure and Effect. Biomarkers of exposure specific to nitrophenols and its metabolites have not been determined. The metabolism of nitrophenols has been examined only in animal models. Additionally, urine has often been tested to identify exposure to nitrophenols. 2-Nitrophenol and 4-nitrophenol conjugates are completely and rapidly excreted in the urine. Therefore, unless a very high dose is given, urinary levels will fall to near zero in a short time (48 hours). It is not known if urinary excretion of 2- or 4-nitrophenol (or their conjugates) can be associated quantitatively with exposure to these chemicals due to other chemicals that are metabolized to form nitrophenols. A data need has been identified to determine biomarkers of exposure that are specific to nitrophenols.

Absorption, Distribution, Metabolism, and Excretion. A data need exists to further understand absorption, distribution, metabolism, and excretion of nitrophenols in humans exposed orally, dermally, and through inhalation. Pharmacokinetic studies in animals exposed to nitrophenols by inhalation, oral, and dermal routes provided limited information. Additional studies are needed to evaluate the toxicokinetics of nitrophenols following exposure in humans. A specific data need exists for further information regarding the possible distribution of 4-nitrophenol through the placental barrier, as fetal hemoglobin might be more sensitive to the effects of 4-nitrophenol.

Comparative Toxicokinetics. There are limited data available that allow for a comparison of the toxicokinetic properties across species. The lack of studies in humans along with the absence of unique biomarkers of exposure make inter-species comparisons of the effects difficult. A data need exists to further understand the toxicokinetics of 2-, 3-, and 4-nitrophenol in humans, as well as to identify unique biomarkers of exposure to these chemicals.

Children's Susceptibility. No human data are available regarding children's susceptibility. Available data from oral developmental studies do not indicate that developing animals are uniquely susceptible to toxicity following exposure to 4-nitrophenol. Developmental effects have not been evaluated in animals following inhalation exposure. Experimental studies in young animals and/or epidemiological data for children would be useful to address these data gaps.

Physical and Chemical Properties. The physical and chemical properties of 2- and 4-nitrophenol have been sufficiently characterized to permit estimation of its environmental fate. There is limited information available regarding the environmental fate of 3-nitrophenol. A data need exists to further characterize the environmental fate of 3-nitrophenol.

Production, Import/Export, Use, Release, and Disposal. Production methods for nitrophenols are known and there does not appear to be a need for further information. The use pattern of nitrophenols is known. Detailed information on the uses of 2-nitrophenol in industry and consumer products is available from Chemical Data Reporting (EPA 2016). Additional data on the uses of nitrophenols are not needed. TRI contains data on releases to air, water, and soil from facilities that produce nitrophenols. Additional data are needed on the environmental release of nitrophenols from uses such as rubber production and pigment/dye production to adequately assess their contribution to human exposure. More information regarding the amount of nitrophenols that are disposed of at hazardous waste sites or abandoned would be useful. No current data are available on the amount of nitrophenols disposed of annually. Methods for disposing of nitrophenols are described in the literature. Sufficient information exists on regulations pertaining to nitrophenols. Nitrophenols are regulated according to the Emergency Planning and Community Right-to-Know Act of 1986.

Environmental Fate. There is scant data available that examines the fate of 2-, 3-, and 4-nitrophenol in water and soil. More data are needed to assess the fate of these compounds in air with more confidence. Based on the compounds' photolytic behavior in water, direct photolysis in air is expected to be the primary fate process in air. Since these compounds have low vapor pressures, their potential for long range atmospheric transport is low. However, no data were available on the vapor-phase photolysis of the compounds that would permit estimation of their half-lives in the atmosphere. If degradation follows simple kinetics, these half-lives are important since they indicate the degree of persistence of a compound in a certain environmental medium.

Bioavailability from Environmental Media. No information was identified regarding absorption of 2-, 3-, or 4-nitrophenol in humans following inhalation, oral, or dermal exposure. Absorption by the inhalation route in animals could be inferred from the appearance of adverse effects after exposure to 4-nitrophenol dusts. However, oral and/or dermal absorption could also have occurred. Limited data obtained in animals indicate that 4-nitrophenol is readily and almost completely absorbed by the oral route when administered by gavage, but no data were available concerning absorption from food or drinking water. Data regarding 2-nitrophenol were not available. An ethanol solution of 4-nitrophenol was not well absorbed when applied to the skin of animals, since most of the dose could be recovered from the application site a week after dosing. It is not known whether 2-nitrophenol can be absorbed through the skin. Knowledge of the compounds' bioavailability will permit estimation of their absorption in a body organ from an environmental medium, in cases where the exposure level is known. There are no animal studies identified for exposure to 3-nitrophenol. Given the lack of literature regarding absorption of 2-, 3-, and 4-nitrophenol in humans and animals, a data need exists to further study the absorption potential of these chemicals following inhalation, oral, and dermal exposure.

Food Chain Bioaccumulation. There is limited information available on bioaccumulation of nitrophenols. Even though nitrophenols bioaccumulate in edible aquatic species, there is no current evidence indicating any transfer from plants to animals. Data for biomagnification of these chemicals are also scant. A data need exists to further study the potential for food chain bioaccumulation of 2-, 3-, and 4-nitrophenol.

Exposure Levels in Environmental Media. Data are not available to establish any ambient level of these compounds in air, drinking water, or foods. Even data on the levels of these compounds under conditions in which they are expected to show elevated values are scarce. Reliable, up-to-date monitoring data for air, drinking water, and foods would allow estimation of the extent of exposure from each of the sources.

Exposure Levels in Humans. Levels of 4-nitrophenol in the urine of general population are presented in Chapter 5. The levels of 4-nitrophenols in other tissues in the general population are unknown. There are no data available on levels 2- or 3-nitrophenol in any body tissue or fluid. No data on the levels of either compound in any body tissue or fluid for populations living near hazardous waste sites are available. More studies need to be done to better understand the exposure of nitrophenols in adults as well as levels of the compounds in populations living near hazardous waste sites.

Exposures of Children. Limited data on exposure to nitrophenols in children were identified. Li et al. (2019) measured pesticide metabolite concentrations in Australian infants and toddlers. There was a significant increase in the concentration of urinary 4-nitrophenol with age, which may suggest that exposure increases as a result of increased activity and dietary intake (Li et al. 2019). As this was the only study that studied 2-, 3-, or 4-nitrophenol exposure in children, a data need exists to further understand the potential for nitrophenols exposures in children.

6.3 ONGOING STUDIES

No ongoing studies were identified for nitrophenols (RePORTER 2022).

CHAPTER 7. REGULATIONS AND GUIDELINES

Pertinent international and national regulations, advisories, and guidelines regarding nitrophenols 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 nitrophenols.

Table 7-1. Regulations and Guidelines Applicable to Nitrophenols

Agency	Description	Information	Reference
	Air		
EPA	RfC		
	4-Nitrophenol	Information reviewed but value not derived	IRIS 2002
	Provisional peer reviewed toxicity values		
	2-Nitrophenol		
	Provisional subchronic RfC	0.0005 mg/m^3 (0.00009 ppm)	EPA 2007b
WHO	Air quality guidelines	No data	WHO 2010
	Water & Food		
EPA	Drinking water standards and health advisories		EPA 2018b
	4-Nitrophenol		
	1-Day health advisory (10-kg child)	0.8 mg/L	
	10-Day health advisory (10-kg child)	0.8 mg/L	
	DWEL	0.3 mg/L	
	Lifetime health advisory	0.06 mg/L	
	National primary drinking water regulations	Not listed	EPA 2009b
	RfD		IRIS 2002
	4-Nitrophenol	Not assessed	
WHO	Drinking water quality guidelines	No data	WHO 2017
FDA	Substances added to food (formerly EAFUS)	Not listed	FDA 2022

Table 7-1. Regulations and Guidelines Applicable to Nitrophenols

Agency	Description	Information	Reference
	Cancer		
HHS	Carcinogenicity classification	No data	NTP 2021
EPA	Carcinogenicity classification		
	4-Nitrophenol	Not assessed	IRIS 2002
	2-Nitrophenol	Inadequate information to assess carcinogenic potential	EPA 2007b
IARC	Carcinogenicity classification	No data	IARC 2022
	Occupational		
OSHA	PEL (8-hour TWA) for general industry, shipyards, and construction	No data	OSHA 2021a, 2021b, 2021c
NIOSH	REL (up to 10-hour TWA)	No data	NIOSH 2018
	Emergency Criteria		
EPA	AEGLs-air	No data	EPA 2018a
DOE	PACs-air		DOE 2018a
	2-Nitrophenol		
	PAC-1[a]	2.1 mg/m^3	
	PAC-2[a]	23 mg/m^3	
	PAC-3[a]	140 mg/m^3	
	3-Nitrophenol		
	PAC-1[a]	2.8 mg/m^3	
	PAC-2[a]	31 mg/m^3	
	PAC-3[a]	180 mg/m^3	
	4-Nitrophenol		
	PAC-1[a]	0.69 mg/m^3	
	PAC-2[a]	7.6 mg/m^3	
	PAC-3[a]	46 mg/m^3	

[a]Definitions of PAC terminology are available from U.S. Department of Energy (DOE 2018b).

AEGL = acute exposure guideline levels; DOE = Department of Energy; DWEL = drinking water equivalent level; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; 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; TWA = time-weighted average; WHO = World Health Organization

CHAPTER 8. REFERENCES

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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 substances 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.

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Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Office of Innovation and Analytics, Toxicology Section, 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 Office of Innovation and Analytics, Toxicology Section, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop S102-1, Atlanta, Georgia 30329-4027.

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MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2-Nitrophenol
CAS Numbers: 88-75-5
Date: April 2023
Profile Status: Final
Route: Inhalation
Duration: Acute

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

Rationale for Not Deriving an MRL: An MRL was not derived for acute inhalation exposure (≤14 days) to 2-nitrophenol. No adequately conducted studies were identified that investigated health effects of 2-nitrophenol for this route and duration.

Agency Contacts (Chemical Managers): Brittany Szafran, D.V.M., Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2-Nitrophenol
CAS Numbers: 88-75-5
Date: April 2023
Profile Status: Final
Route: Inhalation
Duration: Intermediate

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

Rationale for Not Deriving an MRL: An MRL was not derived for intermediate inhalation exposure (15–364 days) to 2-nitrophenol. In the only available intermediate-duration inhalation study evaluating 2-nitrophenol, the only adverse effect noted in rats exposed intermittently for 4 weeks was increased incidence of squamous metaplasia of the nasal epithelium observed in both male and female rats at ≥32.5 mg/m^3 (Hazleton 1984). Although the Hazleton (1984) is a well-conducted study, the study on its own is not strong enough to support the derivation of an MRL. No adverse respiratory effects were noted in acute or inhalation studies evaluating 4-nitrophenol (Hazleton 1983; Smith et al. 1988), and respiratory effects noted following oral exposure to 4-nitrophenol are limited to clinical signs of respiratory distress associated with lethal doses (Branch et al. 1983b; Hazleton 1989). This lack of supporting literature precludes the derivation of an MRL for this route and duration. The relevant NOAEL and LOAEL values are presented in Table A-1.

Table A-1. Summary of Relevant NOAEL and LOAEL Values Following Intermediate-Duration Inhalation Exposure to 2-Nitrophenol

Species	Duration/ route	NOAEL ($NOAEL_{ADJ}$) (mg/m^3)	LOAEL ($LOAEL_{ADJ}$) (mg/m^3)	Effect	Reference
Respiratory effects					
Sprague-Dawley rat	4 weeks 5 days/week 6 hours/day	5 (0.89)	32.5 (5.8)	Increased incidence of squamous metaplasia of the nasal epithelium	Hazleton 1984

Adjusted daily dose = $Intermittent\ dose \times \frac{Exposure\ hours}{24\ hours} \times \frac{Exposure\ days}{7\ days}$

ADJ = adjusted; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

Agency Contacts (Chemical Managers): Brittany Szafran, D.V.M., Ph.D.

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MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2-Nitrophenol
CAS Numbers: 88-75-5
Date: April 2023
Profile Status: Final
Route: Inhalation
Duration: Chronic

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

Rationale for Not Deriving an MRL: An MRL was not derived for chronic inhalation exposure (≥365 days) to 2-nitrophenol. No adequately conducted studies were identified that investigated health effects of 2-nitrophenol for this route and duration.

Agency Contacts (Chemical Managers): Brittany Szafran, D.V.M., Ph.D.

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MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2-Nitrophenol
CAS Numbers: 88-75-5
Date: April 2023
Profile Status: Final
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration oral MRL as the most sensitive endpoint is represented by a serious effect.

Rationale for Not Deriving an MRL: Available acute-duration oral studies are limited to acute lethality studies in rats and mice (Vernot et al. 1977) and a gestational exposure study in rats (Laughlin et al. 1983). The reported LD_{50} values in rats and mice were 620 and 1,300 mg/kg, respectively (Vernot et al. 1977). The only observed health effect following maternal exposure on GDs 6–15 was a 1.9-fold increase in post implantation loss at 1,000 mg/kg/day, compared to control rats (Laughlin et al. 1983). Since the most sensitive adverse effect reported following acute oral exposure to 2-nitrophenol was death, this precludes the derivation of an acute-duration oral MRL (ATSDR 2018).

Agency Contacts (Chemical Managers): Brittany Szafran, D.V.M., Ph.D.

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MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2-Nitrophenol
CAS Numbers: 88-75-5
Date: April 2023
Profile Status: Final
Route: Oral
Duration: Intermediate

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

Rationale for Not Deriving an MRL: No adequately conducted studies were identified that investigated health effects of 2-nitrophenol for this route and duration.

Agency Contacts (Chemical Managers): Brittany Szafran, D.V.M., Ph.D.

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MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2-Nitrophenol
CAS Numbers: 88-75-5
Date: April 2023
Profile Status: Final
Route: Oral
Duration: Chronic

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

Rationale for Not Deriving an MRL: No adequately conducted studies were identified that investigated health effects of 2-nitrophenol for this route and duration.

Agency Contacts (Chemical Managers): Brittany Szafran, D.V.M., Ph.D.

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MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 3-Nitrophenol
CAS Numbers: 554-84-7
Date: April 2023
Profile Status: Final
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 adequately conducted studies were identified that investigated health effects of 3-nitrophenol for this route and duration.

Agency Contacts (Chemical Managers): Brittany Szafran, D.V.M., Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 3-Nitrophenol
CAS Numbers: 554-84-7
Date: April 2023
Profile Status: Final
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 adequately conducted studies were identified that investigated health effects of 3-nitrophenol for this route and duration.

Agency Contacts (Chemical Managers): Brittany Szafran, D.V.M., Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 3-Nitrophenol
CAS Numbers: 554-84-7
Date: April 2023
Profile Status: Final
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 adequately conducted studies were identified that investigated health effects of 3-nitrophenol for this route and duration.

Agency Contacts (Chemical Managers): Brittany Szafran, D.V.M., Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 3-Nitrophenol
CAS Numbers: 554-84-7
Date: April 2023
Profile Status: Final
Route: Oral
Duration: Acute

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

Rationale for Not Deriving an MRL: Available data are limited to an acute lethality study reporting LD_{50} values of 930 and 1,410 mg/kg in rats and mice, respectively (Vernot et al. 1977). These data are not appropriate to support derivation of an acute-duration oral MRL for 3-nitrophenol.

Agency Contacts (Chemical Managers): Brittany Szafran, D.V.M., Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 3-Nitrophenol
CAS Numbers: 554-84-7
Date: April 2023
Profile Status: Final
Route: Oral
Duration: Intermediate

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

Rationale for Not Deriving an MRL: No adequately conducted studies were identified that investigated health effects of 3-nitrophenol for this route and duration.

Agency Contacts (Chemical Managers): Brittany Szafran, D.V.M., Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 3-Nitrophenol
CAS Numbers: 554-84-7
Date: April 2023
Profile Status: Final
Route: Oral
Duration: Chronic

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

Rationale for Not Deriving an MRL: No adequately conducted studies were identified that investigated health effects of 3-nitrophenol for this route and duration.

Agency Contacts (Chemical Managers): Brittany Szafran, D.V.M., Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 4-Nitrophenol
CAS Numbers: 100-02-7
Date: April 2023
Profile Status: Final
Route: Inhalation
Duration: Acute

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

Rationale for Not Deriving an MRL: Inhalation data following acute-duration exposure to 4-nitrophenol are limited to three separate studies from a single report by Smith et al. (1988). The only adverse effects reported in this study include corneal opacity after a 4-hour exposure to 4,059 mg/m^3 and increased methemoglobin observed in rats at ≥112 mg/m^3 following exposure for 2 weeks (Smith et al. 1988). The relevant NOAELs and LOAELs are presented in Table A-2.

A systematic review of the literature was performed for both health effects (see details in Appendix C). This review determined that hematological effects following inhalation exposure to 4-nitrophenol are not classifiable as health effects due to no data in humans and a low level of evidence from animal studies. Therefore, data are inadequate to support selection of methemoglobinemia as the critical effect for MRL derivation. While it was determined that ocular effects are a suspected health effect of 4-nitrophenol, it is likely that observed effects are due to direct ocular contact with dust particles, rather than a systemic effect. This is supported by evidence of ocular effects, including corneal opacity, in rabbits following direct ocular instillation with 4-nitrophenol (EPA 1992b; Monsanto 1983a) and lack of ocular effects following oral or dermal exposure to 4-nitrophenol (Hazleton 1989; NTP 1993). Therefore, this critical effect is not considered appropriate as the basis for an inhalation MRL.

Table A-2. Summary of Relevant NOAEL and LOAEL Values Following Acute-Duration Oral Exposure to 4-Nitrophenol

Species	Duration/ route	NOAEL (mg/m^3)	LOAEL (mg/m^3)	Effect	Reference
Hematological effects					
Crl:CD rat	2 weeks 5 days/week 6 hours/day	ND	294	Methemoglobin increased from 0.2% (in controls) to 0.87%	Smith et al. 1988
Crl:CD rat	2 weeks 5 days/week 6 hours/day	26	112	Methemoglobin increased from 0.5% (in controls) to 1.5%	Smith et al. 1988
Ocular effects					
Crl:CD Rat	4 hours	1,304	4,059 (Serious LOAEL)	Corneal opacity	Smith et al. 1988

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

Agency Contacts (Chemical Managers): Brittany Szafran, D.V.M., Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 4-Nitrophenol
CAS Numbers: 100-02-7
Date: April 2023
Profile Status: Final
Route: Inhalation
Duration: Intermediate

***MRL Summary*:** There are insufficient data for derivation of an intermediate-duration inhalation MRL as the most sensitive endpoint is represented by a serious effect.

Rationale for Not Deriving an MRL: Hazleton (1983) was the only adequately conducted study identified for intermediate-duration inhalation exposures to 4-nitrophenol. The only observed health effect in rats after exposure to 4-nitrophenol for 4 weeks was unilateral and bilateral diffused anterior capsular cataracts at 29.18 mg/m^3. While a systematic review of the evidence (Appendix C) determined that ocular effects are a suspected health effect of 4-nitrophenol, it is likely that observed effects are due to direct ocular contact with dust particles, rather than a systemic effect. This is supported by evidence of ocular effects, including corneal opacity, in rabbits following direct ocular instillation with 4-nitrophenol (EPA 1992b; Monsanto 1983a) and lack of ocular effects following oral or dermal exposure to 4-nitrophenol (Hazleton 1989; NTP 1993). Therefore, this critical effect is not considered appropriate as the basis for an inhalation MRL.

Agency Contacts (Chemical Managers): Brittany Szafran, D.V.M., Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 4-Nitrophenol
CAS Numbers: 100-02-7
Date: April 2023
Profile Status: Final
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 adequately conducted studies were identified that investigated health effects of 4-nitrophenol for this route and duration.

Agency Contacts (Chemical Managers): Brittany Szafran, D.V.M., Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 4-Nitrophenol
CAS Numbers: 100-02-7
Date: April 2023
Profile Status: Final
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 most sensitive endpoint following acute-duration oral exposure to 4-nitrophenol is decreased maternal body weight gain in rats exposed to 27.6 mg/kg/day on GDs 6–15 (EPA 1992a). However, there are inconsistencies in body weight findings following acute-duration oral exposure (Table A-3). A systematic review of the evidence determined that body weight effects are not classifiable as a health effect following oral exposure due to no data in humans and low evidence in laboratory animals (see Appendix C for details). Therefore, it is not appropriate to base the MRL on maternal body weight effects reported by EPA (1992a).

The next most sensitive endpoint is dyspnea and increased mortality at 171 mg/kg in an acute lethality study (Branch et al. 1983b). Due to observed lethality, this precludes the derivation of an acute-duration oral MRL at this dose or based on any effect observed at higher doses (ATSDR 2018).

Table A-3. NOAEL and LOAEL Values for Body Weight Effects Following Acute-Duration Oral Exposure to 4-nitrophenol

Species	Duration	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Sprague-Dawley rat	10 days GDs 6–15	13.8	27.6	12% decrease in maternal body weight	EPA 1992a
Sprague-Dawley rat	Once GD 14, 15, 16, 17, or 18	100	ND		Abu-Qare et al. 2000
Sprague-Dawley rat	Once GD 11	1,000	ND		Kavlock 1990
Wistar rat	Once	200	ND		Li et al. 2017; Tang et al. 2016
Wistar rat	3 days	ND	200 Serious LOAEL	25% decrease in body weight gain	Li et al. 2017; Tang et al. 2016
Sprague-Dawley rat	14 days	200	ND		Koizumi et al. 2001
CD-1 mouse	8 days GDs 7–14	ND	400	18% decrease in maternal body weight gain	Plasterer et al. 1985
CD-1 mouse	8 days	1,000	ND		Plasterer et al. 1985

GD = gestational day; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

Agency Contacts (Chemical Managers): Brittany Szafran, D.V.M., Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 4-Nitrophenol
CAS Numbers: 100-02-7
Date: April 2023
Profile Status: Final
Route: Oral
Duration: Intermediate

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

Rationale for Not Deriving an MRL: The most sensitive effects observed following intermediate-duration oral exposure to 4-nitrophenol included increased mortality preceded by wheezing, dyspnea, and prostration at 140 mg/kg/day (Hazleton 1989). Due to observed lethality, this precludes the derivation of an intermediate-duration oral MRL at this dose or based on any effects observed at higher doses (ATSDR 2018).

Agency Contacts (Chemical Managers): Brittany Szafran, D.V.M., Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 4-Nitrophenol
CAS Numbers: 100-02-7
Date: April 2023
Profile Status: Final
Route: Oral
Duration: Chronic

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

Rationale for Not Deriving an MRL: No adequately conducted studies were identified that investigated health effects of 4-nitrophenol for this route and duration.

Agency Contacts (Chemical Managers): Brittany Szafran, D.V.M., Ph.D.

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR NITROPHENOLS

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 nitrophenols.

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen were conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions, physical and chemical properties, production, use, environmental fate, environmental releases, and environmental and biological monitoring data for nitrophenols. 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 nitrophenols 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 nitrophenols 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
    - Other noncancer effects

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

Cancer
Toxicokinetics
Absorption
Distribution
Metabolism
Excretion
PBPK models
Biomarkers
Biomarkers of exposure
Biomarkers of effect
Interactions with other chemicals
Potential for human exposure
Releases to the environment
Air
Water
Soil
Environmental fate
Transport and partitioning
Transformation and degradation
Environmental monitoring
Air
Water
Sediment and soil
Other media
Biomonitoring
General populations
Occupation populations

B.1.1 Literature Search

The current literature search was intended to update the Draft Toxicological Profile for Nitrophenols released for public comment in 2022; thus, the literature search was restricted to studies published between January 2020 and July 2022. The following main databases were searched in July 2022:

- PubMed
- National Technical Reports Library (NTRL)
- Scientific and Technical Information Network's TOXCENTER

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, Medical Subject Headings (MeSH) headings, and keywords for nitrophenols. 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 nitrophenols 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	
07/2022	(((88-75-5[rn] OR 554-84-7[rn] OR 100-02-7[rn] OR 25154-55-6[rn] OR nitrophenols[mh]) AND (2020:3000[mhda] OR 2020:3000[edat] OR 2020:3000[crdat] OR 2020:3000[dp])) AND (("Nitrophenols/toxicity"[mh] OR "Nitrophenols/adverse effects"[mh] OR "Nitrophenols/poisoning"[mh] OR "Nitrophenols/pharmacokinetics"[mh] OR "Nitrophenol/blood"[mh] OR "Nitrophenol/cerebrospinal fluid"[mh] OR "Nitrophenol/urine"[mh] OR "Nitrophenol/antagonists and inhibitors"[mh] OR "Nitrophenol/pharmacology"[majr]) OR ("Nitrophenol"[mh] AND ("environmental exposure"[mh] OR ci[sh])) OR ("Nitrophenol"[mh] AND toxicokinetics[mh:noexp]) OR ("Nitrophenol/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("Nitrophenol"[mh] AND ("endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR ("Nitrophenol"[mh] AND ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh]))))) OR ((("1-Hydroxy-3-nitrobenzene"[tw] OR "1-Hydroxy-4-nitrobenzene"[tw] OR "2-Hydroxnitrobenzene"[tw] OR "2-Hydroxynitrobenzene"[tw] OR "2-Nitrophenol"[tw] OR "3-Hydroxynitrobenzene"[tw] OR "3-Nitrophenol"[tw] OR "3-nitrofenol"[tw] OR "4-Hydroxy-1-nitrobenzene"[tw] OR "4-Hydroxynitrobenzene"[tw] OR "4-Nitrophenol"[tw] OR "Crump leather-lasting dressing"[tw] OR "Hydroxynitrobenzenes"[tw] OR "Mononitrophenol"[tw] OR "Nitrophenol"[tw] OR "Nitrophenols"[tw] OR "Phenol, 2-nitro-"[tw] OR "Phenol, 3-nitro-"[tw] OR "Phenol, 4-nitro-"[tw] OR "Phenol, m-nitro-"[tw] OR "Phenol, nitro-"[tw] OR "Phenol, o-nitro-"[tw] OR "Phenol, p-nitro-"[tw] OR "m-Hydroxynitrobenzene"[tw] OR "m-Nitrophenol"[tw] OR "o-Hydroxynitrobenzene"[tw] OR "o-Nitrophenol"[tw] OR "ortho-Nitrophenol"[tw] OR "p-Hydroxynitrobenzene"[tw] OR "p-Nitrophenol"[tw] OR "para-Nitrophenol"[tw]) AND (2020:3000[mhda] OR 2020:3000[edat] OR 2020:3000[crdat] OR 2020:3000[dp])) NOT medline[sb]) (((88-75-5[rn] OR 554-84-7[rn] OR 100-02-7[rn] OR 25154-55-6[rn] OR nitrophenols[mh:noexp]) AND (2020:3000[mhda] OR 2020:3000[edat] OR 2020:3000[crdat] OR 2020:3000[dp])) AND (("Nitrophenols/blood"[mh] OR "Nitrophenols/cerebrospinal fluid"[mh] OR "Nitrophenols/urine"[mh] OR

Table B-2. Database Query Strings

Database search date	Query string
	"Nitrophenols/antagonists and inhibitors"[mh] OR "Nitrophenols/pharmacology"[majr]) OR ("Nitrophenols"[mh] AND ("environmental exposure"[mh] OR ci[sh])) OR ("Nitrophenols"[mh] AND toxicokinetics[mh:noexp]) OR ("Nitrophenols/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("Nitrophenols"[mh] AND ("endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR ("Nitrophenols"[mh] AND ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh]))))
NTRL	
07/2022	"Nitrophenols" OR "Mononitrophenol" OR "Hydroxynitrobenzenes" OR "Phenol, nitro-" OR "2-Nitrophenol" OR "o-Hydroxynitrobenzene" OR "o-Nitrophenol" OR "ortho-Nitrophenol" OR "3-Nitrophenol" OR "m-Nitrophenol" OR "1-Hydroxy-4-nitrobenzene" OR "4-Hydroxynitrobenzene" OR "4-Nitrophenol" OR "p-Hydroxynitrobenzene" OR "p-Nitrophenol" OR "para-Nitrophenol" OR "Phenol, 4-nitro-"
Toxcenter	
07/2022	FILE 'TOXCENTER' ENTERED AT 08:40:21 ON 28 JUL 2022 CHARGED TO COST=EH038.08.04.LB.04 L1 14305 SEA FILE=TOXCENTER 88-75-5 OR 554-84-7 OR 100-02-7 L2 14232 SEA FILE=TOXCENTER L1 NOT TSCATS/FS L3 12159 SEA FILE=TOXCENTER L1 NOT PATENT/DT L4 12086 SEA FILE=TOXCENTER L2 NOT PATENT/DT L5 2081 SEA FILE=TOXCENTER L4 AND PY>=2020 ACTIVATE TOXQUERY/Q --------- L6 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L7 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L8 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L9 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L10 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L11 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L12 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L13 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L14 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?)

Table B-2. Database Query Strings

Database search date	Query string
	L15 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?)
	L16 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?)
	L17 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?)
	L18 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
	L19 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L20 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L21 QUE (ENDOCRIN? AND DISRUPT?)
	L22 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L23 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L24 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L25 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)
	L26 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L27 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L28 QUE (NEPHROTOX? OR HEPATOTOX?)
	L29 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L30 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L31 QUE L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29 OR L30
	L32 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?)
	L33 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
	L34 QUE L31 OR L32 OR L33
	L35 QUE (NONHUMAN MAMMALS)/ORGN
	L36 QUE L34 OR L35
	L37 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?)
	L38 QUE L36 OR L37

	L39 556 SEA FILE=TOXCENTER L5 AND L31
	D SCAN L39

Table B-2. Database Query Strings

Database search date	Query string
	FILE 'TOXCENTER' ENTERED AT 12:57:30 ON 28 JUL 2022 CHARGED TO COST=EH038.08.04.LB.04 L1 671 SEA FILE=TOXCENTER 25154-55-6 NOT (88-75-5 OR 554-84-7 OR 100-02-7) L2 670 SEA FILE=TOXCENTER L1 NOT TSCATS/FS L3 483 SEA FILE=TOXCENTER L2 NOT PATENT/DT L4 81 SEA FILE=TOXCENTER L3 AND PY>=2020 ACTIVATE TOXQUERY/Q --------- L5 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L6 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L7 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L8 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L9 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L10 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L11 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L12 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L13 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L14 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?) L15 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) L16 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?) L17 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?) L18 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?) L19 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?) L20 QUE (ENDOCRIN? AND DISRUPT?) L21 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?) L22 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?) L23 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?) L24 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)

Table B-2. Database Query Strings

Database search date	Query string
	L25 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?) L26 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?) L27 QUE (NEPHROTOX? OR HEPATOTOX?) L28 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?) L29 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?) L30 QUE L5 OR L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29 L31 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?) L32 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE) L33 QUE L30 OR L31 OR L32 L34 QUE (NONHUMAN MAMMALS)/ORGN L35 QUE L33 OR L34 L36 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?) L37 QUE L35 OR L36 --------- L38 2 SEA FILE=TOXCENTER L4 AND L31 L39 27 SEA FILE=TOXCENTER L4 AND L37 D SCAN L39

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
07/2022	Compounds searched: 88-75-5; 554-84-7; 100-02-7; 25154-55-6
NTP	
07/2022	"p-Nitrophenol" "4-Nitrophenol" "2-Nitrophenol" "100-02-7" "Nitrophenol, 2-" "o-Nitrophenol" "m-Nitrophenol" "88-75-5" "554-84-7" "Nitrophenol, p-" "3-Nitrophenol" "o-Hydroxynitrobenzene" "ortho-Nitrophenol" "1-Hydroxy-4-nitrobenzene" "4-Hydroxynitrobenzene" "Nitrophenol (p-)" "p-Hydroxynitrobenzene" "para-Nitrophenol" "Phenol, 4-nitro-"
Regulations.gov	
07/2022	p-Nitrophenol para-Nitrophenol

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	Nitrophenol Nitrophenols o-Nitrophenol 2-Nitrophenol Nitrophenol, 2- o-Hydroxynitrobenzene ortho-Nitrophenol 3-Nitrophenol m-Nitrophenol 1-Hydroxy-4-nitrobenzene 4-Hydroxynitrobenzene 4-Nitrophenol Nitrophenol (p-) Nitrophenol, p- p-Hydroxynitrobenzene Phenol, 4-nitro- 88-75-5 554-84-7 100-02-7 Mononitrophenol Hydroxynitrobenzenes Phenol, nitro- 25154-55-6
NPIRS	
07/2022	88-75-5 OR 554-84-7 OR 100-02-7 OR 25154-55-6
NIH RePORTER	
10/2022	Search Criteria-- Fiscal Year: Active Projects; Text Search: "1-Hydroxy-3-nitrobenzene" OR "1-Hydroxy-4-nitrobenzene" OR "2-Hydroxnitrobenzene" OR "2-Hydroxynitrobenzene" OR "2-Nitrophenol" OR "3-Hydroxynitrobenzene" OR "3-Nitrophenol" OR "3-nitrofenol" OR "4-Hydroxy-1-nitrobenzene" OR "4-Hydroxynitrobenzene" OR "4-Nitrophenol" OR "Crump leather-lasting dressing" OR "Hydroxynitrobenzenes" OR "Mononitrophenol" OR "Nitrophenol" OR "Nitrophenols" OR "Phenol, 2-nitro-" OR "Phenol, 3-nitro-" OR "Phenol, 4-nitro-" OR "Phenol, m-nitro-" OR "Phenol, nitro-" OR "Phenol, o-nitro-" OR "Phenol, p-nitro-" OR "m-Hydroxynitrobenzene" OR "m-Nitrophenol" OR "o-Hydroxynitrobenzene" OR "o-Nitrophenol" OR "ortho-Nitrophenol" OR "p-Hydroxynitrobenzene" OR "p-Nitrophenol" OR "para-Nitrophenol" (advanced) Limit to: Project Title, Project Terms, Project Abstracts
Other	Identified throughout the assessment process

The 2022 results were:

- Number of records identified from PubMed, NTRL, and TOXCENTER (after duplicate removal): 1,170
- Number of records identified from other strategies: 35
- Total number of records to undergo literature screening: 1,205

B.1.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies on nitrophenols:

- 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.

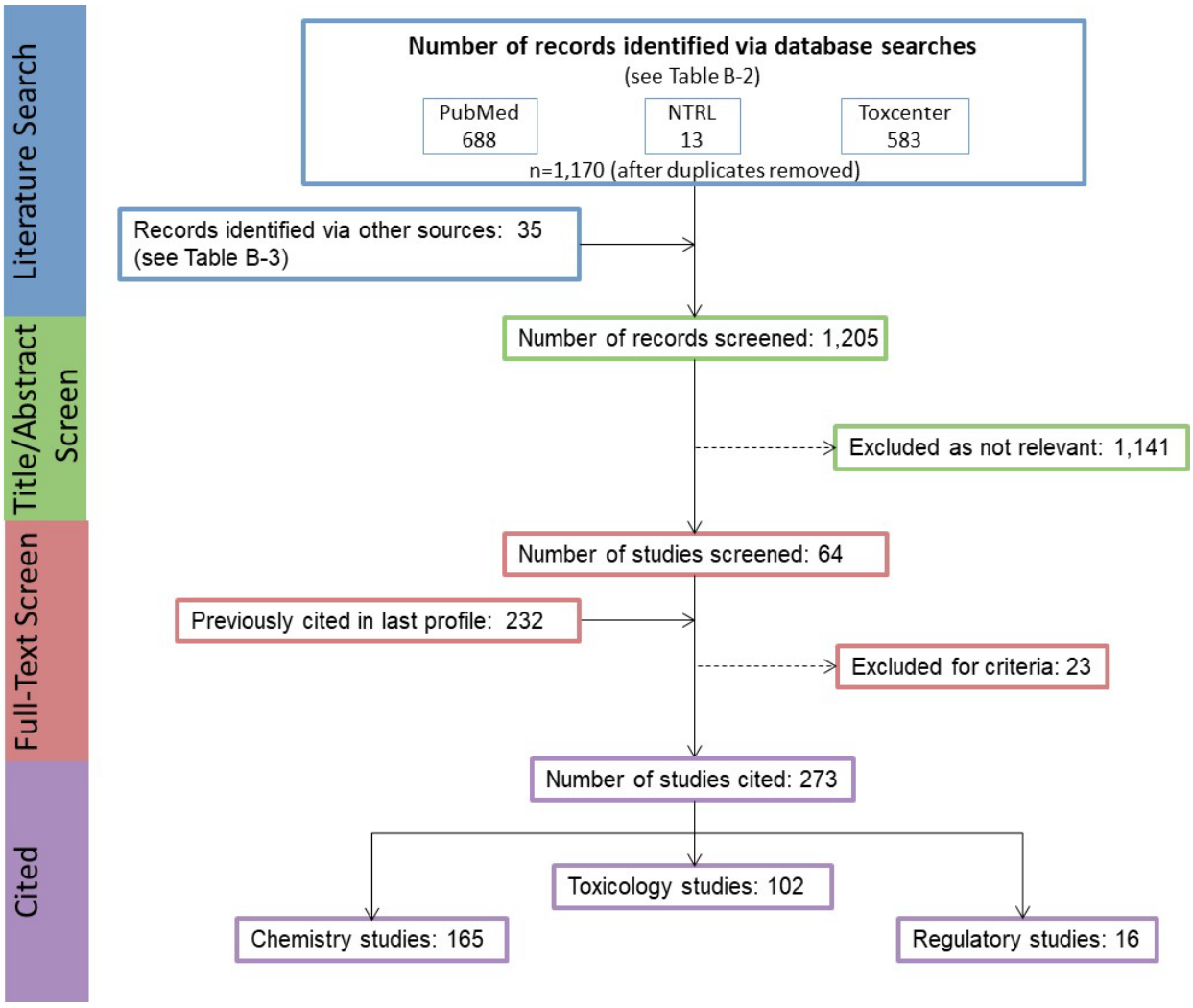
- Number of titles and abstracts screened: 1,205
- Number of studies considered relevant and moved to the next step: 64

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: 64
- Number of studies cited in the pre-public draft of the toxicological profile: 232
- Total number of studies cited in the profile: 273

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

Figure B-1. July 2022 Literature Search Results and Screen for Nitrophenols



APPENDIX C. FRAMEWORK FOR ATSDR'S SYSTEMATIC REVIEW OF HEALTH EFFECTS DATA FOR NITROPHENOLS

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 nitrophenols, ATSDR utilized a slight modification of NTP's Office of Health Assessment and Translation (OHAT) systematic review methodology (NTP 2013, 2015b; 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 nitrophenols:

- 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 nitrophenols. The inclusion criteria used to identify relevant studies examining the health effects of nitrophenols 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.

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

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

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

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
Cancer

C.2 LITERATURE SEARCH AND SCREEN FOR HEALTH EFFECTS STUDIES

A literature search and screen were conducted to identify studies examining the health effects of nitrophenols. The literature search framework for the toxicological profile is discussed in detail in Appendix B.

C.2.1 Literature Search

As noted in Appendix B, the current literature search was intended to update the Draft Toxicological Profile for Nitrophenols released for public comment in 2022. See Appendix B for the databases searched and the search strategy.

A total of 1,205 records relevant to all sections of the toxicological profile were identified (after duplicate removal).

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 nitrophenols.

Title and Abstract Screen. In the Title and Abstract Screen step, 1,205 records were reviewed; 2 documents were considered to meet the health effects inclusion criteria in Table C-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 23 health effect documents (documents identified in the update literature search and documents cited in older versions of the profile) was performed. From those 23 documents, 34 studies were included in the qualitative review.

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 Nitrophenols and overviews of the results of the inhalation, oral, and dermal exposure studies are presented in Sections 2.2–2.18 of the profile and in the Levels of Significant Exposures tables in Section 2.1 of the profile (Tables 2-1, 2-2, and 2-3, respectively).

C.4 IDENTIFY POTENTIAL HEALTH EFFECT OUTCOMES OF CONCERN

No relevant human studies that examined the health effects of exposure to nitrophenols were identified. Overviews of the potential health effect outcomes for 2- and 4-nitrophenol identified in animal studies are presented in Tables C-3 and C-4, respectively. Data for 2-nitrophenol are limited to a single inhalation study evaluating a comprehensive set of endpoints and three oral studies evaluating limited endpoints, and data for 3-nitrophenol are limited to two acute lethality studies. Therefore, available data for 2- and 3-nitrophenol are inadequate to support systematic review. For 4-nitrophenol, animal studies examined a comprehensive set of endpoints following inhalation, oral, or dermal exposure. Body weight effects following oral exposure, hematological effects (methemoglobinemia) following inhalation exposure, and ocular effects (irritation, corneal opacity, cataracts) were considered sensitive outcomes (i.e., effects were

observed at low concentrations or doses). Studies examining these potential outcomes following 4-nitrophenol were carried through to Steps 4–8 of the systematic review. There were 18 studies (published in 14 documents) examining these potential outcomes carried through to Steps 4–8 of the systematic review for 4-nitrophenol.

APPENDIX C

Table C-3. Overview of the Health Outcomes for 2-Nitrophenol 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	1	1	1	1	1	1	1	1	1	1		1	1	1			
		1															
Chronic-duration																	
Oral studies																	
Acute-duration	1													1			
														1			
Intermediate-duration																	
Chronic-duration																	
Dermal studies																	
Acute-duration																	
Intermediate-duration																	
Chronic-duration																	

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.

APPENDIX C

Table C-4. Overview of the Health Outcomes for 4-Nitrophenol 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	3	2	2	2	3		2	2	2	1	2	2	2	2			
	1	1			2					1		1	1				
Intermediate-duration	1	1	1	1	1	1	1	1	1	1	1	1	1	1			
										1							
Chronic-duration																	
Oral studies																	
Acute-duration	8	1		2	2		2	2			2	2	2	5	4		
	3	1		2			2						1				
Intermediate-duration	2	2	2	2	1	1	2	2	1	1	2	2	3	2	1		
		2					1	1					3				
Chronic-duration																	
Dermal studies																	
Acute-duration									3	2							
									3	2							
Intermediate-duration	1		1				1	1	1				1	1	1		2
									1								
Chronic-duration	1	1	1	1		1	1	1	1	1	1	1	1	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 2015a). The risk of bias questions for observational epidemiology studies, human-controlled exposure studies, and animal experimental studies are presented in Tables C-5, C-6, and C-7, respectively. 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-5. Risk of Bias Questionnaire for Observational Epidemiology Studies

Selection bias
Were the comparison groups appropriate?
Confounding bias
Did the study design or analysis account for important confounding and modifying variables?
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?

Table C-6. Risk of Bias Questionnaire for Human-Controlled Exposure Studies

Selection bias
Was administered dose or exposure level adequately randomized?
Was the allocation to study groups adequately concealed?
Performance bias
Were the research personnel and human subjects 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?

Table C-7. 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 animal experimental studies of nitrophenols health effects studies are presented in Table C-8.

APPENDIX C

Table C-8. Summary of Risk of Bias Assessment for 4-Nitrophenol – Experimental Animal Studies

Reference	Risk of bias criteria and ratings								Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias		Detection bias	Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	
Outcome: Hematological effects (inhalation only)									
Inhalation acute exposure									
Smith et al. 1988 (rat, lethal study)	–	–	+	–	++	–	–	+	Third
Smith et al. 1988 (rat, subacute 1)	–	–	+	+	++	–	++	+	Second
Smith et al. 1988 (rat, subacute 2)	–	–	+	+	++	–	++	+	Second
Inhalation intermediate exposure									
Hazleton 1983 (rat)	++	+	+	+	++	++	++	++	First
Outcome: Ocular effects									
Inhalation acute exposure									
Smith et al. 1988 (rat, lethal study)	–	–	+	–	++	–	+	+	Second
Smith et al. 1988 (rat, subacute 1)	–	–	+	–	++	–	+	+	Second
Smith et al. 1988 (rat, subacute 2)	–	–	+	–	++	–	+	+	Second
Inhalation intermediate exposure									
Hazleton 1983 (rat)	++	+	+	–	++	++	++	++	First

APPENDIX C

Table C-8. Summary of Risk of Bias Assessment for 4-Nitrophenol – Experimental Animal Studies

Reference	Risk of bias criteria and ratings								
	Selection bias		Performance bias		Attrition/ exclusion bias		Detection bias	Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	Risk of bias tier
Oral intermediate exposure									
Hazleton 1989 (rat)	++	+	++	–	++	++	++	++	First
Dermal acute exposure (instillation into the eye)									
EPA 1992b (rabbit)	+	– –	+	– –	++	++	+	++	Second
Monsanto 1983a (rabbit)	+	– –	+	– –	++	++	+	++	Second
Dermal chronic exposure									
NTP 1993 (mouse)	+	+	+	+	–	++	+	++	First
Outcome: Body weight effects (oral only)									
Oral Acute exposure									
Abu-Qare et al. 2000 (maternal rat)	–	+	+	+	++	++	+	++	First
EPA 1992a (maternal rat)	+	+	+	+	++	++	+	++	First
Kavlock 1990 (maternal rat)	–	+	+	+	++	+	++	++	First
Koizumi et al. 2001 (rat, 14-day)	+	+	+	+	++	+	++	–	First
Li et al. 2019; Tang et al. 2016 (rat, 1-day)	+	+	+	+	++	++	++	++	First
Li et al. 2019; Tang et al. 2016 (rat, 3-day)	+	+	+	+	++	++	++	++	First

Table C-8. Summary of Risk of Bias Assessment for 4-Nitrophenol – Experimental Animal Studies

Reference	Risk of bias criteria and ratings								
	Selection bias		Performance bias		Attrition/ exclusion bias		Detection bias	Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	Risk of bias tier
Plasterer et al. 1985 (mouse)	–	++	+	+	++	+	+	++	First
Plasterer et al. 1985 (maternal mouse)	+	++	+	+	++	+	+	+	First
Oral intermediate exposure									
Hazleton 1989 (rat)	++	+	++	+	++	++	++	++	First
Koizumi et al. 2001 (rat, 28-day)	+	+	+	+	++	+	++	++	First

*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 HHS, EPA, and IARC. The confidence in the body of evidence for an association or no association between exposure to nitrophenols 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 nitrophenols 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 observational epidemiology (cohort, population, and case-control) studies, human controlled exposure, and experimental animal studies are presented in Tables C-9, C-10, and C-11, respectively. 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-9. Key Features of Study Design for Observational Epidemiology Studies

Exposure was experimentally controlled
Exposure occurred prior to the outcome
Outcome was assessed on individual level rather than at the population level
A comparison group was used

Table C-10. Key Features of Study Design for Human-Controlled Exposure Studies

A comparison group was used or the subjects served as their own control
A sufficient number of subjects were tested
Appropriate methods were used to measure outcomes (i.e., clinically-confirmed outcome versus self-reported)
Appropriate statistical analyses were performed and reported or the data were reported in such a way to allow independent statistical analysis

Table C-11. 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 hematological, respiratory, and ocular effects observed in the observational animal experimental studies are presented in Table C-12.

A summary of the initial confidence ratings for each outcome is presented in Table C-12. 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-13.

Table C-12. Presence of Key Features of Study Design for 4-Nitrophenol—Experimental Animal Studies

Reference	Key features: Concurrent Control Group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	Initial study confidence
Outcome: Hematological effects *(inhalation only)*					
Inhalation acute exposure					
Smith et al. 1988 (rat, lethal study)	No	No	Yes	No	Very Low
Smith et al. 1988 (rat, subacute 1)	Yes	Yes	Yes	No	Moderate
Smith et al. 1988 (rat, subacute 2)	Yes	Yes	Yes	No	Moderate
Inhalation intermediate exposure					
Hazleton 1983 (rat)	Yes	No	Yes	Yes	Moderate
Outcome: Ocular effects					
Inhalation acute exposure					
Smith et al. 1988 (rat, lethal study)	No	Yes	Yes	Yes	Moderate
Smith et al. 1988 (rat, subacute 1)	Yes	Yes	Yes	No	Moderate
Smith et al. 1988 (rat, subacute 2)	Yes	Yes	Yes	No	Moderate
Inhalation intermediate exposure					
Hazleton 1983 (rat)	Yes	Yes	Yes	Yes	High
Oral intermediate exposure					
Hazleton 1989 (rat)	Yes	Yes	Yes	Yes	High
Dermal acute exposure (instillation into the eye)					
EPA 1992b (rabbit)	Yes	Yes	Yes	No	Moderate
Monsanto 1983a (rabbit)	Yes	Yes	Yes	No	Moderate
Dermal chronic exposure					
NTP 1993 (mouse)	Yes	Yes	Yes	Yes	High
Outcome: Body weight effects *(oral only)*					
Oral acute exposure					
Abu-Qare et al. 2000 (maternal rat)	Yes	No	Yes	No	Low
EPA 1992a (maternal rat)	Yes	Yes	Yes	No	Moderate
Kavlock 1990 (maternal rat)	Yes	Yes	Yes	Yes	High
Koizumi et al. 2001 (rat, 14-day)	Yes	Yes	Yes	No	Moderate

Table C-12. Presence of Key Features of Study Design for 4-Nitrophenol—Experimental Animal Studies

Reference	Key features: Concurrent Control Group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	Initial study confidence
Li et al. 2019; Tang et al. 2016 (rat, 1-day)	Yes	Yes	Yes	Yes	High
Li et al. 2019; Tang et al. 2016 (rat, 3-day)	Yes	Yes	Yes	Yes	High
Plasterer et al. 1985 (mouse)	Yes	Yes	Yes	Yes	High
Plasterer et al. 1985 (maternal mouse)	Yes	Yes	Yes	Yes	High
Oral intermediate exposure					
Hazleton 1989 (rat)	Yes	Yes	Yes	Yes	High
Koizumi et al. 2001 (rat, 28-day)	Yes	No	Yes	Yes	Moderate

Table C-13. Initial Confidence Rating for 4-Nitrophenol Health Effects Studies

	Initial study confidence	Initial confidence rating
Outcome: Hematological effects		
Inhalation acute exposure		
Smith et al. 1988 (rat, lethal study)	Very Low	
Smith et al. 1988 (rat, subacute 1)	Moderate	Moderate
Smith et al. 1988 (rat, subacute 2)	Moderate	
Inhalation intermediate exposure		
Hazleton 1983 (rat)	Moderate	Moderate
Outcome: Ocular effects		
Inhalation acute exposure		
Smith et al. 1988 (rat, lethal study)	Moderate	
Smith et al. 1988 (rat, subacute 1)	Moderate	Moderate
Smith et al. 1988 (rat, subacute 2)	Moderate	
Inhalation intermediate exposure		
Hazleton 1983 (rat)	High	High
Oral intermediate exposure		
Hazleton 1989 (rat)	High	High

Table C-13. Initial Confidence Rating for 4-Nitrophenol Health Effects Studies

	Initial study confidence	Initial confidence rating
Dermal acute exposure (instillation into the eye)		
EPA 1992b (rabbit)	Moderate	Moderate
Monsanto 1983a	Moderate	Moderate
Dermal chronic exposure		
NTP 1993 (mouse)	High	High
Outcome: Body weight effects (oral only)		
Oral acute exposure		
Abu-Qare et al. 2000 (maternal rat)	Low	High
EPA 1992a (maternal rat)	Moderate	
Kavlock 1990 (maternal rat)	High	
Koizumi et al. 2001 (rat, 14-day)	Moderate	
Li et al. 2019; Tang et al. 2016 (rat, 1-day)	High	
Li et al. 2019; Tang et al. 2016 (rat, 3-day)	High	
Plasterer et al. 1985 (mouse)	High	
Plasterer et al. 1985 (maternal mouse)	High	
Oral intermediate exposure		
Hazleton 1989 (rat)	High	High
Koizumi et al. 2001 (rat, 28-day)	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 hematological, ocular, and respiratory effects are presented in Table C-14. If the confidence ratings for a particular outcome were based on more than one type of human study, then the highest confidence rating was used for subsequent analyses. An overview of the confidence in the body of evidence for all health effects associated with nitrophenols exposure is presented in Table C-15.

Table C-14. Adjustments to the Initial Confidence in the Body of Evidence in Experimental Studies

	Initial confidence	Adjustments to the initial confidence rating	Final confidence rating
Outcome: Hematological Effects (inhalation only)			
Animal studies	Moderate	-1 risk of bias	Low
Outcome: Ocular Effects			
Animal studies	High	-1 risk of bias	Moderate
Outcome: Body weight Effects			
Animal studies	High	-1 unexplained inconsistency, -1 publication bias	Low

Table C-15. Confidence in the Body of Evidence for 4-Nitrophenol

	Confidence in body of evidence	
Outcome	Human studies	Animal studies
Hematological effects	No data	Low
Ocular effects	No data	Moderate
Body weight effects	No data	Low

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 (Tables C-5, C-6, and C-7). 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 due to 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 nitrophenols, 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 nitrophenols is presented in Table C-16.

Table C-16. Level of Evidence of Health Effects for 4-Nitrophenol

Outcome	Confidence in body of evidence	Direction of health effect	Level of evidence for health effect
Human studies			
Hematological effects	No data		No data
Ocular effects	No data		No data
Body weight effects	No data		No data
Animal studies			
Hematological effects	Low	Health effect	Low
Ocular Effects	Moderate	Health effect	Moderate
Body weight effects	Low	Health effect	Low

C.8INTEGRATE EVIDENCE TO DEVELOP HAZARD IDENTIFICATION CONCLUSIONS

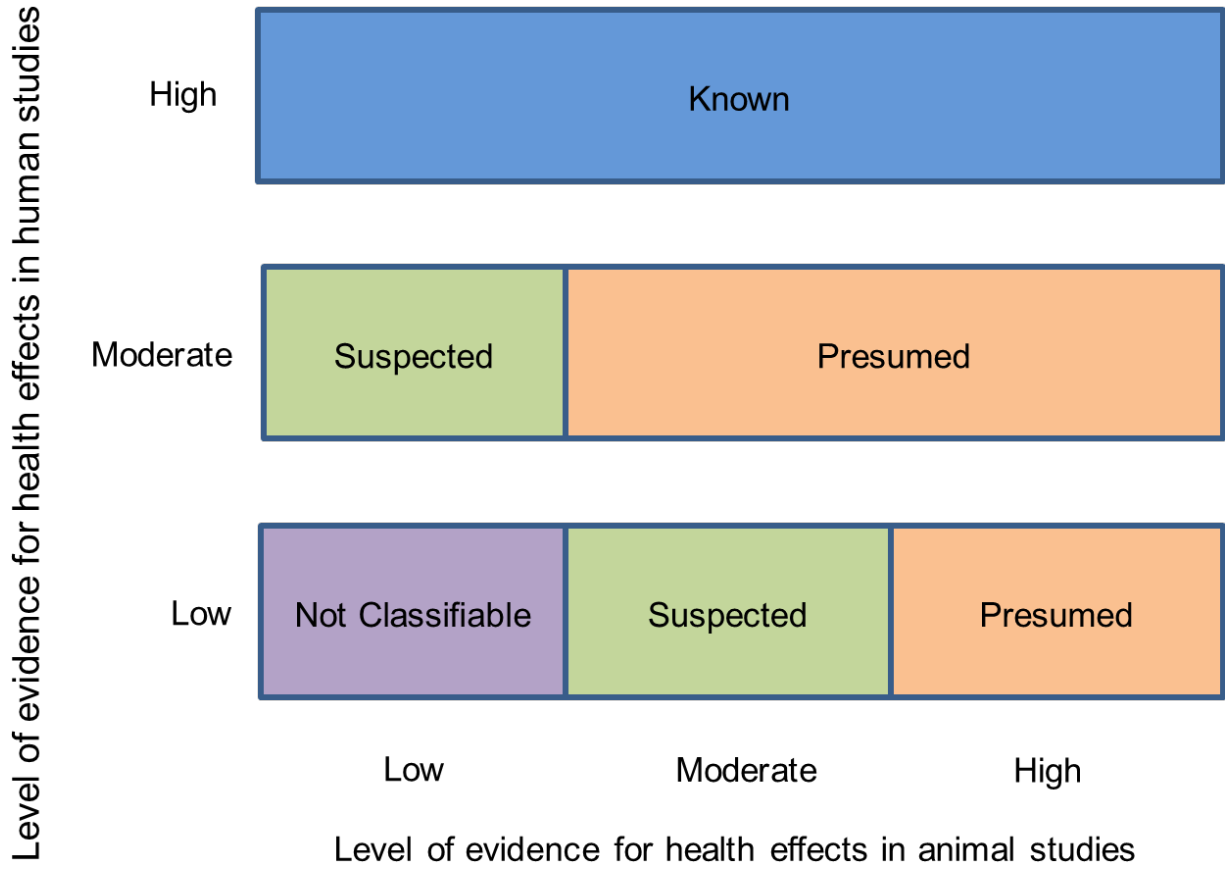
The final step involved the integration of the evidence streams for the human studies and animal studies to allow for a determination of hazard identification conclusions. For health effects, there were four hazard identification conclusion categories:

- **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

Figure C-1. Hazard Identification Scheme



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 nitrophenols are listed below and summarized in Table C-17.

Suspected Health Effects

- Ocular effects
  - No human data regarding ocular effects following exposure to 4-nitrophenol.

- Moderate evidence from animal studies that examine acute- and intermediate-duration inhalation exposure of 4-nitrophenol show changes in ocular function, including corneal opacity, as well as unilateral and bilateral diffused anterior capsular cataracts (Hazleton 1983; Smith et al. 1988). Severe eye irritation, inflammation, neovascularization, visible destruction of iris, and corneal opacity have been observed in rabbits following direct ocular exposure to 4-nitrophenol (EPA 1992b; Monsanto 1983a). It is likely that the ocular effects noted in inhalation studies are due to direct ocular contact with dust particles in the air. No ocular effects were observed following oral or dermal exposure to 4-nitrophenol (Hazleton 1989; NTP 1993).

Not Classifiable

- Hematological effects following inhalation exposure
  - No human studies evaluating hematological endpoints following inhalation exposure to 4-nitrophenol were identified.
  - Low evidence of hematological effects, specifically methemoglobinemia, in laboratory animals due to moderate risk of bias in the study reporting methemoglobinemia following acute inhalation exposure to high concentrations of 4-nitrophenol (Smith et al. 1988). An intermediate-duration inhalation study did not observe methemoglobinemia in rats (Hazleton 1983). This apparent inconsistency may be due to exposure at comparatively lower concentrations by Hazleton (1984), compared to Smith et al. (1988), or due to study design issues.
- Body weight effects following oral exposure
  - No human studies evaluating body weight following inhalation exposure to 4-nitrophenol were identified.
  - Low evidence of body weight effects in laboratory animals due to unexplained inconsistencies across studies and exposure durations. Some acute-duration studies reported decreased body weights (EPA 1992a; Li et a. 2017; Plasterer et al. 1985; Tang et al. 2016), while others did not (Abu-Qare et al. 2000; Kavlock 1990; Koizumi et al. 2001). Body weight effects were not noted in intermediate-duration studies (Hazleton 1989; Koizumi et al. 2001). Additionally, body weight effects are often subjected to publication bias due to lack of reporting in the absence of adverse effects.

Table C-17. Hazard Identification Conclusions for 4- Nitrophenol

Outcome	Hazard identification
Ocular effects	Suspected health effect
Hematological effects (inhalation only)	Health effect not classifiable
Body weight effects (oral only)	Health effect not classifiable

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), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), food intake (FI), gross necropsy (GN), hematology (HE), histopathology (HP), immune function (IX), lethality (LE), neurological function (NX), organ function (OF), ophthalmology (OP), organ weight (OW), reproductive function (RX), 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.

(12) 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.

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

(14) 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.

(15) 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).

(16) 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.

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

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

Figure key[a] (4)	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 (3)	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									

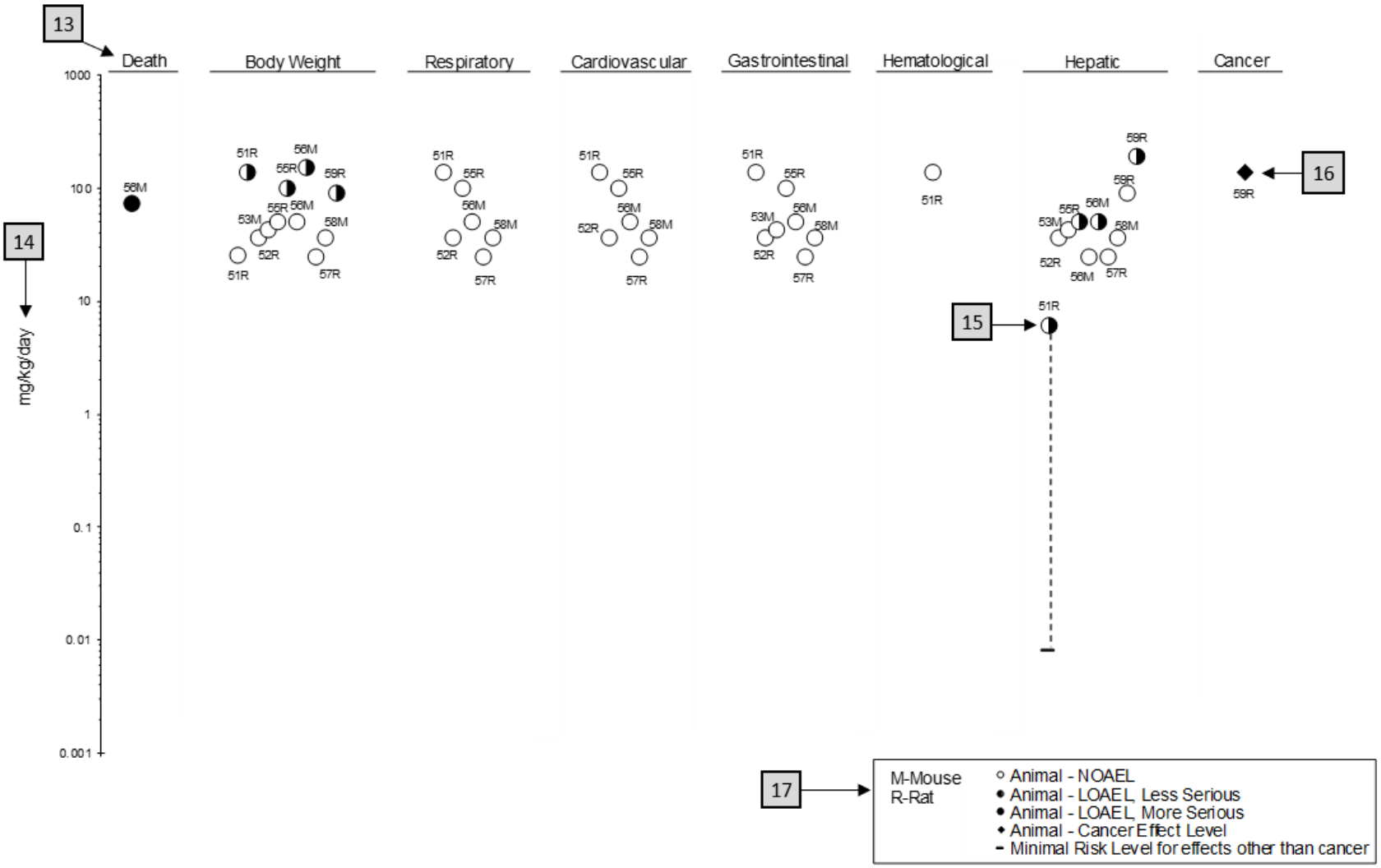
[a]The number corresponds to entries in Figure 2-x.

(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).

APPENDIX D

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

ATSDR develops educational and informational materials for health care providers categorized by hazardous substance, clinical condition, and/or by susceptible population. The following additional materials are available online:

Physician Briefs discuss health effects and approaches to patient management in a brief/factsheet style. *Physician Overviews* are narrated PowerPoint presentations with Continuing Education credit available (see https://www.atsdr.cdc.gov/emes/health_professionals/index.html).

Managing Hazardous Materials Incidents is a 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.html).

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
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
PEHSU	Pediatric Environmental Health Specialty Unit
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
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 limit
REL-C	recommended exposure limit-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
SLOAEL	serious lowest-observed-adverse-effect level
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