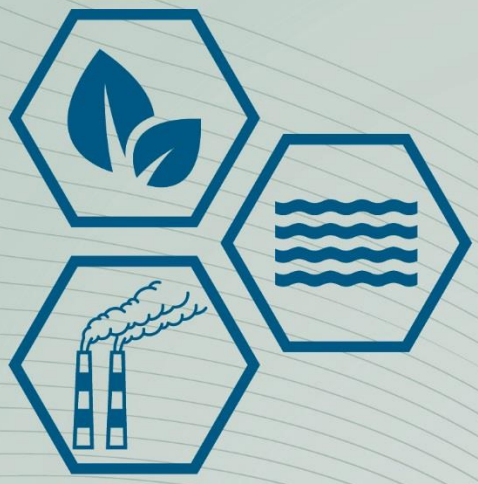

Toxicological Profile for Nitrophenols

Draft for Public Comment

April 2022

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

CS274127-A

FOREWORD

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

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

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

Each profile includes the following:

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

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

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

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

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

Written comments may also be sent to: Agency for Toxic Substances and Disease Registry
Office of Innovation and Analytics
Toxicology Section
1600 Clifton Road, N.E.
Mail Stop S102-1
Atlanta, Georgia 30329-4027

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

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

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VERSION HISTORY

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

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

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

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

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CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

Mononitrophenols 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-). Mononitrophenol isomers (also referred to as "nitrophenols") are primarily used as intermediates to produce dyes, pigments, pharmaceuticals, rubber chemicals, photographic chemicals, 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. Mononitrophenols are expected to be highly soluble in water. They also have low vapor pressures, and therefore potential for long range atmospheric transport is low. The atmospheric half-lives of these compounds are 3 to 18 days.

The general population may be exposed to nitrophenols through the inhalation of ambient air, though there are no recent U.S. air monitoring data for nitrophenols to quantify exposure. Mononitrophenol 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 as a result of the thermal reaction of fuel with oxides of nitrogen. The nitrophenols are released from exhausts of both gasoline- and diesel-powered vehicles.

Nitrophenols have not been detected in drinking water and foods. 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 these two 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 of this profile.

1.2 SUMMARY OF HEALTH EFFECTS

Information on nitrophenols toxicity is limited and comes primarily from oral studies on laboratory animals, followed by inhalation studies on laboratory animals, and a few dermal studies on laboratory

animals. No human studies that focused specifically on isolated exposure to nitrophenols were identified in the literature. All animal studies focused on the toxicity of 4-nitrophenol, with the exception of one inhalation and one oral study that focused on 2-nitrophenol. No animal studies focusing on 3-nitrophenol toxicity were identified. The existing experimental animal database is limited regarding the health effects of nitrophenols due to the fact that for many endpoints, there are only a small number of well-conducted studies, and the majority of the literature is over 20 years old. Additionally, many chronic toxic endpoints as well as early life stage health effects have not been adequately characterized in the currently available literature. The available literature suggests that the main toxicity targets of nitrophenols in mammals appear to include the eyes, respiratory, and hematological systems. Evaluation of the existing animal database found mixed results with respect to hepatic, renal, and gastrointestinal toxicity, as well as body weight changes in response to 4-nitrophenol exposure, with some studies observing effects while others did not. Figure 1-1 shows the health effects found in animals following inhalation exposure to 4-nitrophenol. Figure 1-2 shows health effects found in animals following oral exposure to 4-nitrophenol. A systematic review was conducted on the hematological, respiratory, and ocular endpoints after exposure to 4-nitrophenol. Weight-of-evidence conclusions are defined in Appendix C. The review resulted in the following hazard identification conclusions:

- Hematological effects are a suspected health effect of 4-nitrophenol exposure.
- Respiratory effects are a suspected health effect of 4-nitrophenol exposure.
- Ocular effects are not classifiable (defined as low evidence from animal studies and an absence of human studies) as a health effect of 4-nitrophenol exposure.

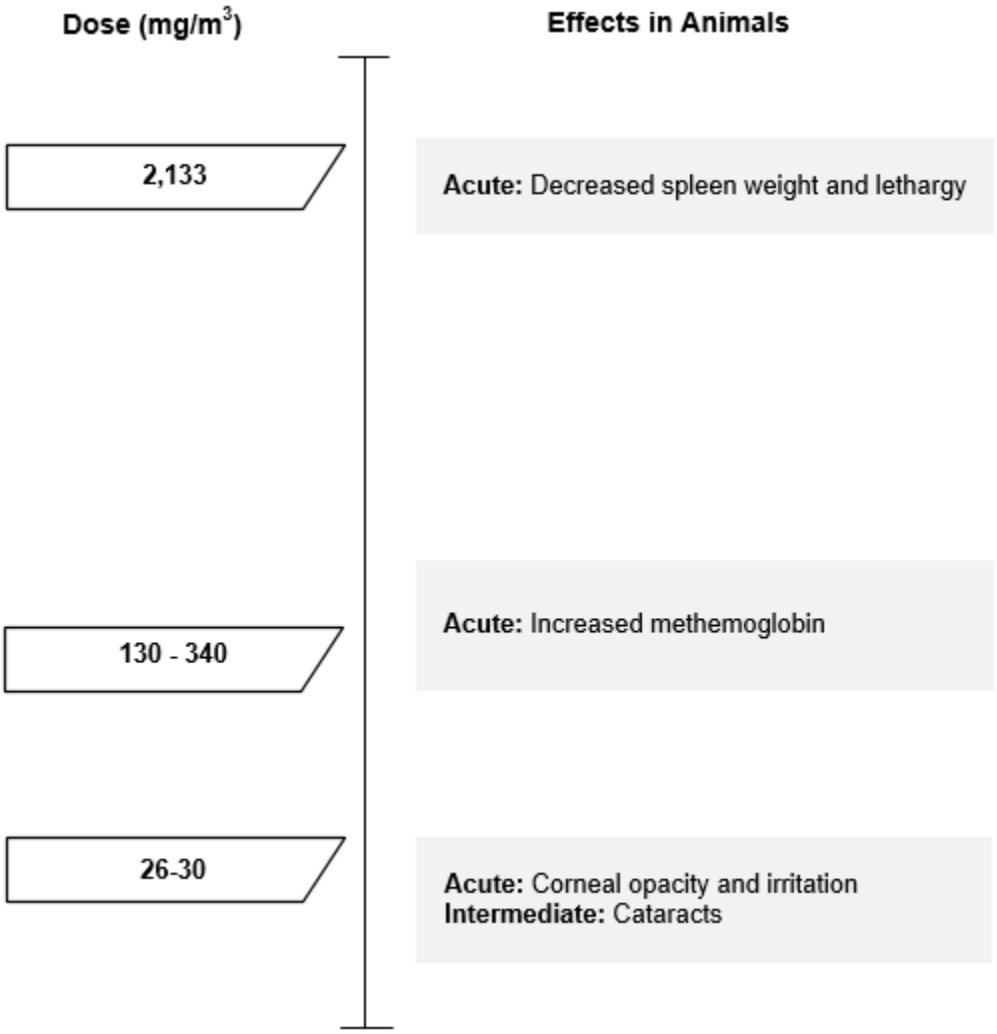
Respiratory Effects. No evidence from human studies was identified or evaluated in this systematic review for respiratory endpoints. Experimental animal studies provide moderate evidence of an association between 4-nitrophenol exposure and adverse respiratory effects. Increased lung weight was observed in rats after acute (≤14 days) inhalation exposure, while wheezing and dyspnea were observed in rats after acute oral exposure to 4-nitrophenol. However, no significant respiratory effects were observed in an intermediate-duration (>14 –364 days) inhalation study and an intermediate-duration oral study. A single intermediate inhalation exposure study of 2-nitrophenol in rats observed a significant increase in squamous metaplasia of the nasal epithelium.

Hematological Effects. No evidence from human studies was identified or evaluated in this systematic review for hematological endpoints. Experimental animal studies provide moderate evidence of an

association between 4-nitrophenol exposure and adverse hematological effects. An increase in methemoglobin was showed in rats after acute-duration inhalation exposure, in addition to elevated erythrocytes, hemoglobin, hematocrit, and creatinine. An intermediate-duration inhalation study of 4-nitrophenol observed a significant increase in methemoglobin in rats at lower concentration groups, but this same result was not observed at higher concentrations, indicating that it might not be a true effect. It is also possible, however, that there are compensatory mechanisms involved when the animals are exposed to the higher doses of nitrophenols, thus mitigating the health effects observed at lower doses. Hematological effects were not observed in acute- or intermediate-duration oral studies of 4-nitrophenol in rats. A single intermediate-duration inhalation exposure study of 2-nitrophenol in rats also showed an increase in methemoglobin in a lower concentration group, but not in the higher concentration groups, indicating that it might not be a true effect.

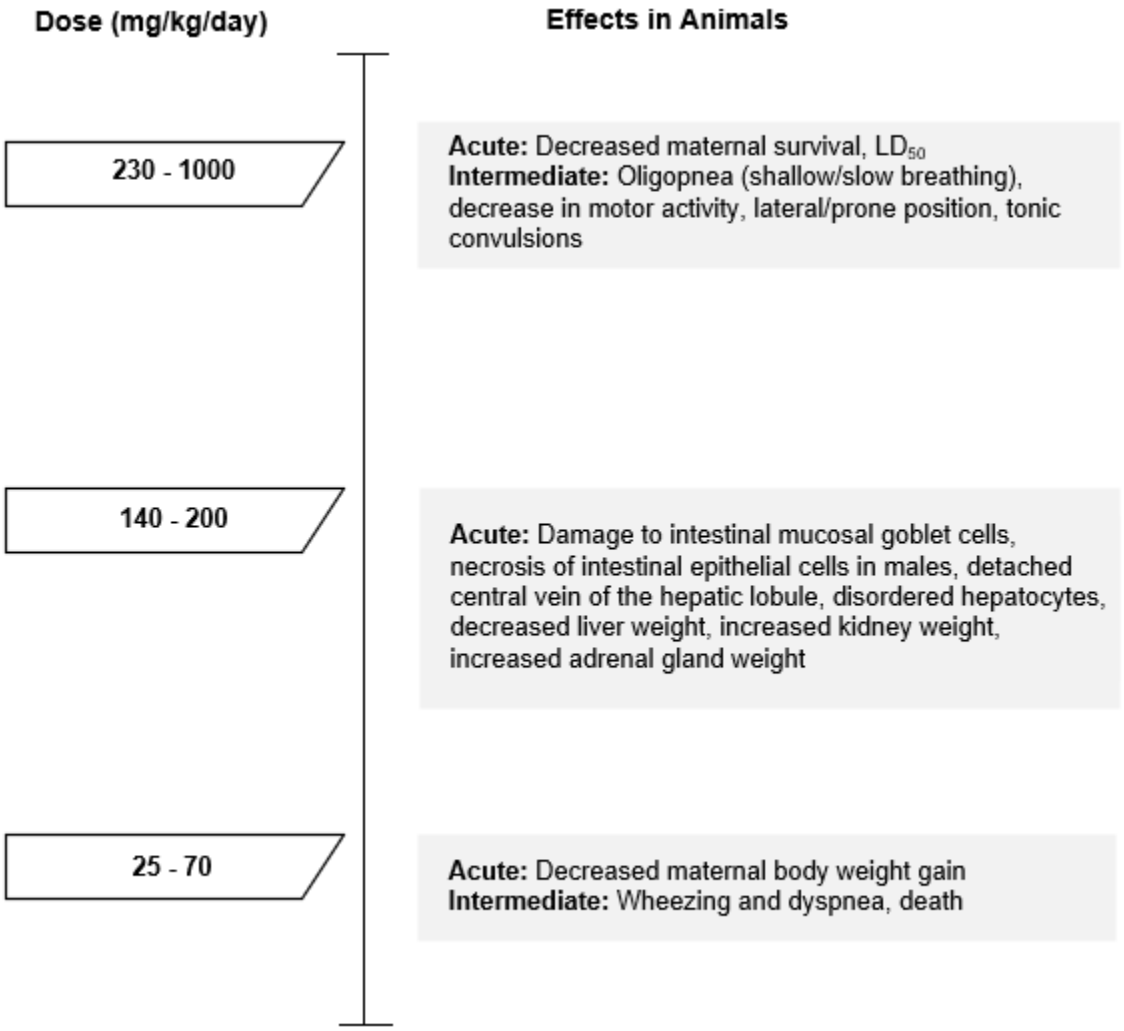
Ocular Effects. No evidence from human studies was identified or evaluated in this systematic review for ocular endpoints. Experimental animal studies provide low evidence of an association between 4-nitrophenol exposure and adverse ocular effects, particularly after inhalation and dermal exposure. Acute inhalation exposure led to corneal opacity and ocular irritation in rats, and cataracts have been observed in rats after intermediate inhalation exposure. No ocular effects were observed in an intermediate oral gavage study in rats, and no other oral studies observing ocular effects were identified. Severe conjunctival irritation and corneal opacity, along with irritation and visible destruction of the iris were observed after acute dermal exposure to the conjunctival sac of one eye in rabbits. However, this study did not include a control group, and no ocular effects were observed in available intermediate or chronic dermal studies. A single intermediate inhalation exposure study of 2-nitrophenol in rats found no ocular effects.

Figure 1-1. Health Effects Found in Animals Following Inhalation Exposure to 4-Nitrophenol*



*Health effects resulting from acute-duration exposure to 2-nitrophenol were not included in this figure. See **Error! Reference source not found.** for further detail on effects of 2-nitrophenol.

Figure 1-2. Health Effects Found in Animals Following Oral Exposure to 4-Nitrophenol



1.3 MINIMAL RISK LEVELS (MRLS)

The databases for 2-, 3-, and 4-nitrophenol were all considered inadequate for the derivation of MRLs for any exposure route and duration. Table 1-1 shows that all exposure durations and routes for each chemical have insufficient data for the derivation of an MRL. The rationale for not deriving each MRL is discussed in greater detail in Appendix A.

Ocular and hematological effects appear to be the most sensitive targets of inhaled 4-nitrophenol (Figure 1-3). Respiratory and body weight effects appear to be the most sensitive targets of oral exposure to 4-nitrophenol (Figure 1-4). The sensitive endpoints observed in animal studies are at relatively high doses compared to typical human exposures.

Figure 1-3. Summary of Sensitive Targets of 4-Nitrophenol – Inhalation

Ocular and hematological effects are the most sensitive targets of 4-nitrophenol inhalation exposure.

Numbers in circles are the lowest LOAELs among health effects in animals.

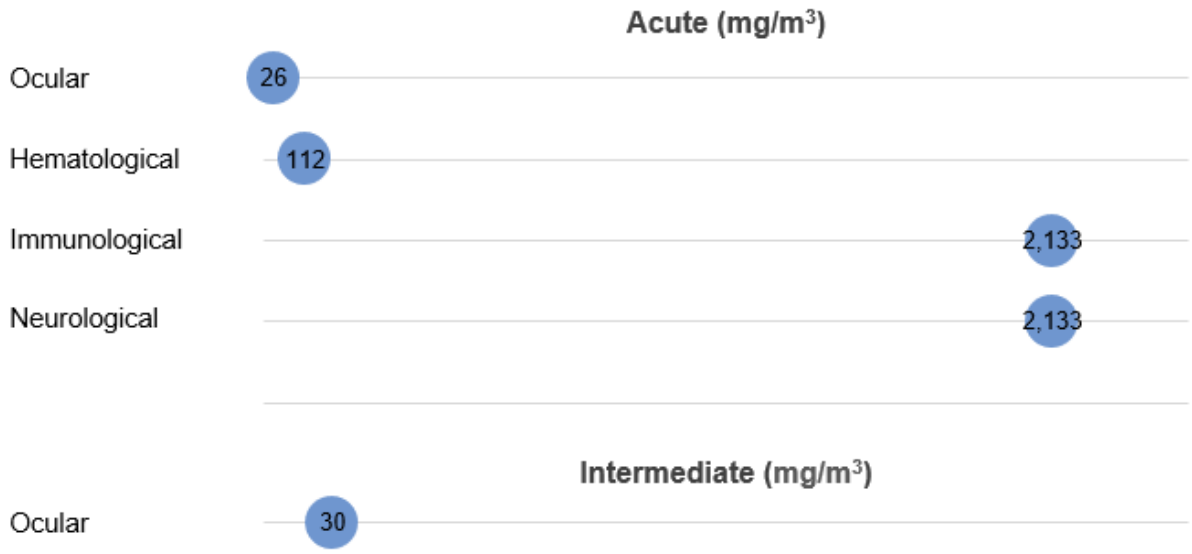


Figure 1-4. Summary of Sensitive Targets of 4-Nitrophenol – Oral

Respiratory and body weight effects are the most sensitive targets of 4-nitrophenol oral exposure.
Numbers in circles are the lowest LOAELs among health effects in animals.

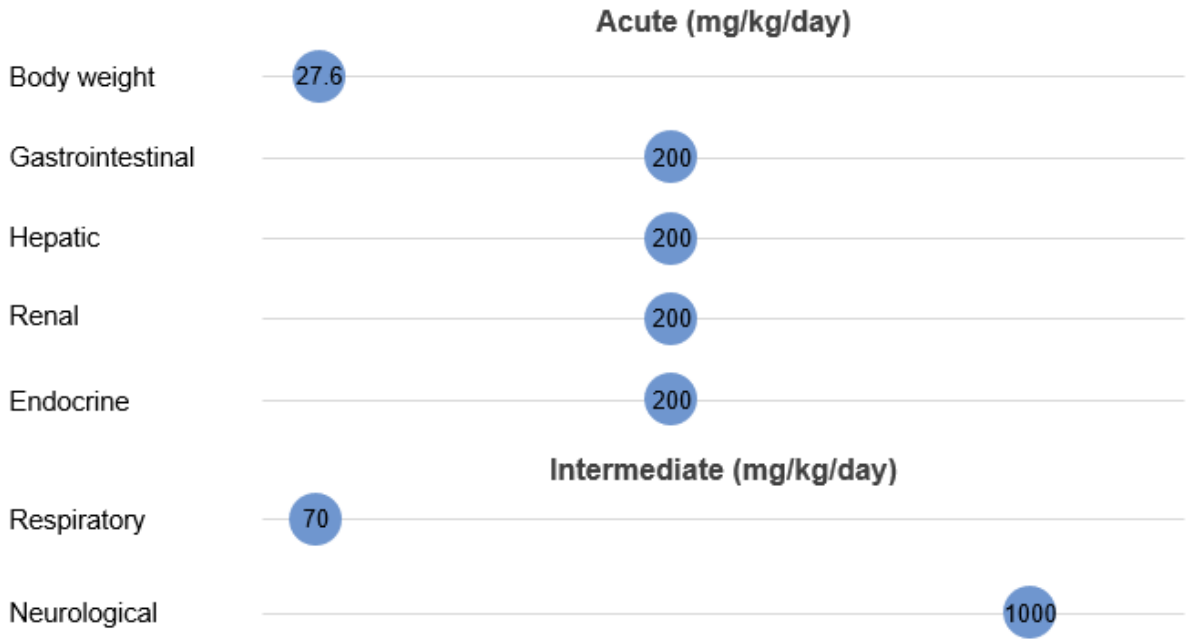


Table 1-1. Minimum Risk Levels (MRLs) for Nitrophenols[a]

Exposure duration	Provisional MRL	Critical effect(s)	Point of departure	Uncertainty factor	Reference
No MRLs were derived for any exposure route or duration for any of 2-, 3-, or 4-Nitrophenol.					

[a] See Appendix A for additional information

CHAPTER 2. HEALTH EFFECTS

OVERVIEW

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 are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a

considerable amount of judgment may be required in establishing whether an endpoint should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these endpoints. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose, frequency, 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 health effects of nitrophenols have been evaluated in experimental animal studies only. As illustrated in Figure 2-1, most of the health effects data come from oral and inhalation studies. Animal data are available for each exposure route and exposure duration category, however there are limited studies available for each. The majority of the studies evaluating the toxicity of nitrophenols focus on 4-nitrophenol, while only one study focused on the toxicity of 2-nitrophenol. No studies were identified in the literature that evaluated the toxicity of 3-nitrophenol. Many of the studies evaluating the toxicity of nitrophenols have evaluated a suite of endpoints. Body weight effects are the most examined effect in the literature, followed by hepatic, and neurological effects. The genotoxicity of 2- and 4-nitrophenol have also been examined, but no genotoxicity studies of 3-nitrophenol were identified in the literature.

Research on the health effects of nitrophenols suggest several sensitive endpoints of toxicity:

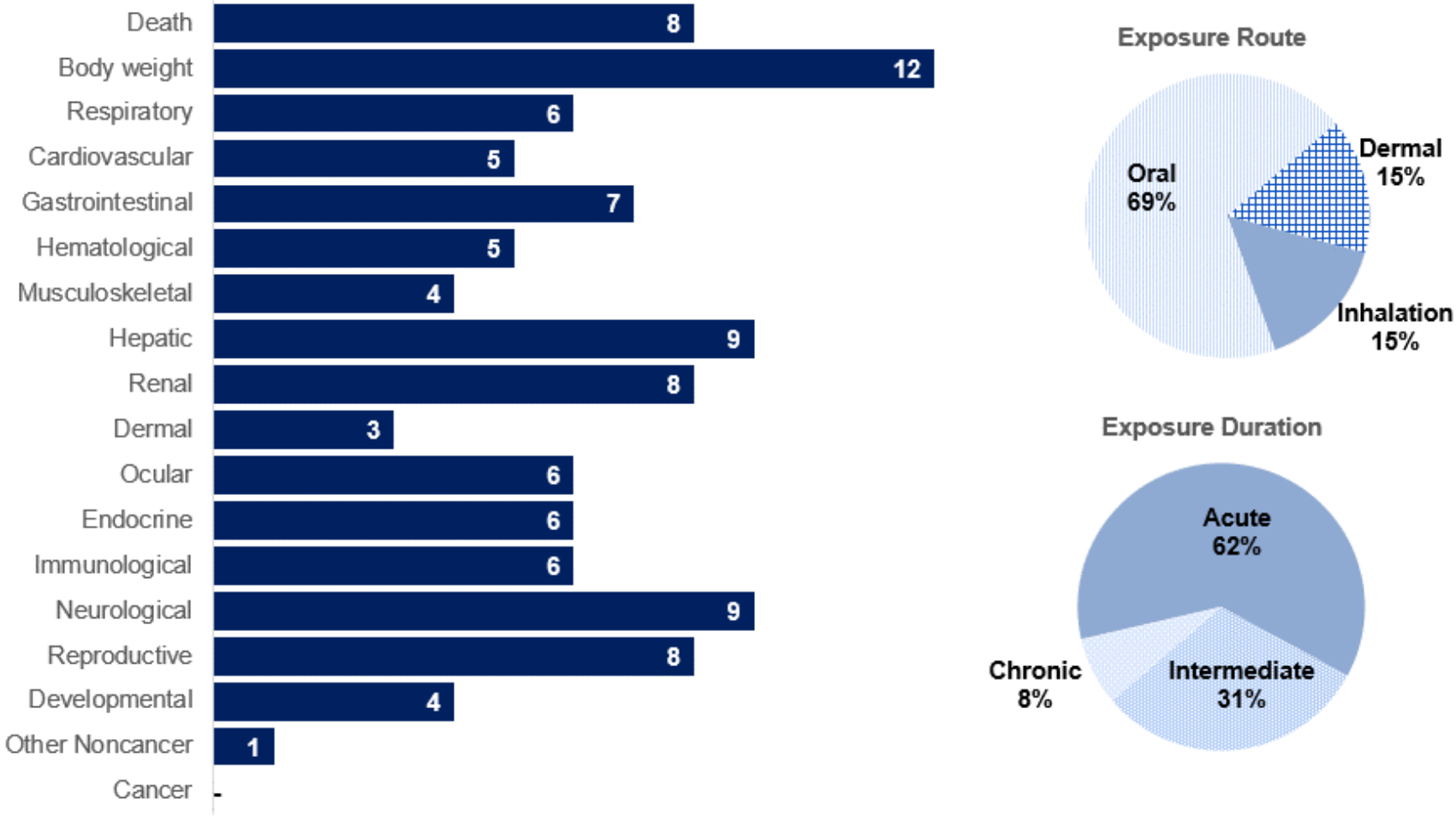
- **Respiratory Endpoints.** Studies of respiratory effects of 4-nitrophenol exposure in animals have shown wheezing and dyspnea after oral exposure, and increased lung weight after inhalation exposure, however these effects were not consistently observed. Animal inhalation exposure to 2-nitrophenol has led to a significant increase in squamous metaplasia of the nasal epithelium.
- **Hematological Endpoints.** Studies of hematological effects in animals have been mixed, though an increase in methemoglobin, erythrocytes, hemoglobin, hematocrit, and creatinine have been observed after inhalation exposure to 4-nitrophenol. Results of a study investigating hematological effects in animals after 2-nitrophenol inhalation exposure were inconclusive.

- **Ocular Endpoints.** Animal studies on ocular effects of 4-nitrophenol have observed cataracts, corneal opacity, and ocular irritation after inhalation exposure, though no ocular effects were observed after oral exposure. Dermal exposure to 4-nitrophenol showed mixed results, with direct ocular application leading to severe conjunctival irritation, corneal opacity, and visible destruction of the iris, however these results were observed in a study that did not contain a control group. No ocular effects were observed after animal inhalation exposure to 2-nitrophenol.

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

Most studies examined the potential body weight, hepatic, neurological, renal, and reproductive effects of nitrophenols

Studies evaluated health effects in only [redacted] (counts represent studies examining endpoint)



*Includes studies discussed in Chapter 2. A total of 13 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

Table 2-1. Levels of Significant Exposure to Nitrophenols – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effects
ACUTE EXPOSURE									
Smith et al. 1988									**4-nitrophenol**
1	RAT (Albino) 10M	2 weeks 5 days/week 6 hours/day	0, 294, 2,133	BC BW GN HE HP OW UR	Bd wt	2,133			
					Resp	2,133			
					Hemato	294		2,133	Methemoglobin increase of 665%. Recovery day 14 erythrocytes, hemoglobin, and methemoglobin remained elevated by 7%, 7.5% and 250% respectively.
					Hepatic	2,133			
					Renal	2,133			
					Ocular		294		Corneal opacity and irritation
					Immuno	294	2,133		Decreased mean absolute and mean relative spleen weight (not otherwise described)
					Neuro	294	2,133		Lethargy observed (not otherwise described)
Smith et al. 1988									**4-nitrophenol**
2	RAT (Albino) 10M	2 weeks 5 days/week 6 hours/day	0, 26, 112	BC BW CS GN HE HP OW UR	Bd wt	112			
					Hemato	26		112	Methemoglobin increase 200%
					Ocular		26		Corneal opacity and irritation
INTERMEDIATE EXPOSURE									

Table 2-1. Levels of Significant Exposure to Nitrophenols – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effects
Hazleton 1983									**4-nitrophenol**
3	RAT (Sprague-Dawley) 15M,15F	4 weeks 5 days/week 6 hours/day	0, 1, 5, 30	BC BI BW CS GN HP OW	Bd wt	30			
					Resp	30			
					Cardio	30			
					Gastro	30			
					Hemato	30			
					Musc/skel	30			
					Hepatic	30			
					Renal	30			
					Ocular	5		30	Cataracts in 11/30
					Endocr	30			
					Immuno	30			
					Neuro	30			
					Repro	30			
Hazleton 1984									**2-nitrophenol**
4	RAT (Sprague-Dawley) 15M, 15F	4 weeks 5 days/week 6 hours/day	0, 5, 32.5, 61.5	BC BI BW CS GN HE HP LE OW OF	Bd wt	61.5			
					Resp	5	32.5		Squamous metaplasia in nasal cavity in 10/10 males and 9/10 females
					Cardio	61.5			
					Gastro	61.5			

Table 2-1. Levels of Significant Exposure to Nitrophenols – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effects
					Hemato	61.5			
					Musc/skel	61.5			
					Hepatic	61.5			
					Renal	61.5			
					Ocular	61.5			
					Immuno	61.5			
					Neuro	61.5			
					Repro	61.5			

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

AST = aspartate aminotransferase; BC = blood chemistry; BI = biochemical indices; BW or Bd wt = body weight; CS = clinical signs; F= female(s); GN = gross necropsy; HE = hematological; HP = histopathology; Immuno = immunological; LE = lethality; LOAEL = lowest-observed-adverse-effect-level; M = male(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect-level; NS = not specified; OF = organ function; OW = organ weight; Resp = respiratory; UR = urinalysis

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

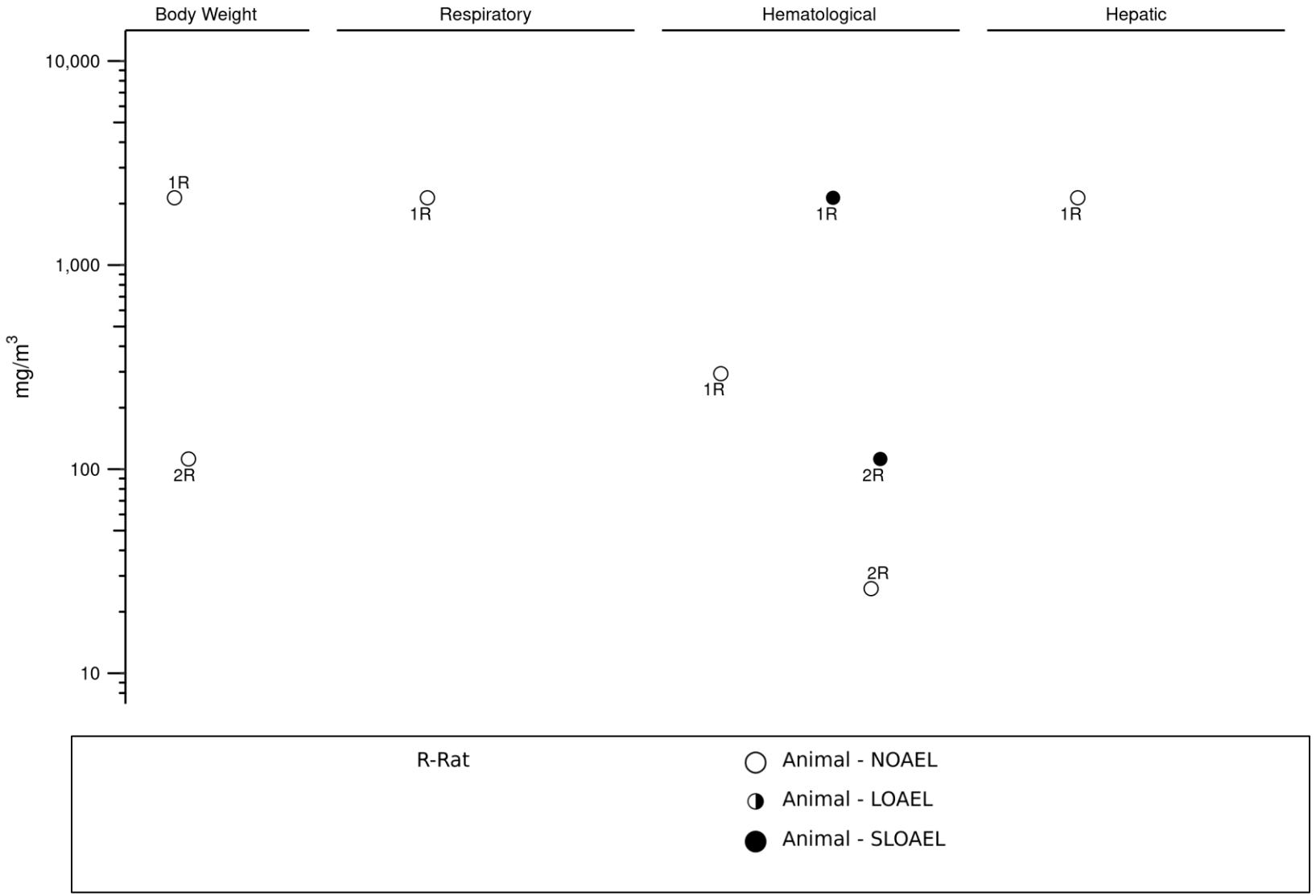


Figure 2-2. Levels of Significant Exposure to Nitrophenols – Inhalation
Acute (≤14 days)

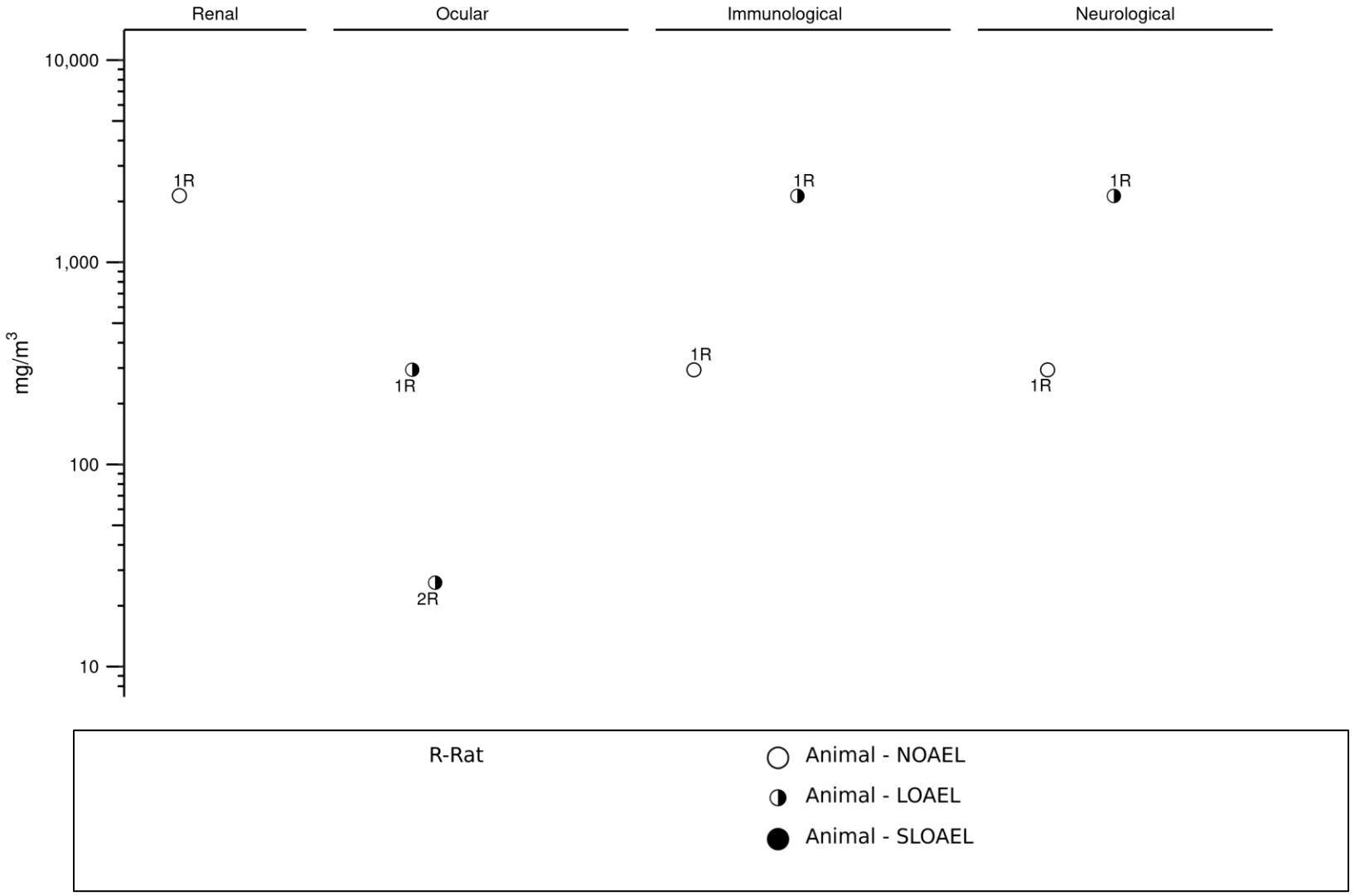


Figure 2-2. Levels of Significant Exposure to Nitrophenols – Inhalation
Intermediate (15-364 days)

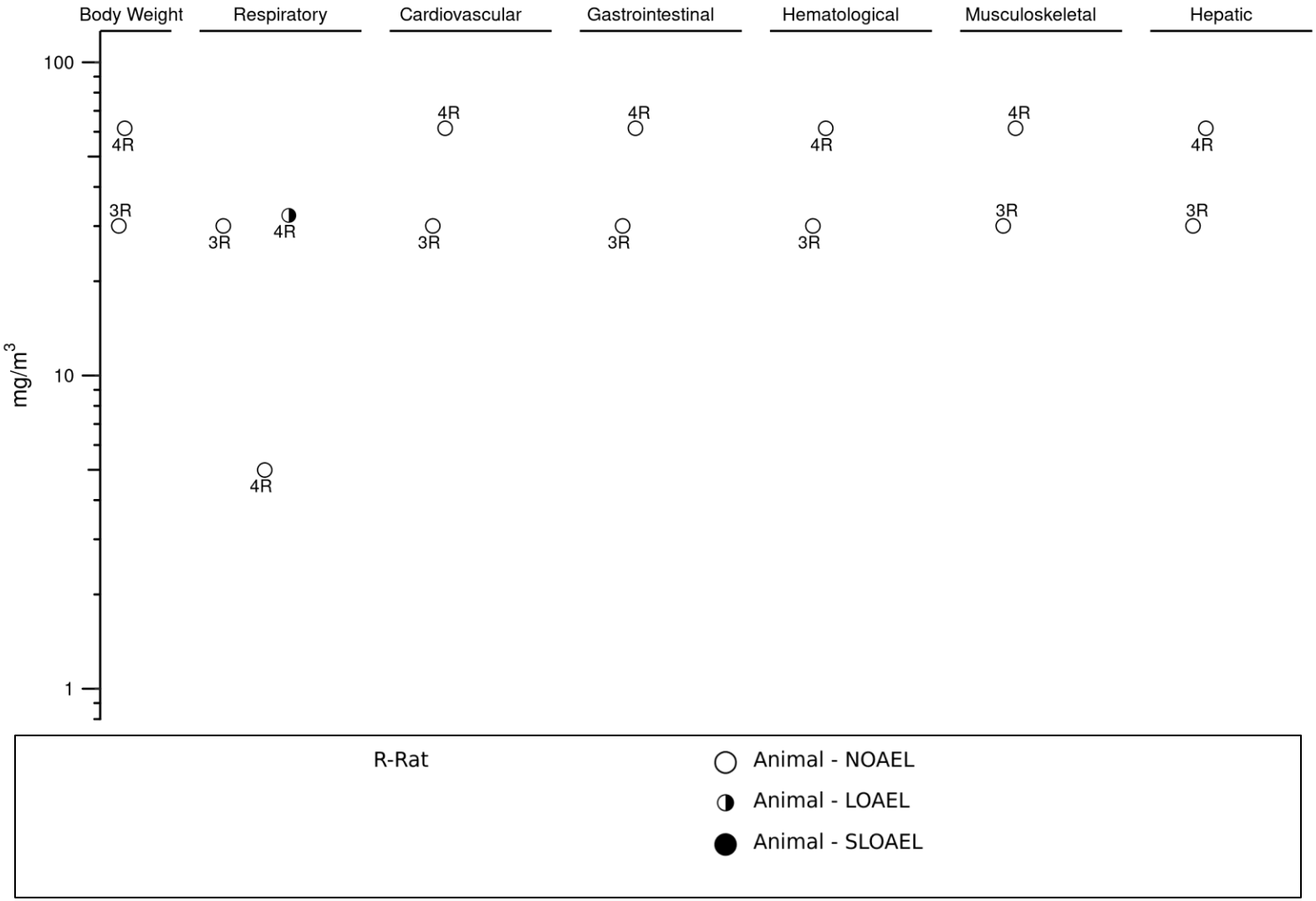


Figure 2-2. Levels of Significant Exposure to Nitrophenols – Inhalation
Intermediate (15-364 days)

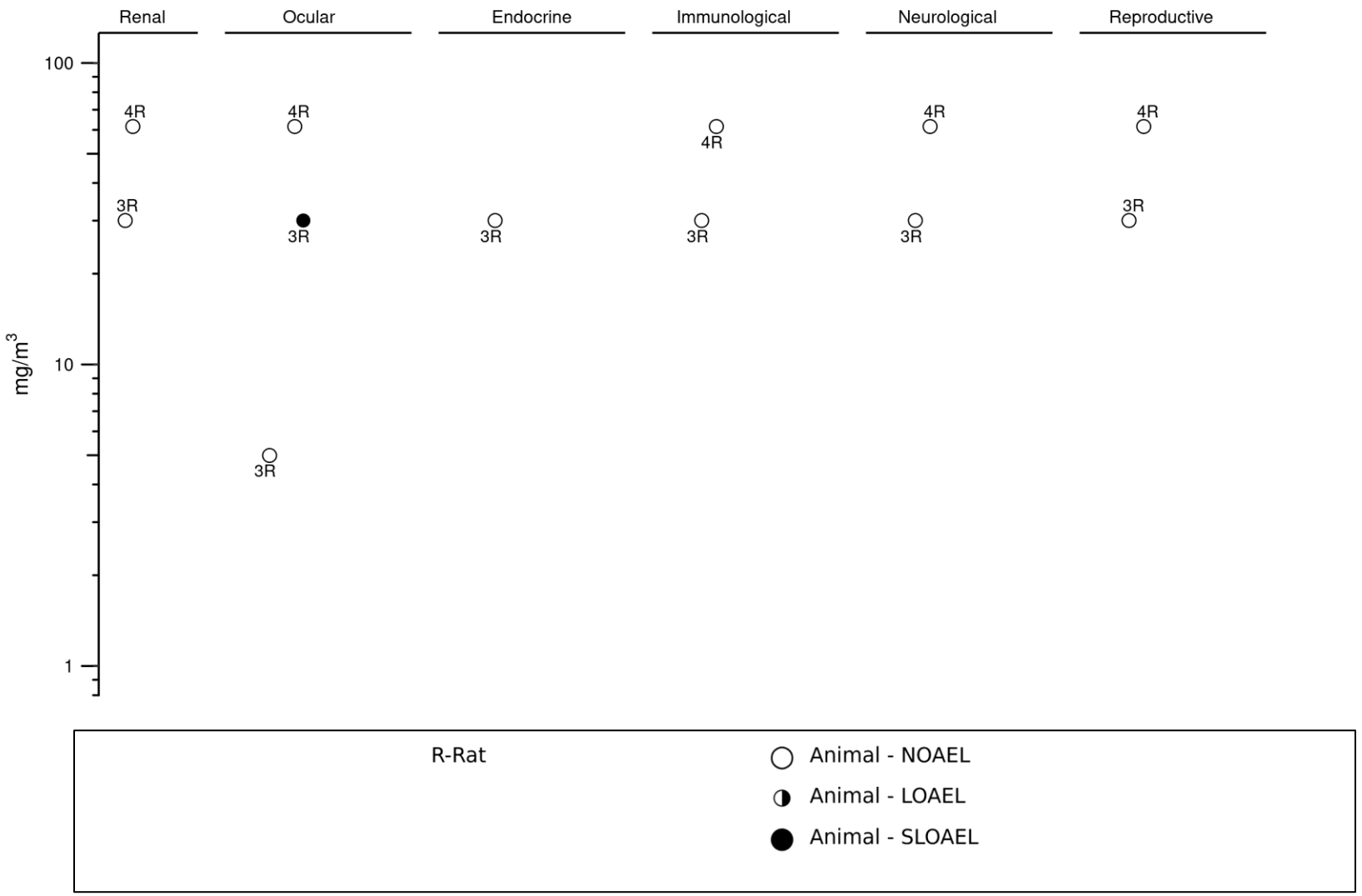


Table 2-2. Levels of Significant Exposure to Nitrophenols – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
ACUTE EXPOSURE									
Abu-Qare et al. 2000									**4-nitrophenol**
1	RAT (Sprague Dawley) 21F	Once (GW)	0, 100	BI BW HE OW UR	Bd wt	100			
					Hemato	100			
					Neuro	100			
					Repro	100			
					Develop	100			
Angerhofer and Weeks 1992									**4-nitrophenol**
2	RAT (Sprague-Dawley) 20F	10 days GD6-GD16 (GW)	0, 1.4, 13.8, 27.6	BW DX GN	Bd wt	13.8	27.6		Maternal body weight gain decreased by 12%
					Develop	27.6			
Kavlock 1990									**4-nitrophenol**
3	RAT (Sprague-Dawley) 12F	Once on GD11 (GW)	0, 333, 667, 1,000	BW DX RX	Death			667	3/13 rats died
					Bd wt	1,000			
					Repro	1,000			
					Develop	1,000			
Li et al. 2017									**4-nitrophenol**
4	RAT (Wistar) 9M	Once (G)	0, 200	BW HP OF OW	Bd wt	200			
					Hepatic		200		The central vein of the hepatic lobule was detached, and the hepatocytes were disordered

Table 2-2. Levels of Significant Exposure to Nitrophenols – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Li et al. 2017									**4-nitrophenol**
5	RAT (Wistar) 12M	3 days (G)	0, 200	BW HP OF OW	Bd wt			200	25% decrease
					Hepatic		200		Hepatic sinusoid was wider compared to the control group, and the hepatocytes were disordered
Monsanto 1990									**2- nitrophenol**
6	Rat (Sprague-Dawley) 5F	9 days, daily (GO)	0, 50, 125, 250, 500, 1,000	BW, DX, RX, UR	Bd wt	1,000			
					Renal	1,000			
					Repro	500		1,000	92% increase in resorptions; 68% increase in post-implantation losses
Tang et al. 2016									**4-nitrophenol**
7	RAT (Wistar) 4-6M	Once (GO)	0, 200	BW HP OW RX	Bd wt	200			
					Gastro		200		Damage to the intestinal mucosal goblet cells and necrosis of intestinal epithelial cells
Tang et al. 2016									**4-nitrophenol**
8	RAT (Wistar) 6M	3 days (GO)	0, 200	BW HP OW RX	Bd wt			200	40% decrease body weight gain

Table 2-2. Levels of Significant Exposure to Nitrophenols – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Gastro		200		Damage to the intestinal mucosal goblet cells and necrosis of intestinal epithelial cells
					Hepatic		200		12% decrease in relative liver weight
					Renal		200		14% increase in relative kidney weight
					Endocr		200		41% increase in relative adrenal gland weight
					Immuno	200			
					Repro	200			
Plasterer et al. 1985									**4-nitrophenol**
9	MOUSE (CD1) 10F	8 days (GO)	0, 400	BW CS RX DX	Death			400	Decreased maternal survival by 19%
					Bd wt		400		Decreased weight gain by 18%
					Repro	400			
					Develop	400			
Plasterer et al. 1985									**4-nitrophenol**
10	MOUSE (CD1) 10F	8 days (GO)	0, 62.5, 125, 250, 500, 1,000	CS	Death			625.7	LD_{50}
					Bd wt	1,000			
INTERMEDIATE EXPOSURE									

Table 2-2. Levels of Significant Exposure to Nitrophenols – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Hazleton 1989									**4-nitrophenol**
11	RAT (Sprague-Dawley) 20M,20F	13 weeks 7 days/week (GW)	0,25,70, 140	BW,OW, FI,GN, HP,BC, CS,BI	Death			25 F	1/20 died
								70 M	1/20 died
					Bd wt	140			
					Resp	25 F	70 F		Wheezing, dyspnea
						70 M	140 M		Wheezing, dyspnea
					Cardio	140			
					Gastro	140			
					Hemato	140			
					Musc/skel	140			
					Hepatic	140			
					Renal	140			
					Dermal	140			
					Ocular	140			
					Endocr	140			
					Neuro	140			
					Repro	140			
Koizumi et al. 2001									**4-nitrophenol**
12	RAT (Sprague-Dawley) 12M, 12F	18 days (G)	0, 80, 110, 160	BI BW CS HE HP LE OF OW UR	Bd wt	160			
					Resp	160			
					Cardio	160			

Table 2-2. Levels of Significant Exposure to Nitrophenols – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Gastro	160			
					Hepatic	160			
					Renal	160			
					Endocr	160			
					Immuno	160			
					Neuro	160			
					Repro	160			
Koizumi et al. 2001									**4-nitrophenol**
13	RAT (Sprague-Dawley) 6M, 6F	18 days (G)	0, 110, 160, 230, 320	BI BW CS HE HP LE OF OW UR	Death			320 F	6/6 died
								230 M	3/6 died
Koizumi et al. 2001									**4-nitrophenol**
14	RAT (Sprague-Dawley) 12M, 12F	28 days (G)	0, 60, 160, 400, 1,000	BI BW FI GN HE HP OW UR	Death			1,000	10/12 M and 10/12 F died
					Bd wt	1,000			
					Resp	400	1,000		Oligopnea (shallow/slow breathing) in 12/12 M and 12/12 F
					Cardio	1,000			
					Gastro	1,000			
					Hepatic	1,000			
					Renal	1,000			
					Endocr	1,000			
					Immuno	1,000			

Table 2-2. Levels of Significant Exposure to Nitrophenols – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Neuro	400	1,000		Decrease in locomotor activity in 12/12 M and 12/12 F; prone/lateral position in 10/12 M and 10/12 F; tonic convulsions in 3/12 M and 4/12 F
					Repro	1,000			

[a]The number corresponds to entries in Figure 2-3.

BC = blood chemistry; BI = biochemical indices; BW or Bd wt = body weight; CS = clinical signs; DX = developmental toxicity; F= female(s); FI = food intake; G = gavage, neat or not specified vehicle; GN = gross necropsy; GO = gavage with oil vehicle; GW = gavage with aqueous vehicle; HE = hematological; HP = histopathology; Immuno = immunological; LE = lethality; LOAEL = lowest-observed-adverse-effect-level; M = male(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect-level; NS = not specified; OF = organ function; OW = organ weight; Resp = respiratory; RX= reproductive toxicity; UR = urinalysis

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

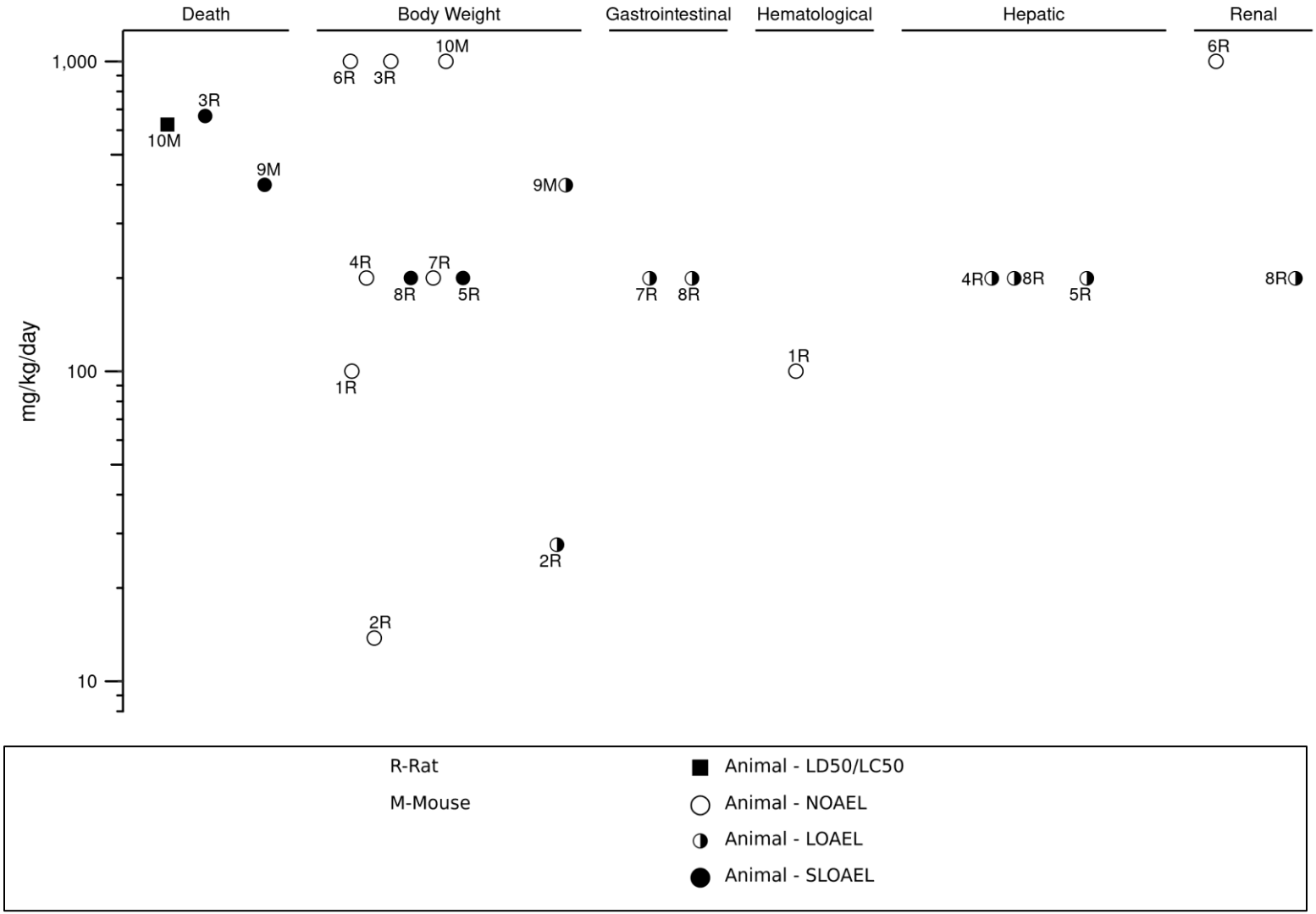


Figure 2-3. Levels of Significant Exposure to Nitrophenols – Oral

Acute (≤14 days)

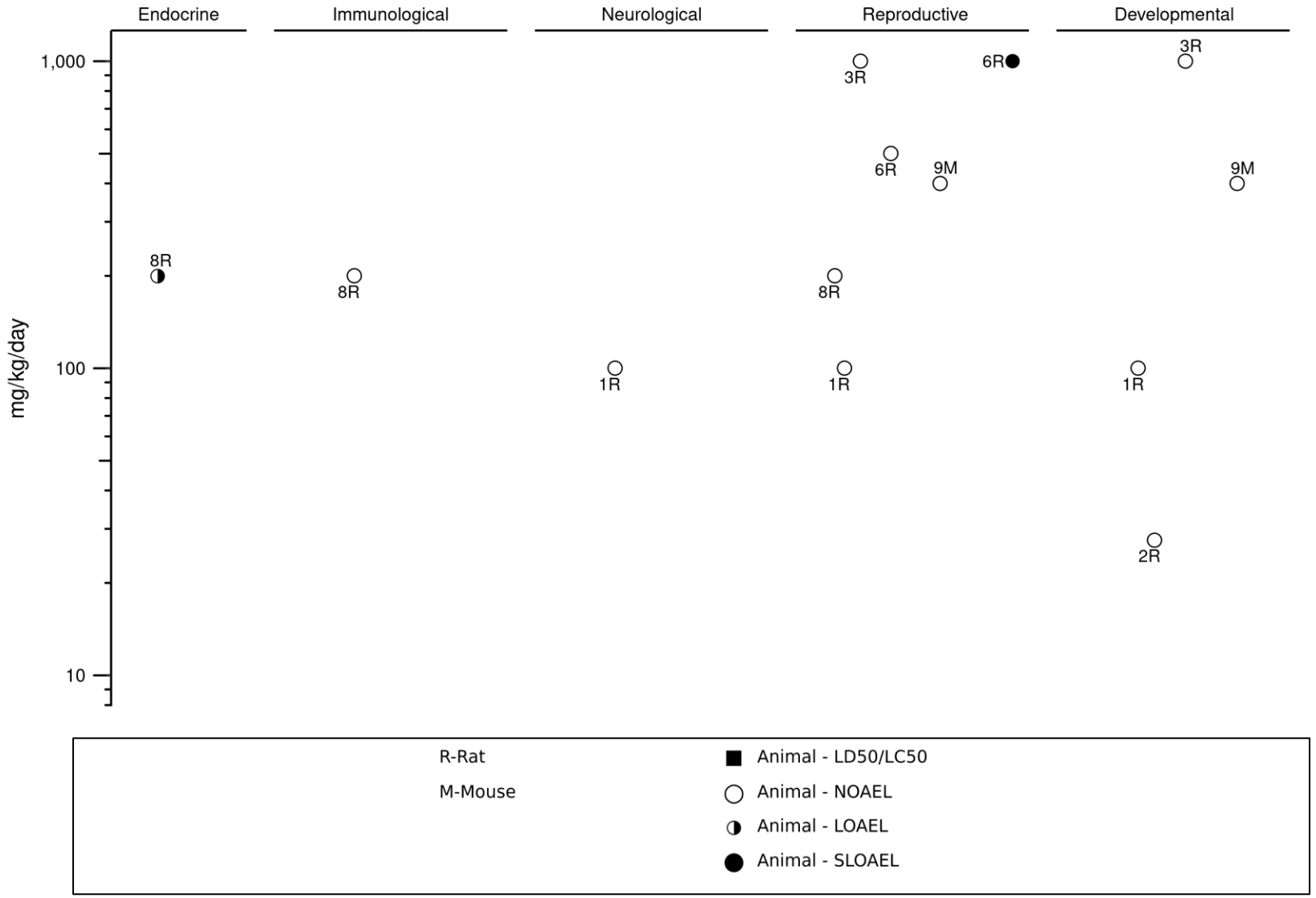
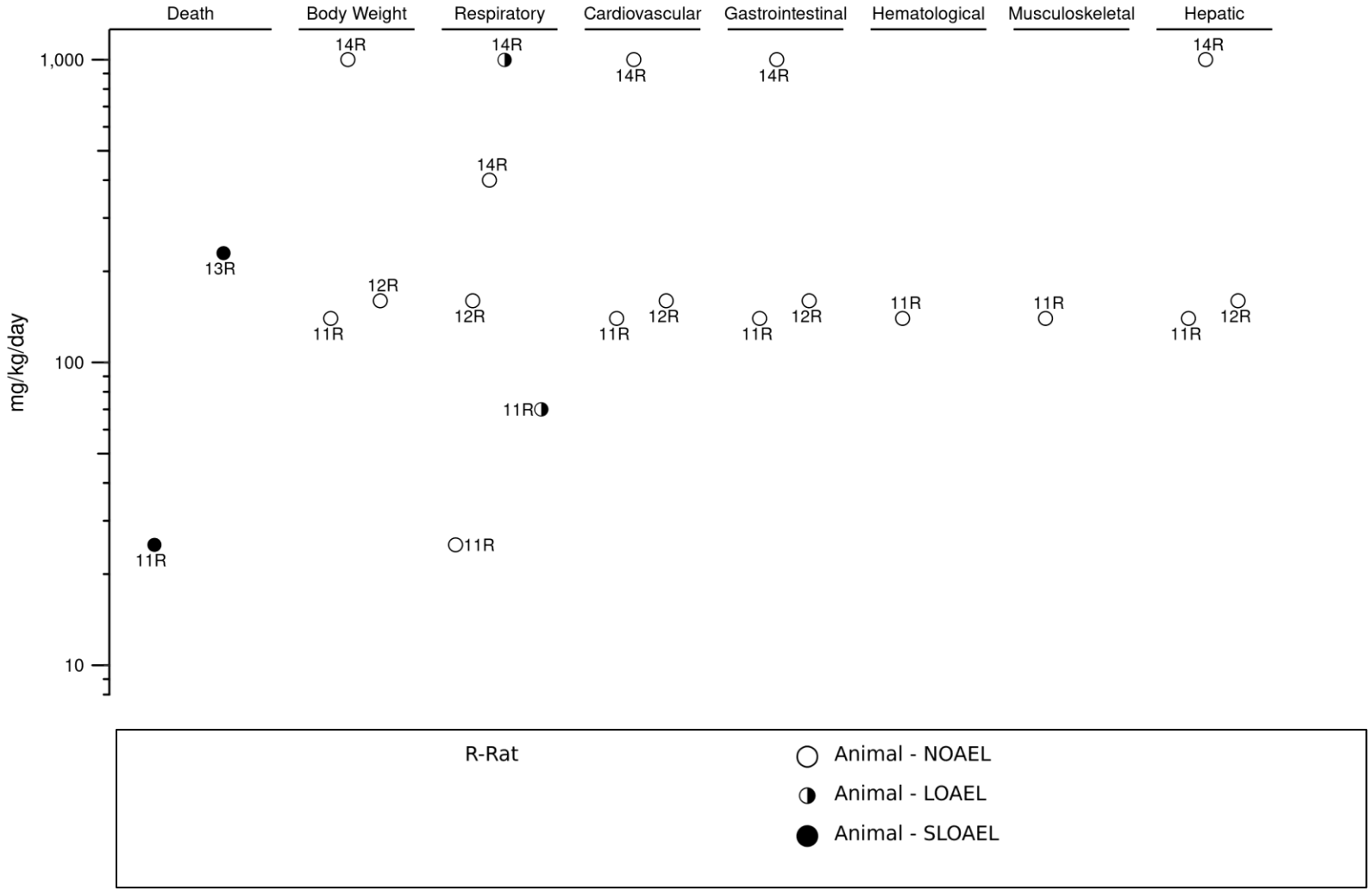


Figure 2-3. Levels of Significant Exposure to Nitrophenols – Oral*

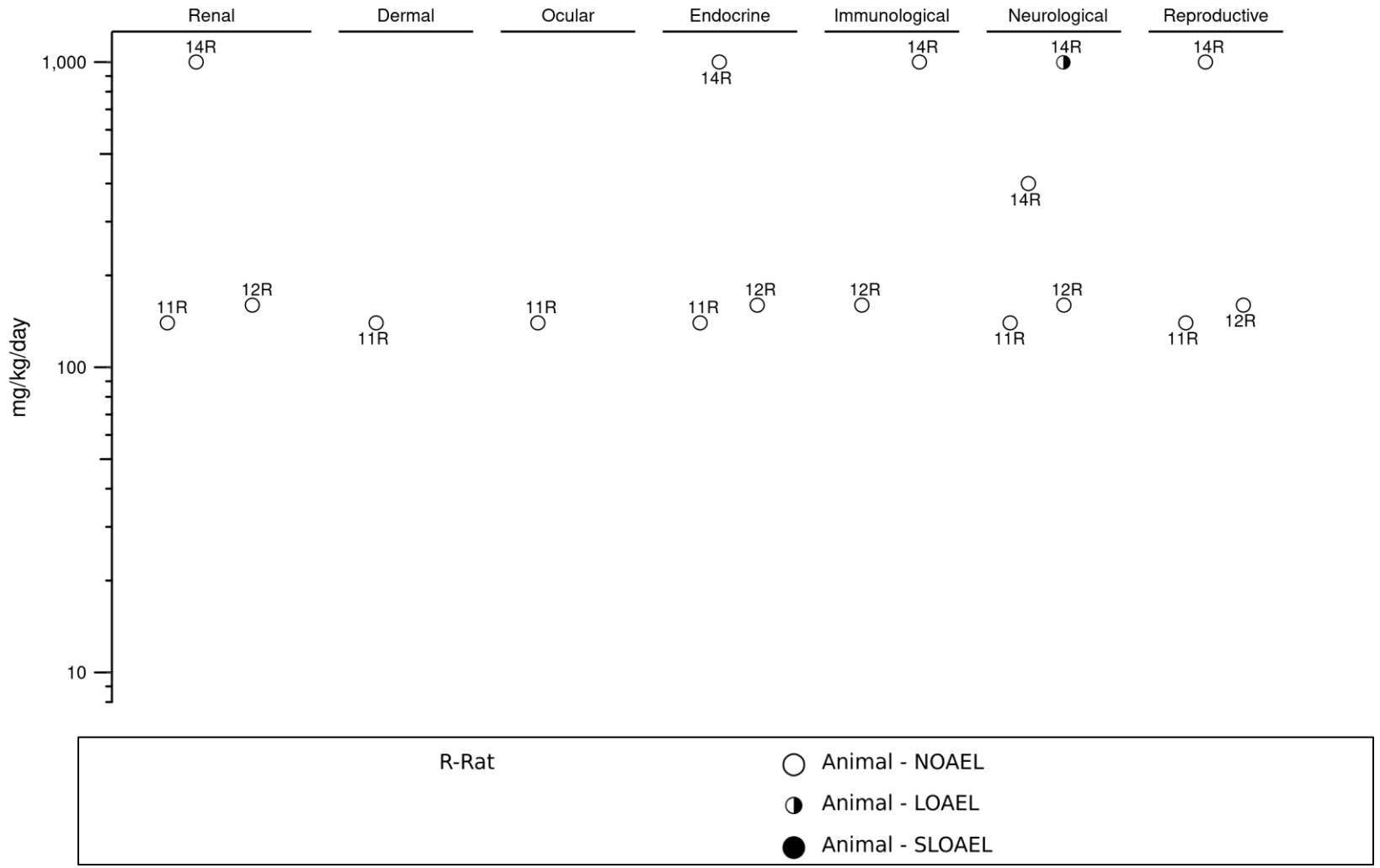
Intermediate (15-364 days)



*Differences in levels of health effects and cancer effects between males 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.

Figure 2-3. Levels of Significant Exposure to Nitrophenols – Oral*

Intermediate (15-364 days)



*Differences in levels of health effects and cancer effects between males 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.

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
INTERMEDIATE EXPOSURE									
Angerhofer 1985									**4-nitrophenol**
1	RAT (Sprague-Dawley) 12M, 24F	20 weeks 5 days/week (140 days prior to mating, through gestation and lactation) F0 generation	0, 50, 100, 250 mg/kg/day	BW DX HP OW RX	Bd wt	250			
					Resp	250			
					Cardio	250			
					Gastro	250			
					Musc/skel	250			
					Hepatic	250			
					Renal	250			
					Dermal		50		Erythema, scaling, scabbing and cracking
					Ocular	250			
					Endocr	250			
					Immuno	250			
					Neuro	250			
					Repro	250			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Angerhofer 1985									**4-nitrophenol**
2	RAT (Sprague-Dawley) 13M, 26F	24 weeks 5 days/week F1 generation	0, 50, 100, 250 mg/kg/day	BW DX HP OW RX	Bd wt	100	250		Weight increased by 12%
					Resp	250			
					Cardio	250			
					Gastro	250			
					Musc/skel	250			
					Hepatic	250			
					Renal	250			
					Dermal		50		Erythema, scaling, scabbing, and cracking
					Ocular	250			
					Endocr	250			
					Immuno	250			
					Neuro	250 F			
						100 M	250 M		10% decrease in relative brain weight
					Repro	250			
					Develop	250			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Angerhofer 1985									**4-nitrophenol**
3	RAT (Sprague-Dawley) 10M, 10F	24 weeks 5 days/week F2 generation, dosing was done to F1 generation	0, 50, 100, 250 mg/kg/day	BW DX HP OW RX	Bd wt	250			
					Resp	250			
					Cardio	250			
					Gastro	250			
					Musc/skel	250			
					Hepatic	250			
					Renal	250			
					Dermal	250			
					Ocular	250			
					Endocr	250			
					Immuno	250			
					Neuro	250			
					Repro	250			
					Develop	250			
CHRONIC EXPOSURE									
NTP 1993									**4-nitrophenol**
4	MOUSE (Swiss-Webster) 60M, 60F	78 weeks 3 days/week	0, 40, 80, 160 mg/kg/day	CS GN HP LE OF	Bd wt	160			
					Resp	160			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Cardio	160			
					Gastro	160			
					Musc/skel	160			
					Hepatic	160			
					Renal	160			
					Dermal	160			
					Ocular	160			
					Endocr	160			
					Immuno	160			
					Neuro	160			
					Repro	160			

BW or Bd wt = body weight; CS = clinical signs; DX = developmental toxicity; F= female(s); GN = gross necropsy; HP = histopathology; Immuno = immunological; LE = lethality; LOAEL = lowest-observed-adverse-effect-level; M = male(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect-level; OF = organ function; OW = organ weight; Resp = respiratory; RX = reproductive toxicity

2.2 DEATH

Inhalation

No studies were identified regarding death in humans after inhalation exposure of any duration to 2-, 3-, or 4-nitrophenol. No studies were identified regarding death in animals after acute or chronic inhalation exposure to 2-nitrophenol. No studies were identified regarding death in animals after inhalation exposure of any duration to 3-nitrophenol. No studies were identified regarding death in animals after chronic inhalation exposure to 4-nitrophenol.

Hazleton (1984) reported no mortality effects in Sprague-Dawley rats after intermittent intermediate-duration inhalation exposure to 2-nitrophenol for 4 weeks, 5 days/week, 6 hours/day at measured concentrations up to 61.5 mg/m^3. Exposures were conducted in glass and steel inhalation chambers, with chamber concentrations of 2-nitrophenol vapors measured at least twice per day. 2-nitrophenol vapors were produced in the study by sweeping the headspace of a glass generation flask containing melted 2-nitrophenol into the inhalation chambers. This is the only inhalation study on the mortality effects of 2-nitrophenol (Hazleton 1984).

There are no available studies showing that inhalation exposure to 4-nitrophenol in animals produces mortality.

The data on mortality from acute inhalation exposure in animals is limited to three studies. Acute inhalation exposure to 4-nitrophenol in rats at levels up to 4,059 mg/m^3 for 4 hours produced no mortality (Smith et al. 1988); however, no control group was included in this study. Smith et al. (1988) conducted another study (with a control group) of 4-nitrophenol intermittent inhalation exposure in rats for 2 weeks at levels up to 2,133 mg/m^3 and no deaths were reported. In both of these studies conducted by Smith et al. (1988), 4-nitrophenol dust was generated using a 3-stage glass dust generator containing 4-nitrophenol sodium salt (composed of 75% 4-nitrophenol, sodium salt, and 25% water), with atmospheric concentrations taken at 30 or 60 minute intervals using three sampling ports at nose-level in the inhalation chamber. Another study investigated death after intermediate inhalation exposure to 4-nitrophenol in which rats were exposed to a concentration of 30 mg/m^3 intermittently for 4 weeks and no deaths were reported (Hazleton 1983). This study generated 4-nitrophenol dust using Wright dust-feed mechanisms that fed dust into exposure chambers using a turret that mixed the dust with air. Nominal chamber concentrations were measured each time new test material was measured, and three gravimetric samples were taken from each chamber each day.

Oral

No studies were identified regarding death in humans after oral exposure of any duration to 2-, 3-, or 4-nitrophenol. No studies were identified regarding death in animals after chronic oral exposure to 4-nitrophenol.

Vernot et al. (1977) estimated LD_{50} values for 2-, 3-, and 4-nitrophenol in rats and mice based on a single oral dose of the chemical. LD_{50} values were estimated as follows for rats and mice, respectively: 2,830 mg/kg and 1,300 mg/kg for 2-nitrophenol, 930 mg/kg and 1,410 mg/kg for 3-nitrophenol, and 620 mg/kg and 470 mg/kg for 4-nitrophenol. This was the only study that focused on death in animals after oral exposure to 2- or 3-nitrophenol.

In animals, acute oral administration of 4-nitrophenol at high doses caused death. A single dose of 667 mg/kg of aqueous 4-nitrophenol administered by gavage on gestational day 11 caused death in 3 out of 13 pregnant female Sprague-Dawley rats (Kavlock 1990). Gavage oil administration of 4-nitrophenol to CD1 female mice once per day for 8 days caused death at doses of 400 mg/kg/day and above (Plasterer et al. 1985). An LD_{50} for 4-nitrophenol in mice was estimated from this study at 625.7 mg/kg (Plasterer et al. 1985). Death was observed in 4 of 5 male Sprague-Dawley rats after a single gavage dose of 268 mg/kg, and in 3 of 5 Sprague-Dawley female rats after a single gavage dose of 171 mg/kg (Branch and Stout 1983a); however, the study did not include a control group, which could call into question the rigor with which the study was conducted. A study in rats exposed on gestational day 6-16 reported no excess deaths in mothers or fetuses at the highest dose tested of 27.6 mg/kg (Angerhofer and Weeks 1992).

Intermediate administration of 4-nitrophenol has also caused death. Gavage administration of 4-nitrophenol to Sprague-Dawley rats once per day for 18 days produced death at 230 mg/kg/day in male rats (3/6 died) and 320 mg/kg/day in female rats (6/6 died) (Koizumi et al. 2001). However, a 28-day follow-up study in the same publication did not report mortality in Sprague-Dawley rats at doses of 160 mg/kg/day or 400 mg/kg/day, but did produce significant mortality at 1,000 mg/kg/day (10/12 males and 10/12 females died). A longer duration intermediate gavage study of 13 weeks produced mortality at concentrations as low as 25 mg/kg/day in female Sprague-Dawley rats (1/20) and 70 mg/kg/day in male Sprague-Dawley rats (1/20) (Hazleton 1989).

The LD_{50} values and the doses associated with death in each species and duration of exposure category from each reliable study are recorded in Table 2-2 and plotted in Figure 2-3.

Dermal

No studies were identified that evaluated death in humans after dermal exposure of any duration to 2-, 3-, or 4-nitrophenol. No studies were identified that evaluated death in animals after acute or chronic dermal exposure to 2-nitrophenol. No studies were identified that evaluated death in animals after dermal exposure of any duration to 3-nitrophenol.

No fatalities have been observed after acute or intermediate dermal exposure to nitrophenols in animals. Branch and Stout (Branch and Stout 1983b) topically applied 4-nitrophenol at 5,000 mg/kg once to a group of 10 rabbits in order to assess an LD_{50}, but found that no death occurred from this dose (no control group was included). Dermal administration of ~39 mg/kg/day of 2-nitrophenol diluted in dioxane to mice 2 days/week for 12 weeks did not produce mortality (Boutwell and Bosch 1959). A multigenerational study of 4-nitrophenol in rats did not produce evidence of mortality after dermal daily doses of 250 mg/kg/day for 5 days/week for 20 weeks in the F0 generation, nor following exposure 5 days/ week for 24 weeks in the F1 generation. The dosing of the F1 generation also did not produce any subsequent early mortality in the F2 generation of rats (Angerhofer 1985). In this multigenerational study, the original rats purchased for the study were delineated as the F0 generation, and dosing occurred both prior to the mating of the F0 generation, as well as throughout the breeding, gestation, and lactation periods. The F1 generation was weaned approximately 3 weeks after birth, and then were subsequently dosed in the same manner as the F0 generation. The F2 generation was not dosed other than the exposure the rats received in gestation and through the mothers' lactation (Angerhofer 1985). Dermal administration of ~39 mg/kg/day of 4-nitrophenol diluted in dioxane to mice 2 days/week for 12 weeks did not produce mortality (Boutwell and Bosch 1959).

2.3 BODY WEIGHT

Inhalation

No studies were identified regarding body weight effects in humans after inhalation exposure of any duration to 2-, 3-, or 4-nitrophenol. No studies were identified regarding body weight effects in animals after acute or chronic inhalation exposure to 2-nitrophenol. No studies were identified regarding body weight effects in animals after inhalation exposure of any duration to 3-nitrophenol. No studies were identified regarding body weight effects in animals after chronic inhalation exposure to 4-nitrophenol.

Hazleton (1984) found no body weight effects following intermediate-duration, inhalation exposure to 2-nitrophenol in rats intermittently for 4 weeks at concentrations as high as 61.5 mg/m^3.

Smith et al. (1988) found a suppression of weight gain in an acute study of intermittent 4-nitrophenol inhalation exposure in Albino rats for 2 weeks at levels as low as 294 mg/m^3; however, the study reports no additional quantitative information about the weight gain suppression. In a second acute study at levels of 26 mg/m^3 and 112 mg/m^3, both test groups showed decreased weight gain, but the control group also showed a similar decrease in weight gain (Smith et al. 1988). No further details were included (Smith et al. 1988).

The highest NOAEL values and all LOAEL values from each reliable study for body weight effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-2.

Oral

No studies were identified regarding body weight effects in humans after oral exposure of any duration to 2, 3-, or 4-nitrophenol. No studies were identified regarding body weight effects in animals after oral exposure of any duration to 2- or 3-nitrophenol. No studies were identified regarding body weight effects in animals after chronic oral exposure to 4-nitrophenol.

Acute oral doses of 4-nitrophenols have shown mixed effects with respect to body weight effects, even for studies using the same animal species. In a 3-day study of daily oral gavage oil administration of 4-nitrophenol in Wistar rats, Tang et al. (2016) found a 40% decrease in body weight gain at 200 mg/kg/day compared to controls; however, these effects were no longer noted in a group of rats allowed to recover for a three-day period. Additionally, there were no significant differences in body weight gain at this same dose in a group of rats with only one day of administration (Tang et al. 2016). Li et al. (2017) found a 25% decrease in body weight after a three-day exposure to 4-nitrophenol at 200 mg/kg/day in male Wistar rats, but no body weight effects were noted in a similar exposure study after a three-day recovery period. Plasterer et al. (1985) showed an 18% decrease in weight gain in CD1 mice following a daily administration of 400 mg/kg/day 4-nitrophenol by gavage oil for 8 days. Abu-Qare et al. (2000) found no body weight effects after one gavage dose of 100 mg/kg/day 4-nitrophenol in Sprague-Dawley rats, and Kavlock (1990) found no effects after one gavage dose of 1,000 mg/kg/day in the same rat species. However, acute oral gavage administration of 4-nitrophenol in water in Sprague-Dawley rats caused a 12% decrease in maternal weight gain at 27.6 mg/kg/day; this study identified a NOAEL of 13.8 mg/kg/day for body weight effects (Angerhofer and Weeks 1992).

Intermediate duration exposure to 4-nitrophenol showed no body weight effects following daily doses by gavage of up to 1,000 mg/kg/day in Sprague-Dawley rats for 18 days, 28 days, or 13 weeks (Hazleton 1989; Koizumi et al. 2001).

The highest NOAEL and LOAEL values from each reliable study for body weight effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-3.

Dermal

No studies were identified regarding body weight effects in humans after dermal exposure of any duration to 2-, 3-, or 4-nitrophenol. No studies were identified regarding body weight effects in animals after dermal exposure of any duration to 2- or 3-nitrophenol. No studies were identified regarding body weight effects in animals after acute dermal exposure to 4-nitrophenol.

Only one study investigated body weight effects after intermediate dermal exposure to 4-nitrophenol. An intermediate duration three-generation rat reproductive study found no body weight effects after exposure to 250 mg/kg/day for 20 weeks (once per day, five days per week) in the F0 generation or in the F2 generation (which had no additional dosing beyond what was performed on the F1 generation). However, the F1 generation showed a 12% increase in body weight compared to the control group at 250 mg/kg/day; the NOAEL is 100 mg/kg/day for this effect in the F1 generation (Angerhofer 1985). A chronic duration, 78 week, dermal mouse study (Swiss-Webster mice, 3 day per week) of 4-nitrophenol showed no significant body weight effects at doses up to 160 mg/kg (NTP 1993).

Other

Daily subcutaneous injection of 4-nitrophenol with doses up to 100 mg/kg/day in ovariectomized female Wistar-Imamichi rats showed no effect on body weight when compared to controls (Li et al. 2006). Daily subcutaneous injection of 4-nitrophenol in testosterone-implanted castrated male Wistar-Imamichi rats also showed no effect in doses up to 1 mg/kg/day, which was the highest dose tested (Li et al. 2006).

2.4 RESPIRATORY

Inhalation

Based on a systematic evaluation of the literature, respiratory toxicity is a suspected health effect of exposure to 4-nitrophenol. The full results of the systematic review are presented in Appendix C. No studies were identified regarding respiratory effects in humans after inhalation exposure of any duration to 2-, 3-, or 4-nitrophenol. No studies were identified regarding respiratory effects in animals after acute or chronic inhalation exposure to 2-nitrophenol, after any duration of exposure to 3-nitrophenol, or after chronic inhalation exposure to 4-nitrophenol.

One study reported respiratory effects after inhalation exposure to 2-nitrophenol in rats. An intermediate duration study of 2-nitrophenol intermittent inhalation exposure in rats showed a significant increase in squamous metaplasia of the nasal epithelium at concentrations of 32.5 mg/m^3 and higher after 4 weeks, with effectively 100% of the rats treated at and above this level of exposure exhibiting the effect (Hazleton 1984). The 5 mg/m^3 dose is considered the NOAEL for respiratory effects in this study. No other studies were identified regarding respiratory effects following inhalation exposure to 2-nitrophenol, however based on Hazleton (1984), the respiratory endpoint appears to be the most sensitive endpoint for 2-nitrophenol inhalation.

Inhalation exposure to 4-nitrophenol has also led to respiratory effects in rats. Smith et al. (1988) reported decreased absolute and relative lung weight in rats after intermittent exposure to 4-nitrophenol for 2 weeks at 2,133 mg/m^3, with the effect remaining even after a 14 day recovery period. The precise amount of this decrease in lung weight, however, was not quantified in the study, which prevents the assessment of the significance of this effect.

An intermediate duration study of intermittent 4-nitrophenol exposure for 4 weeks in rats showed no significant respiratory effects at concentrations up to 30 mg/m^3 (Hazleton 1983).

The highest NOAEL values and all LOAEL values from each reliable study for respiratory effects in each species and duration category are recorded in Table 2-1, and plotted in Figure 2-2.

Oral

No studies were identified regarding respiratory effects in humans after oral exposure of any duration to 2-, 3-, or 4-nitrophenol. No studies were identified regarding respiratory effects in animals after oral exposure of any duration to 2- or 3-nitrophenol. No studies were identified regarding respiratory effects in animals after chronic oral exposure to 4-nitrophenol.

Dyspnea was observed in all dose groups in a single-dose oral toxicity study of 4-nitrophenol in rats, with gavage administered doses as low as 70 mg/kg; however, this study did not include a control group, which complicates the interpretation of these results (Branch and Stout 1983a). This was the only acute oral toxicity study that investigated respiratory effects identified in the literature.

Intermediate-duration oral studies of 4-nitrophenol showed mixed results with respect to respiratory effects. Hazleton (1989) showed that daily gavage administration of 4-nitrophenol for 13 weeks at doses as low as 70 mg/kg/day caused female Sprague-Dawley rats to exhibit a significant increase in wheezing and dyspnea compared with controls; the NOAEL reported for this effect in this study is 25 mg/kg/day.

For male rats, these effects were noted at 140 mg/kg/day, with an associated NOAEL of 70 mg/kg/day. No histological alterations in the trachea or lungs were observed in males or females. Koizumi et al. (2001) noted that all Sprague-Dawley rats exposed to 1,000 mg/kg/day via gavage exhibited oligopnea (shallow/slow breathing). A separate study of rats exposed for 18 days at doses of 160 mg/kg/day showed no significant respiratory effects (Koizumi et al. 2001).

The highest NOAEL and LOAEL values from each reliable study for respiratory effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-3.

Dermal

No studies were identified regarding respiratory effects in humans after dermal exposure of any duration to 2-, 3-, or 4-nitrophenol. No studies were identified regarding respiratory effects in animals after dermal exposure of any duration to 2- or 3-nitrophenol. No studies were identified regarding respiratory effects in animals after acute dermal exposure to 4-nitrophenol.

A three-generation intermediate-duration dermal study of rats showed no histopathological effects to respiratory organs at doses as high as 250 mg/kg/day (Angerhofer 1985). NTP (1993) sought to study the toxicology and carcinogenicity of 4-nitrophenol in Swiss-Webster mice by applying doses of 0, 40, 80, or 160 mg/kg to the interscapular skin 3 days/week for 78 weeks. Although this study showed increased incidence of lung neoplasms in males in the 40 mg/kg dose group, this increase was not dose-dependent; thus, these effects were not considered to be related to the administration of 4-nitrophenol. As a result, the NOAEL for respiratory effects in this study was determined to be 160 mg/kg.

Other

Intraperitoneal injection of nitrophenols in rats has shown a potential to increase respiration rates (Cameron 1958; Grant 1959). 2-, 3-, and 4-Nitrophenol were administered at doses of 120 mg, 45 mg, and 14 mg, respectively. Average increases in respiration rates of: 31% for 2-nitrophenol, 24% for 3-nitrophenol, and 2% for 4-nitrophenol (compared with a prior control period) were reported (Grant 1959). However, a control group that received an intraperitoneal injection of normal saline also experienced a 2% increase in respiration rate compared to the prior control period, which suggests the small increase in

respiration rate observed in rats injected with 4-nitrophenol is not significant (Grant 1959). The toxicological significance of these findings is unclear.

2.5 CARDIOVASCULAR

Inhalation

No studies were identified regarding cardiovascular effects in humans after inhalation exposure of any duration to 2-, 3-, or 4-nitrophenol. No studies were identified regarding cardiovascular effects in animals after acute or chronic inhalation exposure to 2- or 4-nitrophenol. No studies were identified regarding cardiovascular effects in animals after inhalation exposure of any duration to 3-nitrophenol.

Only two studies investigated cardiovascular effects after inhalation exposure to nitrophenols. No organ weight or histopathological changes related to the heart were observed after intermediate inhalation exposure to 2-nitrophenol at concentrations up to 61.5 mg/m^3 (Hazleton 1984). Similarly, no organ weight or histopathological changes related to the heart were observed after intermediate inhalation exposure to 4-nitrophenol at concentrations up to 30 mg/m^3 (Hazleton 1983).

The highest NOAEL values from each reliable study for cardiovascular effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-2.

Oral

No studies were identified regarding cardiovascular effects in humans after oral exposure of any duration to 2-, 3-, or 4-nitrophenol. No studies were identified regarding cardiovascular effects in animals after oral exposure of any duration to 2- or 3-nitrophenol. No studies were identified regarding cardiovascular effects in animals after acute or chronic oral exposure to 4-nitrophenol.

Data are limited to two animal studies examining cardiovascular effects after oral exposure to 4-nitrophenol. No organ weight or histopathological changes related to the heart were observed after intermediate duration gavage administration of 4-nitrophenol at doses up to 140 mg/kg/day in rats (Hazleton 1989). Similarly, no organ weight or histopathological changes related to the heart were observed in after intermediate duration gavage administration of 4-nitrophenol to rats at doses up to 1,000 mg/kg/day (Koizumi et al. 2001).

The highest NOAEL values from each reliable study for cardiovascular effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-3.

Dermal

No studies were identified regarding cardiovascular effects in humans after dermal exposure of any duration to 2-, 3-, or 4-nitrophenol. No studies were identified regarding cardiovascular effects in animals after dermal exposure of any duration to 2- or 3-nitrophenol. No studies were identified regarding cardiovascular effects in animals after acute dermal exposure to 4-nitrophenol.

The limited available data (2 animal studies) reported no cardiovascular effects from dermal exposure to 4-nitrophenol. Intermediate dermal exposure to 4-nitrophenol in a three-generation study showed no cardiovascular effects in any of the generations of rats following exposure to 250 mg/kg/day (Angerhofer 1985). No neoplasms or other histopathological effects of the heart were observed after chronic dermal exposure of mice to 4-nitrophenol at levels up to 160 mg/kg (NTP 1993).

2.6 GASTROINTESTINAL

Inhalation

No studies were identified regarding gastrointestinal effects in humans after inhalation exposure of any duration to 2-, 3-, or 4-nitrophenol. No studies were identified regarding gastrointestinal effects in animals after acute or chronic inhalation exposure to 2-nitrophenol. No studies were identified regarding gastrointestinal effects in animals after inhalation exposure of any duration to 3-nitrophenol. No studies were identified regarding gastrointestinal effects in animals after acute or chronic inhalation exposure to 4-nitrophenol.

Limited information from two animal studies suggests that inhalation exposure to 2- or 4-nitrophenol was not associated with gastrointestinal effects. No histopathological changes to the gastrointestinal system were observed after intermediate inhalation exposure to 2-nitrophenol in rats at concentrations up to 61.5 mg/m^3 (Hazleton 1984). No histopathological changes to the gastrointestinal system were observed after intermediate inhalation exposure to 4-nitrophenol in rats at concentrations up to 30 mg/m^3 (Hazleton 1983).

The highest NOAEL values from each reliable study for gastrointestinal effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-2.

Oral

No studies were identified regarding gastrointestinal effects in humans after oral exposure of any duration to 2-, 3-, or 4-nitrophenol. No studies were identified regarding gastrointestinal effects in animals after oral exposure of any duration to 2- or 3-nitrophenol. No studies were identified regarding gastrointestinal effects in animals after chronic oral exposure to 4-nitrophenol.

There is limited evidence suggesting possible gastrointestinal effects after acute oral exposure to 4-nitrophenol. Tang et al. (2016) found damage to the intestinal mucosal goblet cells and necrosis of intestinal epithelial cells in rats after both a single gavage oil dose of 200 mg/kg of 4-nitrophenol, or after 3 days of gavage oil administration of 200 mg/kg/day 4-nitrophenol. However, these two studies presented in Tang et al. (2016) were the only acute oral studies to investigate gastrointestinal effects. Intermediate oral exposure to 4-nitrophenol by gavage at doses up to 1,000 mg/kg/day for 28 days or at doses up to 140 mg/kg/day for 13 weeks showed no significant effects, though it is unclear that these studies looked specifically at the gastrointestinal endpoints observed in Tang et al. (2016) (Hazleton 1989; Koizumi et al. 2001).

The highest NOAEL and LOAEL values from each reliable study for gastrointestinal effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-3.

Dermal

No studies were identified regarding gastrointestinal effects in humans after dermal exposure of any duration to 2-, 3-, or 4-nitrophenol. No studies were identified regarding gastrointestinal effects in animals after dermal exposure of any duration to 2- or 3-nitrophenol. No studies were identified regarding gastrointestinal effects in animals after acute dermal exposure to 4-nitrophenol.

Limited information from two animal studies suggests that dermal exposure to 4-nitrophenol was not associated with gastrointestinal effects. No gastrointestinal effects were observed in a three-generation rat study with dermal doses of 4-nitrophenol as high as 250 mg/kg/day (Angerhofer 1985). Similarly, no gastrointestinal effects were observed in a chronic duration study of mice with doses as high as 160 mg/kg (NTP 1993).

2.7 HEMATOLOGICAL

Inhalation

Based on a systematic evaluation of the literature, hematological effects are considered suspected health effects of exposure to 4-nitrophenol. The full results of the systematic review are presented in Appendix

C. No studies were identified regarding hematological effects in humans after inhalation exposure of any duration to 2-, 3-, or 4-nitrophenol. No studies were identified regarding hematological effects in animals after acute or chronic inhalation exposure to 2-nitrophenol. No studies were identified regarding hematological effects in animals after inhalation exposure of any duration to 3-nitrophenol. No studies were identified regarding hematological effects in animals after chronic inhalation exposure to 4-nitrophenol.

Studies in laboratory animals provide evidence suggesting that intermediate inhalation exposure to 2-nitrophenol causes changes in methemoglobin levels. Hazleton (1984) found an increase in methemoglobin levels in both male (2.3%) and female (4.1%) rats after exposure to 2-nitrophenol at concentrations as low as 5 mg/m^3 for 4 weeks. However, no statistically significant increases in methemoglobin levels occurred in the higher dose groups, which brings into question the validity of the finding in the 5 mg/m^3 group (Hazleton 1984). The study authors did not provide a specific reason for the lack of significant effect of 2-nitrophenol on methemoglobin levels in the higher dose groups.

Hematological effects were also noted in studies investigating inhalation exposure to 4-nitrophenol. After exposing albino rats to 4-nitrophenol concentrations of 0, 26, or 112 mg/m^3 for 6 hours/day for 10 days, Smith et al. (1988) found that methemoglobin increased by 200% in males in the 112 mg/m^3 concentration group (1.5% methemoglobin in the 112 mg/m^3 group versus 0.5% methemoglobin in the control group). However, the levels returned to normal after a 14-day recovery period (0.2% methemoglobin); the NOAEL for these effects was 26 mg/m^3. Another study within this same publication that exposed albino rats to 4-nitrophenol concentrations of 0, 294, and 2,133 mg/m^3 for 10 days also found that methemoglobin levels increased by 665% (1.53% methemoglobin in the 2,133 mg/m^3 group versus 0.20% methemoglobin in the control group); the NOAEL for these effects was 294 mg/m^3. After 14 days of recovery, methemoglobin levels remained elevated by 250% (0.70% methemoglobin). In general, increases in total methemoglobin result in lower oxygen carrying and delivery capacity, which can cause hypoxia. High levels of methemoglobin may be associated with cyanosis and fatigue, weakness, dyspnea, headache, and dizziness. One rat in the Smith et al. (1988) study became cyanotic after the first exposure to this 4-nitrophenol concentration of 2,133 mg/m^3. It is estimated that rats have 2-5 times as much methemoglobin reductase activity, or the enzyme responsible for controlling the amount of methemoglobin in blood, than humans (Bloom and Brandt 2019). Thus, humans could potentially be more sensitive to 4-nitrophenol toxicity than rats. Other hematological effects observed included elevated erythrocytes, hemoglobin, hematocrit, and creatinine at 2,133 mg/m^3 4-nitrophenol (Smith et al. 1988).

Hazleton (1983) performed an intermediate-duration inhalation study of 4-nitrophenol toxicity in rats, exposing the animals intermittently to concentrations of 0, 1, 5, and 30 mg/m^3 for 5 weeks. There were no hematological effects noted in the 1 mg/m^3 concentration group; at 5 mg/m^3 there was a statistically significant increase in methemoglobin compared to controls, but there was no similar increase in methemoglobin in the 30 mg/m^3 concentration group (Hazleton 1983). As these results did not show a clear dose-response relationship between 4-nitrophenol exposure and increases in methemoglobin, the mechanistic link and the toxicological significance of the finding are unclear.

The highest NOAEL values and all LOAEL values from each reliable study for hematological effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-2.

Oral

No studies were identified regarding hematological effects in humans after oral exposure of any duration to 2-, 3-, or 4-nitrophenol. No studies were identified regarding hematological effects in animals after oral exposure of any duration to 2-nitrophenol or 3-nitrophenol. No studies were identified regarding hematological effects in animals after chronic oral exposure to 4-nitrophenol.

Limited information from two animal studies suggests that oral exposure to 4-nitrophenol was not associated with hematological effects. No hematological effects were observed in female rats following a single dose of 100 mg/kg 4-nitrophenol by gavage (Abu-Qare et al. 2000), nor were any hematological effects observed in an intermediate duration study administering daily gavage doses up to 140 mg/kg/day 4-nitrophenol seven days per week for 13 weeks (Hazleton 1989).

The highest NOAEL values from each reliable study for hematological effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-3.

Dermal

No studies were identified regarding hematological effects in humans or animals after dermal exposure of any duration to 2-, 3-, or 4-nitrophenol.

2.8 MUSCULOSKELETAL

Inhalation

No studies were identified regarding musculoskeletal effects in humans after inhalation exposure of any duration to 2-, 3-, or 4-nitrophenol. No studies were identified regarding musculoskeletal effects in

animals after acute or chronic inhalation exposure to 2-nitrophenol. No studies were identified regarding musculoskeletal effects in animals after inhalation exposure of any duration to 3-nitrophenol. No studies were identified regarding musculoskeletal effects in animals after acute or chronic inhalation exposure to 4-nitrophenol.

No musculoskeletal effects were observed in two studies of inhalation exposure to 2-nitrophenol or 4-nitrophenol. Hazleton (1984) found no musculoskeletal effects in rats following intermittent exposure to 2-nitrophenol for 4 weeks at concentrations up to 61.5 mg/m^3. This study monitored for changes in the thoracic spinal cord, skeletal muscle, sternum, femur, and head. Similarly, Hazleton (1983) found no musculoskeletal effects of intermediate inhalation exposure to 4-nitrophenol in rats at concentrations up to 30 mg/m^3. Hazleton (1983) monitored for changes in the thoracic spinal cord, skeletal muscle, sternum, and femur.

The highest NOAEL values from each reliable study for musculoskeletal effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-2.

Oral

No studies were identified regarding musculoskeletal effects in humans after oral exposure of any duration to 2-, 3-, or 4-nitrophenol. No studies were identified regarding musculoskeletal effects in animals after oral exposure of any duration to 2- or 3-nitrophenol. No studies were identified regarding musculoskeletal effects in animals after acute or chronic oral exposure to 4-nitrophenol.

Hazleton (1989) found no musculoskeletal effects of gavage administered 4-nitrophenol 7 days/week for 13 weeks at doses up to 140 mg/kg/day. This study monitored for changes in skeletal muscle, the sternum, the femur, and the head.

The highest NOAEL values from each reliable study for musculoskeletal effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-3.

Dermal

No studies were identified regarding musculoskeletal effects in humans after dermal exposure of any duration to 2-, 3-, or 4-nitrophenol. No studies were identified regarding musculoskeletal effects in animals after dermal exposure of any duration to 2- or 3-nitrophenol. No studies were identified regarding musculoskeletal effects in animals after acute dermal exposure to 4-nitrophenol.

No musculoskeletal effects were observed in a three-generation rat study with dermal doses of 4-nitrophenol as high as 250 mg/kg/day (Angerhofer 1985). Similarly, no musculoskeletal effects were observed in a 78-week chronic duration study of mice exposed to 4-nitrophenol at doses as high as 160 mg/kg (NTP 1993).

2.9 HEPATIC

Inhalation

No studies were identified regarding hepatic effects in humans after inhalation exposure of any duration to 2-, 3-, or 4-nitrophenol. No studies were identified regarding hepatic effects in animals after acute or chronic inhalation exposure to 2-nitrophenol. No studies were identified regarding hepatic effects in animals after inhalation exposure of any duration to 3-nitrophenol. No studies were identified regarding hepatic effects in animals after chronic inhalation exposure to 4-nitrophenol.

Female rats exhibited statistically significant increases in absolute liver weight, as well as increased liver/brain weight ratio after intermediate exposure to 5 mg/m^3 2-nitrophenol; however, this increase was not concentration-dependent as female rats in the higher concentration groups of 32.5 mg/m^3 and 61.5 mg/m^3 did not exhibit the same increase in liver weight or liver/brain weight ratio (Hazleton 1984). The reason for the lack of dose-dependency in the observed hepatic effects was not known. Male rats showed no differences in these outcomes compared with the control group in the same study (Hazleton 1984).

Two studies have examined hepatic effects after inhalation exposure to 4-nitrophenol. Male Albino rats exhibited an 11% increase in AST after intermittent exposure to 2,133 mg/m^3 4-nitrophenol for 2 weeks, however this magnitude of change of a liver enzyme is not large enough to be considered a LOAEL (Smith et al. 1988). Both male and female Sprague-Dawley rats intermittently exposed to 4-nitrophenol for 4 weeks exhibited no change in AST or other hepatic effects at concentrations up to 30 mg/m^3 (Hazleton 1983).

The highest NOAEL values and all LOAEL values from each reliable study for hepatic effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-2.

Oral

No studies were identified regarding hepatic effects in humans after oral exposure of any duration to 2-, 3-, or 4-nitrophenol. No studies were identified regarding hepatic effects in animals after oral exposure of

any duration to 2- or 3-nitrophenol. No studies were identified regarding hepatic effects in animals after chronic oral exposure to 4-nitrophenol.

There is limited evidence to suggest that acute oral exposure to 4-nitrophenol may be associated with hepatic effects in rats. One single gavage administered dose of 200 mg/kg 4-nitrophenol led to the detachment of the central vein of the hepatic lobule, along with the disordering of hepatocytes in male Wistar rats (Li et al. 2017). A second study by Li et al. (2017) observed a widening of the hepatic sinusoid after 3 daily gavage doses of 200 mg/kg 4-nitrophenol, along with further disordering of hepatocytes. In the group of rats that were allowed to recover for three days after exposure, the authors observed a reversal of the histological changes in the liver, which were hypothesized to be caused by a reversal in the 4-nitrophenol-induced changes in the aryl hydrocarbon receptor signaling pathway (Li et al. 2017). Additionally, Tang et al. (2016) reported a 12% decrease in absolute liver weight in rats after three daily gavage administered doses of 200 mg/kg 4-nitrophenol.

Intermediate oral exposure to 4-nitrophenol has generally shown no significant effects related to the liver. While 18 days of daily gavage administration of 160 mg/kg/day, 4-nitrophenol led to a 6% increase in absolute liver weight in male rats, this increase in liver weight is not considered large enough to constitute an adverse effect. Female rats in this same dosing schedule also did not exhibit an increase in liver weight (Koizumi et al. 2001). Additionally, 28 days of daily gavage administration from this same study showed no hepatic effects in rats at doses up to 1,000 mg/kg/day 4-nitrophenol (Koizumi et al. 2001), and daily 13 weeks of gavage administration of 140 mg/kg/day 4-nitrophenol in rats also showed no hepatic effects (Hazleton 1989).

The highest NOAEL and LOAEL values from each reliable study for hepatic effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-3.

Dermal

No studies were identified regarding hepatic effects in humans after dermal exposure of any duration to 2-, 3-, or 4-nitrophenol. No studies were identified regarding hepatic effects in animals after dermal exposure of any duration to 2- or 3-nitrophenol. No studies were identified regarding hepatic effects in animals after acute dermal exposure to 4-nitrophenol.

No hepatic effects were observed in a three-generation intermediate duration rat study with dermal doses of 4-nitrophenol as high as 250 mg/kg/day (Angerhofer 1985). Similarly, no hepatic effects were observed in a 78-week chronic duration study of mice with doses as high as 160 mg/kg (NTP 1993).

Other

Subcutaneous injection of 100 mg/kg/day 4-nitrophenol daily for 28 days caused a statistically significant decrease in the antioxidant activities of superoxide dismutase and catalase, which help to defend against oxidative stress (Chen et al. 2016). This same subcutaneous injection of 4-nitrophenol also caused statistically significant increases in the hepatic markers of ALT, AST, AKP, and TBIL (Chen et al. 2016). However, there was no effect on absolute or relative liver weight in these animals.

2.10 RENAL

Inhalation

No studies were identified regarding renal effects in humans after inhalation exposure of any duration to 2-, 3-, or 4-nitrophenol. No studies were identified regarding renal effects in animals after acute or chronic inhalation exposure to 2-nitrophenol. No studies were identified regarding renal effects in animals after inhalation exposure of any duration to 3-nitrophenol. No studies were identified regarding renal effects in animals after chronic inhalation exposure to 4-nitrophenol.

Hazleton (1984) reported no renal effects of intermittent inhalation exposure to 2-nitrophenol in rats at concentrations up to 61.5 mg/m^3 for 4 weeks.

Smith et al. (1988) observed darker urine and proteinuria, as well as a 13% decrease in urine volume after intermittent exposure to 294 mg/m^3 4-nitrophenol for 2 weeks, but found no significant renal effects. Hazleton (1983) found no renal effects of intermediate intermittent inhalation exposure to 4-nitrophenol at concentrations up to 30 mg/m^3 for 4 weeks.

The highest NOAEL values from each reliable study for hematological effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-2.

Oral

No studies were identified regarding renal effects in humans after oral exposure of any duration to 2-, 3-, or 4-nitrophenol. No studies were identified regarding renal effects in animals after oral exposure of any duration to 2- or 3-nitrophenol. No studies were identified regarding renal effects in animals after chronic oral exposure to 4-nitrophenol.

Tang et al. (2016) observed a 14% increase in kidney weight after three days of daily oral gavage administration of 200 mg/kg/day 4-nitrophenol.

Intermediate oral exposure to 4-nitrophenol showed mixed results for renal effects. Hazleton (1989) reported no renal effects following daily gavage of 4-nitrophenol administered 7 days/week, for 13 weeks at doses up to 140 mg/kg/day in 6-week-old Sprague-Dawley rats. Koizumi et al. (2001) also observed no renal effects of daily oral gavage doses of 4-nitrophenol for 18 days (days 4 through 21 after birth) at doses up to 160 mg/kg/day in newborn Sprague-Dawley rats. However, in an additional study in this same Koizumi et al. (2001) publication, male Sprague-Dawley rats (at 6 weeks of age) administered oral gavage doses of 4-nitrophenol for 28 days had a 100% increase in eosinophilic bodies in proximal tubular cells at 400 mg/kg/day, but not at 160 mg/kg/day; while female Sprague-Dawley rats had no renal effects up to the 1,000 mg/kg/day dose. This increase in eosinophilic bodies in proximal tubular cells observed in the male rats, however, is not considered to be relevant to human toxicity (Koizumi et al 2001).

The highest NOAEL and LOAEL values from each reliable study for renal effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-3.

Dermal

No studies were identified regarding renal effects in humans after dermal exposure of any duration to 2-, 3-, or 4-nitrophenol. No studies were identified regarding renal effects in animals after dermal exposure of any duration to 2- or 3-nitrophenol. No studies were identified regarding renal effects in animals after acute dermal exposure to 4-nitrophenol.

No renal effects were observed in a three-generation intermediate duration rat study with dermal doses of 4-nitrophenol as high as 250 mg/kg/day (Angerhofer 1985). Similarly, no renal effects were observed in a chronic duration study of mice with doses as high as 160 mg/kg (NTP 1993).

2.11 DERMAL

Inhalation

No studies were identified regarding dermal effects in humans or animals after inhalation exposure of any duration to 2-, 3-, or 4-nitrophenol.

Oral

No studies were identified regarding dermal effects in humans after oral exposure of any duration to 2-, 3-, or 4-nitrophenol. No studies were identified regarding dermal effects in animals after oral exposure of

any duration to 2- or 3-nitrophenol. No studies were identified regarding dermal effects in animals after acute or chronic oral exposure to 4-nitrophenol.

Hazleton (1989) observed no dermal effects in rats after intermediate oral gavage exposure to 4-nitrophenol once per day, 7 days/week, for 13 weeks at doses up to 140 mg/kg/day.

The highest NOAEL values from each reliable study for dermal effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-3.

Dermal

No studies were identified regarding dermal effects in humans after dermal exposure of any duration to 2-, 3-, or 4-nitrophenol. No studies were identified regarding dermal effects in animals after dermal exposure of any duration to 2- or 3-nitrophenol, and no acute-duration studies investigating dermal effects in animals exposed dermally to 4-nitrophenol were identified.

Branch and Stout (Branch and Stout 1983b) topically applied 5,000 mg/kg once to a group of 10 rabbits and found various signs of localized dermal effects, including erythema in the exposed area, edema of the skin, dark brown discoloration of the dermal tissue, sloughing and scarring of the skin, hardening of the skin of the exposed area, and epidermal desquamation. However, the results of this study should be interpreted with caution as the study did not include a control group.

In a three-generation rat study, Angerhofer (1985) provided evidence for dermal effects of 4-nitrophenol at the lowest doses administered. In both the F0 and F1 generations, patterns of dermal irritation consisting of varying degrees of erythema, scaling, scabbing, and cracking were observed at 4-nitrophenol dermal doses as low as 50 mg/kg/day when administered once per day, 5 days/week, for 20 weeks (Angerhofer 1985). These dermal effects were not present in the F2 generation, although the F2 generation was not directly exposed to the chemical (Angerhofer 1985).

No dermal effects were observed in a chronic-duration dermal study of mice with doses as high as 160 mg/kg (NTP 1993).

2.12 OCULAR

Inhalation

Based on a systematic evaluation of the literature, ocular effects are not classifiable as a health effect of exposure to 4-nitrophenol. The full results of the systematic review are presented in Appendix C. No

studies were identified regarding ocular effects in humans after inhalation exposure of any duration to 2-, 3-, or 4-nitrophenol. No studies were identified regarding ocular effects in animals after acute or chronic inhalation exposure to 2-nitrophenol. No studies were identified regarding ocular effects in animals after inhalation exposure of any duration to 3-nitrophenol. No studies were identified regarding ocular effects in animals after chronic inhalation exposure to 4-nitrophenol.

Hazleton (1984) found no ocular effects of intermediate inhalation exposure to 2-nitrophenol in rats at concentrations up to 61.5 mg/m^3.

Acute inhalation of 4-nitrophenol has been shown to cause ocular effects in rats. Corneal opacity and irritation was observed in male rats after intermittent inhalation exposure for 2 weeks at concentrations as low as 26 mg/m^3 (Smith et al. 1988). The rats did recover from the ocular effects, however, after a 14-day recovery period (Smith et al. 1988).

Intermediate inhalation of 4-nitrophenol has also been shown to cause ocular effects in rats. After 30 mg/m^3 of intermittent 4-nitrophenol exposure for 4 weeks, both male and female rats exhibited unilateral and bilateral diffused anterior capsular cataracts; the NOAEL for these effects in this study was 5 mg/m^3 (Hazleton 1983).

The highest NOAEL values and all LOAEL values from each reliable study for ocular effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-2.

Oral

No studies were identified regarding ocular effects in humans after oral exposure of any duration to 2-, 3-, or 4-nitrophenol. No studies were identified regarding ocular effects in animals after oral exposure of any duration to 2- or 3-nitrophenol. No studies were identified regarding ocular effects in animals after acute or chronic oral exposure to 4-nitrophenol.

Hazleton (1989) observed no ocular effects in rats after intermediate oral gavage exposure to 4-nitrophenol daily, 7 days/week, for 13 weeks at doses up to 140 mg/kg/day.

The highest NOAEL values from each reliable study for ocular effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-3.

Dermal

No studies were identified regarding ocular effects in humans after dermal exposure of any duration to 2-, 3, or 4-nitrophenol. No studies were identified regarding ocular effects in animals after dermal exposure of any duration to 2- or 3-nitrophenol.

Severe conjunctival irritation and corneal opacity, along with irritation and visible destruction of the iris were observed after a single dose of 100 mg 4-nitrophenol was placed into the conjunctival sac of one eye of male rabbits, followed by a seven day observation period (Weeks 1992). However, the reliability of the study may be questionable due to the lack of control animals, as well as the incomplete reporting of the study results.

No ocular effects were observed in a three-generation rat study with dermal doses of 4-nitrophenol as high as 250 mg/kg/day (Angerhofer 1985). Similarly, no ocular effects were observed in a chronic duration study of mice with doses as high as 160 mg/kg (NTP 1993).

2.13 ENDOCRINE

Inhalation

No studies were identified regarding endocrine effects in humans after inhalation exposure of any duration to 2-, 3-, or 4-nitrophenol. No studies were identified regarding endocrine effects in animals after inhalation exposure of any duration to 2- or 3-nitrophenol. No studies were identified regarding endocrine effects in animals after acute or chronic inhalation exposure to 4-nitrophenol.

Hazleton (1983) found no endocrine effects of intermittent inhalation exposure to 4-nitrophenol for 4 weeks in rats at concentrations up to 30 mg/m^3, as judged by organ weight and histopathology of adrenals, thyroid, pituitary gland, thymus, pancreas, testes, and ovaries.

The highest NOAEL values from each reliable study for endocrine effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-2.

Oral

No studies were identified regarding endocrine effects in humans after oral exposure of any duration to 2-, 3-, or 4-nitrophenol. No studies were identified regarding endocrine effects in animals after oral exposure of any duration to 2- or 3-nitrophenol. No studies were identified regarding endocrine effects in animals after chronic oral exposure to 4-nitrophenol.

Tang et al. (2016) observed a 41% increase in adrenal gland weight after three days of daily gavage oil administration of 200 mg/kg/day 4-nitrophenol. However, no endocrine effects of intermediate duration, oral exposure to 4-nitrophenol in rats were found at doses up to 1,000 mg/kg/day after histopathological examination and organ weight evaluation of the pituitary gland, thymus, thyroid, adrenals, testes, ovaries, and pancreas (Hazleton 1989; Koizumi et al. 2001).

The highest NOAEL and LOAEL values from each reliable study for endocrine effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-3.

Dermal

No studies were identified regarding endocrine effects in humans after dermal exposure of any duration to 2-, 3-, or 4-nitrophenol. No studies were identified regarding endocrine effects in animals after dermal exposure of any duration to 2- or 3-nitrophenol. No studies were identified regarding endocrine effects in animals after acute dermal exposure to 4-nitrophenol.

No endocrine effects were observed in a three-generation rat study with dermal doses of 4-nitrophenol as high as 250 mg/kg/day after histopathology of the thymus, thyroid, testes, ovaries, pancreas, and adrenal glands (Angerhofer 1985). Similarly, no endocrine effects were observed in a chronic duration study of mice with doses as high as 160 mg/kg after histopathologic examination of the adrenal gland, testes, ovaries, pancreas, parathyroid gland, pituitary gland, thymus, and thyroid gland (NTP 1993).

Other

Although there is no evidence of endocrine toxicity after exposure to 4-nitrophenol through oral, inhalation, or dermal routes, 4-nitrophenol has been shown to alter endocrine function after parenteral exposure in both male and female rodents. Li et al. (2006) showed that male rats exposed to 0.1 mg/kg/day 4-nitrophenol for 7 days via subcutaneous injections exhibited a significant increase in luteinizing hormone (LH) and follicle stimulating hormone (FSH) in the plasma at 0.1 mg/kg/day; this indicates that 4-nitrophenol has estrogenic and anti-androgenic activities *in vivo*. Li et al. (2009) also showed that acute exposure to 4-nitrophenol by subcutaneous injections at 0.01 mg/kg/day altered the plasma concentrations of luteinizing hormone (LH), follicle stimulating hormone (FSH) and testosterone in male rats (Li et al. 2009). Zhang et al. (2017) showed that a single exposure to 4-nitrophenol via subcutaneous injections to neonatal female rats (treated at post-natal day [PND] 0) at 10 mg/kg/day potentially affects the expression of estrogen receptor β (ERβ) in the rat ovaries, resulting in disrupted steroidogenesis during ovarian development and delayed puberty. Zhang et al. (2013) also demonstrated

that a daily exposure by subcutaneous injections for 4 weeks in male rats to a dose of 1 mg/kg 4-nitrophenol increased serum testosterone and hyperplasia of Leydig cells in the testes.

Zhang et al. (2013) observed a significant decrease in the levels of estradiol and aromatase expression along with an increase in the expression of the estrogen receptors α and β after a daily 4-week exposure to 10 mg/kg/day of 4-nitrophenol. Zhang et al. (2015) observed that intermediate exposure to 100 mg/kg/day of 4-nitrophenol by subcutaneous injection resulted in a significant decrease in sperm counts and serum testosterone levels, as well as morphological changes in the testes (Zhang et al. 2015).

Given the lack of corroborating evidence of these observed endocrine outcomes in studies using the oral, inhalation, and dermal routes of exposure, these results should be treated with caution regarding making generalizations about the effects of 4-nitrophenol on endocrine toxicity.

2.14 IMMUNOLOGICAL

Inhalation

No studies were identified regarding immunological effects in humans after inhalation exposure of any duration to 2-, 3-, or 4-nitrophenol. No studies were identified regarding immunological effects in animals after acute or chronic inhalation exposure to 2-nitrophenol. No studies were identified regarding immunological effects in animals after inhalation exposure of any duration to 3-nitrophenol. No studies were identified regarding immunological effects in animals after chronic inhalation exposure to 4-nitrophenol.

Hazleton (1984) found no immunological effects of intermittent inhalation exposure to 2-nitrophenol for 4 weeks in rats at concentrations up to 61.5 mg/m^3.

Decreased spleen weight was observed in rats after a 10-day exposure to 2,133 mg/m^3 4-nitrophenol; the NOAEL reported in this study for this effect was 294 mg/m^3 (Smith et al. 1988). Hazleton (1983) found no immunological effects in rats after intermittent inhalation exposure to 4-nitrophenol for 4 weeks at concentrations up to 30 mg/m^3.

The highest NOAEL values and all LOAEL values from each reliable study for immunological effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-2.

Oral

No studies were identified regarding immunological effects in humans after oral exposure of any duration to 2-, 3-, or 4-nitrophenol. No studies were identified regarding immunological effects in animals after oral exposure of any duration to 2- or 3-nitrophenol. No studies were identified regarding immunological effects in animals after chronic oral exposure to 4-nitrophenol.

Tang et al. (2016) observed no immunological effects after 3 days of daily gavage administration of 200 mg/kg/day 4-nitrophenol in male rats. Similarly, Koizumi et al. (2001) observed no immunological effects following 28-day gavage administration at doses as high as 1,000 mg/kg/day.

The highest NOAEL values from each reliable study for immunological effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-3.

Dermal

No studies were identified regarding immunological effects in humans after dermal exposure of any duration to 2-, 3-, or 4-nitrophenol. No studies were identified regarding immunological effects in animals after dermal exposure of any duration to 2- or 3-nitrophenol. No studies were identified regarding immunological effects in animals after acute duration dermal exposure to 4-nitrophenol.

No immunological effects were observed in a three-generation rat study with dermal doses of 4-nitrophenol as high as 250 mg/kg/day (Angerhofer 1985). Similarly, no immunological effects were observed in a chronic duration study of mice with doses as high as 160 mg/kg (NTP 1993).

2.15 NEUROLOGICAL

Inhalation

No studies were identified regarding neurological effects in humans after inhalation exposure of any duration to 2-, 3-, or 4-nitrophenol. No studies were identified regarding neurological effects in animals after acute or chronic inhalation exposure to 2-nitrophenol. No studies were identified regarding neurological effects in animals after inhalation exposure of any duration to 3-nitrophenol. No studies were identified regarding neurological effects in animals after chronic inhalation exposure to 4-nitrophenol.

Hazleton (1984) found no neurological effects of intermediate-duration inhalation exposure for 4 weeks to 2-nitrophenol in rats at concentrations up to 61.5 mg/m^3.

Lethargy was observed in rats after acute intermittent inhalation exposure for 2 weeks at a concentration of 2,133 mg/m^3 4-nitrophenol; the NOAEL reported in this study for this effect was 294 mg/m^3 (Smith et

al. 1988). Hazleton (1983) found no neurological effects in rats after intermittent 4 week exposure to 4-nitrophenol at concentrations up to 30 mg/m^3.

The highest NOAEL values and all LOAEL values from each reliable study for neurological effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-2.

Oral

No studies were identified regarding neurological effects in humans after oral exposure of any duration to 2-, 3-, or 4-nitrophenol. No studies were identified regarding neurological effects in animals after oral exposure of any duration to 2- or 3-nitrophenol. No studies were identified regarding neurological effects in animals after chronic oral exposure to 4-nitrophenol.

Oral exposure to 4-nitrophenol has shown mixed results with respect to neurological effects. Abu-Qare et al. (2000) observed no neurological effects after a single gavage administered dose of 100 mg/kg/day 4-nitrophenol in female Sprague-Dawley rats. Hazleton (1989) observed similar results in an intermediate duration gavage administration study in Sprague-Dawley rats, finding no neurological effects at doses as high as 140 mg/kg/day after 13 weeks of exposure. However, Koizumi et al. (2001) observed a decrease in motor activity and tonic convulsions in rats in the prone/lateral position after the first dose in a 28-day 1,000 mg/kg/day exposure to 4-nitrophenol via gavage. Branch and Stout (1983b) also observed neurological effects in Sprague-Dawley albino rats after a single oral gavage exposure to 4-nitrophenol at 70 mg/kg; however, this study did not include a control group, which may call into question the validity of the findings (Branch and Stout 1983a). The effects of exposure to 4-nitrophenol at 70 mg/kg included lethargy and salivation (Branch and Stout 1983a). More serious neurological effects observed included convulsions in both males and females at a higher dose of 268 mg/kg (Branch and Stout 1983a).

The highest NOAEL and LOAEL values from each reliable study for neurological effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-3.

Dermal

No studies were identified regarding neurological effects in humans after dermal exposure of any duration to 2-, 3-, or 4-nitrophenol. No studies were identified regarding neurological effects in animals after dermal exposure of any duration to 2- or 3-nitrophenol. No studies were identified regarding neurological effects in animals after acute dermal exposure to 4-nitrophenol.

Transient hyperexcitability when being handled was observed after 15 weeks of exposure in several male Sprague-Dawley rats in the F0 generation of a three-generation study of 4-nitrophenol while receiving doses of 50 mg/kg/day (5 days/week for 20 weeks); for females, no neurological effects were reported at doses up to 250 mg/kg/day in the F0 generation (Angerhofer 1985). Decreased brain weight (10% decrease) was also observed in the male rats of the F1 generation of this study at 250 mg/kg/day. No effects were noted in males at 100 mg/kg/day, and no neurological effects were reported in females at doses up to 250 mg/kg/day in the F1 generation (Angerhofer 1985). No neurological effects were observed in either sex of the F2 generation of the same study with dermal doses of 4-nitrophenol as high as 250 mg/kg/day (Angerhofer 1985). No discussion of the possible reasons for the differences in effects between the generations was presented by the study author; however, it may be because the F2 generation was not directly exposed to the chemical. No neurological effects were observed in a chronic duration study of mice with doses as high as 160 mg/kg (NTP 1993).

2.16 REPRODUCTIVE

Inhalation

No studies were identified regarding reproductive effects in humans after inhalation exposure of any duration to 2-, 3-, or 4-nitrophenol. No studies were identified regarding reproductive effects in animals after acute or chronic inhalation exposure to 2-nitrophenol. No studies were identified regarding reproductive effects in animals after inhalation exposure of any duration to 3-nitrophenol. No studies were identified regarding reproductive effects in animals after acute or chronic inhalation exposure to 4-nitrophenol.

Hazleton (1984) found no histopathological or organ weight reproductive effects of intermittent intermediate inhalation exposure to 2-nitrophenol for 4 weeks in rats at concentrations up to 61.5 mg/m^3. Hazleton (1983) also found no histopathological or organ weight reproductive effects in rats after an intermittent 4 week exposure to 4-nitrophenol at concentrations up to 30 mg/m^3.

The highest NOAEL values from each reliable study for hematological effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-2.

Oral

No studies were identified regarding reproductive effects in humans after oral exposure of any duration to 2-, 3-, or 4-nitrophenol. No studies were identified regarding developmental effects in animals after oral exposure of acute and chronic duration to 2-nitrophenol. No studies were identified regarding

reproductive effects in animals after oral exposure of any duration to 3-nitrophenol. No studies were identified regarding reproductive effects in animals after chronic oral exposure to 4-nitrophenol.

In an acute exposure study where female Sprague-Dawley rats mated and were exposure orally via gavage with 2-nitrophenol dissolved in corn oil daily for 9 days, a 68% increase in post-implantation losses and a 92% increase in resorption were observed at the dose of 1,000 mg/kg/day. There were no effects observed at 50, 125, 250, or 500 mg/kg/day (Monsanto 1990).

No reproductive effects were observed in male or female rats after acute gavage administration of 4-nitrophenol at doses as high as 1,000 mg/kg/day (Abu-Qare et al. 2000; Kavlock 1990; Tang et al. 2016). There were no reproductive effects observed in female mice after acute gavage administration of 4-nitrophenol at 400 mg/kg/day for 8 days, though there was a slight non-statistically significant reduction in the average number of live pups per litter (Plasterer et al. 1985). Similar results were observed in intermediate oral gavage studies in rats, with no observable reproductive effects in males or females at doses as high as 1,000 mg/kg/day (Hazleton 1989; Koizumi et al. 2001).

The highest NOAEL values from each reliable study for reproductive effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-3.

Dermal

No studies were identified regarding reproductive effects in humans after dermal exposure of any duration to 2-, 3-, or 4-nitrophenol. No studies were identified regarding reproductive effects in animals after dermal exposure of any duration to 2- or 3-nitrophenol. No studies were identified regarding reproductive effects in animals after acute dermal exposure to 4-nitrophenol.

No reproductive effects were observed in a three-generation rat study with dermal doses of 4-nitrophenol as high as 250 mg/kg/day, which included breeding and litter observations, reproductive success, as well as histological observations of reproductive organs (Angerhofer 1985). Similarly, no histological reproductive effects were observed in a chronic duration study of mice with doses as high as 160 mg/kg (NTP 1993).

Other

Although there is no evidence of reproductive toxicity after exposure to 4-nitrophenol through oral, inhalation, or dermal routes, 4-nitrophenol has been shown to alter reproductive function after parenteral exposure in both male and female rodents. Li et al. (2006) showed that male rats exposed to 0.1

mg/kg/day 4-nitrophenol for 7 days via subcutaneous injections exhibited a decrease in weight of seminal vesicles, ventral prostate, and glans penis; there were no effects noted in the male rats following exposure to 0.01 mg/kg/day. Li et al. (2006) also demonstrated that this exposure increased uterine weight at 10 mg/kg/day, but not at 1 mg/kg/day, in female rats. Luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels in the plasma were not altered in females, but these hormones increased significantly in males at 0.1 mg/kg/day; this indicates that 4-nitrophenol has estrogenic and anti-androgenic activities *in vivo* (Li et al. 2006). Li et al. (2009) also showed that acute exposure to 4-nitrophenol by subcutaneous injections at 0.01 mg/kg/day altered the plasma concentrations of luteinizing hormone (LH), follicle stimulating hormone (FSH) and testosterone in male rats (Li et al. 2009).

Zhang et al. (2017) showed that a single exposure to 4-nitrophenol via subcutaneous injections to neonatal female rats (treated at post-natal day [PND] 0) at 10 mg/kg/day caused an increase in the ratio of primordial and primary follicles in female rats at PND 14 and 21. Zhang et al. (2017) also demonstrated that female mice had a significantly delayed timing of vaginal opening after this subcutaneously injected dose. Additionally, there was a significant increase in the expression of steroidogenic enzymes at postnatal day 14 (Zhang et al. 2017). Zhang et al. (2017) also provides evidence that acute exposure to 4-nitrophenol potentially affects the expression of estrogen receptor β (ERβ) in the rat ovaries, resulting in the disrupted steroidogenesis during ovarian development and the delayed puberty (Zhang et al. 2017).

In an intermediate exposure study to 4-nitrophenol via intraperitoneal injections at 10 mg/kg/day, severe damage was observed in the seminiferous tubules in male adult mice, potentially caused by an increase in reactive oxidative species (Mi et al. 2013). A 3 mg/kg/day dose of 4-nitrophenol induced oxidative stress in testes of male rats after an intratesticular intermediate exposure (Zhang et al. 2016). Zhang et al. (2013) also demonstrated that a daily exposure by subcutaneous injections for 4 weeks in male rats to a dose of 1 mg/kg 4-nitrophenol increased serum testosterone and hyperplasia of Leydig cells in the testes.

Zhang et al. (2013) observed a significant decrease in the levels of estradiol and aromatase expression along with an increase in the expression of the estrogen receptors α and β after a daily 4-week exposure to 10 mg/kg/day 4-nitrophenol (Zhang et al. 2013). Zhang et al. (2015) observed that intermediate exposure to 100 mg/kg/day 4-nitrophenol by subcutaneous injection resulted in a significant decrease in sperm counts and serum testosterone levels, as well as morphological changes in the testes (Zhang et al. 2015).

Given the lack of corroborating evidence of these observed reproductive outcomes in studies using the oral, inhalation, and dermal routes of exposure, these results should be treated with caution regarding making generalizations about the effects of 4-nitrophenol on reproductive toxicity.

2.17 DEVELOPMENTAL

Inhalation

No studies were identified regarding developmental effects in humans or animals after inhalation exposure of any duration to 2-, 3-, or 4-nitrophenol.

Oral

No studies were identified regarding developmental effects in humans after oral exposure of any duration to 2-, 3-, or 4-nitrophenol. No studies were identified regarding developmental effects in animals after oral exposure of any duration to 2- or 3-nitrophenol. No studies were identified regarding developmental effects in animals after intermediate or chronic oral exposure to 4-nitrophenol.

The available literature on acute oral exposure to 4-nitrophenol has not identified any associations with developmental effects. Kavlock (1990) found no statistically significant differences in the viability and weight of rat offspring, nor were there any differences in overt malformations in offspring after gavage administration of a single dose of 4-nitrophenol on gestational day 11 at doses up to 1,000 mg/kg. Kavlock (1990) did classify 4-nitrophenol as an active developmental toxicant with respect to reducing litter biomass; however, the results of the study do not support this conclusion. Abu-Qare et al. (2000) noted no observable fetal toxic effects after gavage administration of a single dose of 100 mg/kg 4-nitrophenol to pregnant Sprague-Dawley rats based on gross examination. Plasterer et al. (1985) found mouse pups had no structural abnormalities or differences in body weight after 8 days of daily gavage oil doses of 400 mg/kg/day 4-nitrophenol to pregnant mothers starting on gestational day seven. No developmental effects were observed when pregnant Sprague-Dawley rats were exposed to 4-nitrophenol from gestational day 6 through day 16 (Angerhofer and Weeks 1992).

The highest NOAEL values from each reliable study for developmental effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-3.

Dermal

No studies were identified regarding developmental effects in humans after dermal exposure of any duration to 2-, 3-, or 4-nitrophenol. No studies were identified regarding developmental effects in animals after dermal exposure of any duration to 2- or 3-nitrophenol. No studies were identified regarding developmental effects in animals after acute or chronic dermal exposure to 4-nitrophenol.

No developmental effects were observed in a three-generation intermediate duration rat study with dermal doses of 4-nitrophenol as high as 250 mg/kg/day (Angerhofer 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 (Angerhofer 1985).

2.18 CANCER

Inhalation

No studies were identified regarding cancer effects in humans or animals after inhalation exposure of any duration to 2-, 3-, or 4-nitrophenol.

Oral

No studies were identified regarding cancer effects in humans or animals after oral exposure of any duration to 2-, 3-, or 4-nitrophenol.

Dermal

There is only one study of carcinogenicity of 4-nitrophenol, which was the NTP (1993) study. This study was a chronic duration cancer assessment study in mice that administered dermal doses of 4-nitrophenol up to 160 mg/kg 3 days/week for 78 weeks. All organs and tissues were examined for gross lesions at the end of the study. No dose-related increases in malignant neoplasms were observed for any of the organs/tissues, despite the overall incidence of benign and malignant neoplasms being elevated in male mice in the low- and mid-dose groups. The authors concluded 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. The National Toxicology Program of the U.S. Department of Health and Human Services (NTP) has not classified the nitrophenols with regard to their human carcinogenicity. The Environmental Protection Agency (EPA) has classified 4-nitrophenol as Group D for carcinogenicity, indicating that there is inadequate information to determine its cancer potential. EPA has not evaluated 2- or 3-nitrophenol for carcinogenicity. The International Agency for Research on Cancer (IARC) has not classified the nitrophenols with regard to their human carcinogenicity.

2.19 GENOTOXICITY

No studies were identified regarding the genotoxic effects of 2-, 3- or 4-nitrophenol in humans or animals by inhalation, oral, or dermal routes. No information was available regarding mutagenicity of 2- and 3-nitrophenol *in vivo*, and only one study investigated the mutagenicity of 4-nitrophenol *in vivo*. *In vitro* studies only examined the genotoxic effects of 2- and 4-nitrophenol. 4-Nitrophenol was not mutagenic *in vivo* as judged by the dominant lethal assay and the host-mediated assay in mice, nor *in vitro* as judged by the spot test (Buselmaier et al. 1973).

As indicated in Table 2-3, 2-nitrophenol did not increase the frequency of reverse mutations in *Salmonella typhimurium* or in *Escherichia coli* in the presence or absence of metabolic activation, nor did it induce DNA damage when tested in *Bacillus subtilis* or in *Salmonella typhimurium*. No data were available regarding genotoxic properties of 2-nitrophenol in eukaryotic organisms.

The *in vitro* genotoxicity of 4-nitrophenol has been investigated in prokaryotic organisms and in mammalian cell systems. The overall evidence indicates that 4-nitrophenol is not mutagenic in the presence or absence of activating systems in *S. typhimurium, E. coli,* and *Drosophila melanogaster* (Table 2-4). One positive result was reported by Shimizu and Yano (1986) of 4-nitrophenol induced DNA damage when tested in *B. subtilis* by the ret assay. According to Shimizu and Yano (1986), this assay appears to be more sensitive for nitro compounds in general than the standard Ames Test. Weaker genotoxic effects were reported in two studies (Adler et al. 1976; Garrett and Lewtas 1983). The hypothesis that reduction of the nitro group is required to observe mutagenic effects was tested by Dellarco and Prival (1989); these authors did not observe an increase in mutagenicity when 2- or 4-nitrophenol was incubated in the presence of S-9 and flavin mononucleotide mixture in *S. typhimurium*. 4-Nitrophenol was generally not found to be mutagenic when tested in mammalian cells with or without metabolic activation (Amacher and Turner 1982; Hartmann and Speit 1997; Oberly et al. 1984; Probst et al. 1981; Richard and Clark 1990). NTP (1993) found that 4-nitrophenol induced chromosomal aberrations in Chinese hamster ovary cells with activation but not without activation. This is supported by two other studies that looked at the same cells; Garrett and Lewtas (1983) reported weak inhibition of DNA synthesis, and Andrews (1990a) reported chromosomal aberrations. No data were available regarding genotoxic properties of 4-nitrophenol in eukaryotic organisms, *in vivo*. Based on the available evidence, it does not appear that exposure to 2-nitrophenol or 4-nitrophenol is genotoxic to humans.

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

Species (test system)	End Point	Results Activation With	Results Activation Without	Reference
Prokaryotic organisms				
Salmonella typhimurium (plate incorporation)	Gene mutation	No data	-	Chiu et al. 1978
S. typhimurium (plate incorporation)	Gene mutation	-	-	Suzuki et al. 1983
S. typhimurium (plate incorporation)	Gene mutation	-	-	Dellarco and Prival 1989
S. typhimurium (plate incorporation)	Gene mutation	-	-	Shimizu and Yano 1986
Escherichia coli sd-4-73 (spot test)	Gene mutation	No data	-	Szybalski 1958
Bacillus subtilis (plate incorporation)	DNA damage	No data	-	Shimizu and Yano 1986
S.typhimurium (plate incorporation)	DNA damage	-	-	Bonnefoy et al. 2012
S.typhimurium (plate incorporation)	DNA damage	-	-	Degirmenci et al. 2000

- Negative result

Table 2-5. Genotoxicity of 4-Nitrophenol *In Vitro*

Species (test system)	End Point	Results Activation With	Results Activation Without	Reference
Prokaryotic organisms				
Salmonella typhimurium (plate incorporation)	Gene mutation	-	-	Suzuki et al. 1983
S.typhimurium (plate incorporation)	Gene mutation	-	-	Probst et al. 1981
S.typhimurium (plate incorporation)	Gene mutation	-	-	Haworth et al. 1983
S.typhimurium (plate incorporation)	Gene mutation	-	-	Shimizu and Yano 1986
S.typhimurium (plate incorporation)	Gene mutation	-	-	Dellarco and Prival 1989
Escherichia coli (plate incorporation)	Gene mutation	-	-	Probst et al. 1981
Escherichia coli (spot test)	Gene mutation	-	-	Szybalski 1958
E. coli (plate incorporation)	Prophage induction	-	No data	Ho and Ho 1981
Proteus mirabilis	DNA damage	No data	(+)	Adler et al. 1976
E.coli	DNA repair	No data	-	Rashid and Mumma 1986
S.typhimurium (disc assay)	DNA repair	No data	-	Rashid and Mumma 1986
Bacillus subtilis (plate incorporation)	DNA damage	No data	+	Shimizu and Yano 1986
S.typhimurium (plate incorporation)	DNA damage	No data	(+)	Andrews 1990b
S.typhimurium (plate incorporation)	Gene mutation	-	-	NTP 1993

Table 2-5. Genotoxicity of 4-Nitrophenol *In Vitro*

Species (test system)	End Point	Results Activation With	Results Activation Without	Reference
Drosophila melanogaster	Gene mutation	-	-	NTP 1993
Mammalian organisms				
Rat hepatocytes (culture)	DNA repair	No data	-	Probst et al. 1981
Mouse lymphoma cells	Forward mutation	-	-	Oberly et al. 1984
Mouse lymphoma cells	Forward mutation	-	No data	Amacher and Turner 1982
Chinese hamster ovary cells (culture)	Inhibition of DNA synthesis	No data	(+)	Garrett and Lewtas 1983
Chinese hamster ovary cells (culture)	Chromosomal aberrations	-	+	Andrews 1990a
Mouse L5178Y lymphoma TK +/- cells	Gene mutation	-	-	Richard and Clark 1990
Chinese hamster ovary cells (culture)	Chromosomal aberrations	+	-	NTP 1993
Chinese hamster ovary cells (culture)	DNA damage	-	-	Hartmann and Speit 1997

+ Positive result; - Negative result; (+) Weakly positive result

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: Absorption of 4-Nitrophenol through both dermal and oral exposure is species-dependent, though it is believed to be rapid in all cases. Orally administered 4-nitrophenol is rapidly absorbed through the gastrointestinal tract.

- Distribution: Upon absorption, 4-nitrophenol is widely distributed in the body after oral exposure. Results suggest that while the majority of the oral exposure to 4-nitrophenol is distributed to the gastrointestinal tract for excretion, the liver and kidney may also play roles in metabolizing 4-nitrophenol after oral exposure. 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 rats results in very minimal body burden of 4-nitrophenol (0.4%), with the majority of 4- nitrophenol being excreted via urine (63%) and feces (3%).

- Metabolism: Both 2-nitrophenol 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-aminophenol 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.

- Excretion: The majority of nitrophenols are excreted rapidly in the urine with small amounts excreted in the feces, though information is limited with respect to the excretion of 2- and 3-nitrophenol. After a 100 mg/kg dose of 4-nitrophenol in rats, the administered dose was excreted as 4% glucuronides, 8% sulfates, 11% hot-acid hydrolysates, 16% non-conjugated compounds, and 61% water-soluble metabolites. Excretion of 4-nitrophenol appears to be more rapid after oral and intravenous administration, as compared with dermal administration of the chemical.

Observed half-life values for 4-nitrophenol ranged from 0.6 to 5 hours depending on species, exposure pathways, and sex in the animal literature. The urinary excretion rate was modeled to be three to seven times faster for the conjugate than for 4-nitrophenol in female weanling pigs.

3.1.1 Absorption

No studies were identified regarding the rate and extent of absorption in humans or animals following inhalation exposure to 2-, 3- and 4-nitrophenol.

No studies were identified regarding absorption of 2-, 3- or 4-nitrophenol in humans following oral exposure.

4-nitrophenol is rapidly absorbed in animals after oral exposure. Abu-Qare et al. (2000) observed that 36% of a single oral gavage dose of 4-nitrophenol in Sprague-Dawley rats was absorbed in the gastrointestinal tract after 30 minutes. The 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 dosed studies that measured metabolites in the excreta indicate 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.

No studies were identified regarding the absorption in humans or animals following dermal exposure to 2- and 3- nitrophenol or in humans following dermal exposure to 4-nitrophenol.

Dermal application of 4-nitrophenol in animals showed species-dependent absorption. Topically applied ^{14}C-labeled 4-nitrophenol was absorbed in rabbits at a rate of 35% and in dogs at 11% in seven days (Snodgrass 1983). The rate of absorption was determined by quantifying the radio labeled 4-nitrophenol in the urine over seven days (Snodgrass 1983). In rabbits, the absorption rate for dermal exposure peaked on day one after topical application at approximately 27% of the dose in the first day; whereas in the dogs the absorption rate peaked on day two with a 4% absorption of the applied dose during the second day

after application (Snodgrass 1983). Unabsorbed 4-nitrophenol accounted for 53% and 86% of the applied dose in the rabbits and dogs, respectively (Snodgrass 1983).

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 one hour after dosing for males and two hours after dosing for females (Eichenbaum et al. 2009).

3.1.2 Distribution

There were no studies that quantitatively described distribution in humans and/or animals following inhalation exposure to 2-, 3-, and 4- nitrophenol.

No studies were identified that quantitatively described distribution in humans and/or animals following oral exposure to 2- or 3-nitrophenol or in humans following oral exposure to 4-nitrophenol. In the only animal study identified for this topic, Abu-Qare et al. (2000) measured tissue concentrations at various time points after a single oral dose of 100 mg/kg ^{14}C-labeled 4-nitrophenol to pregnant Sprague-Dawley rats. This study found that over 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). These results suggest that while the majority of 4-nitrophenol was distributed to the gastrointestinal tract, the liver and kidney may also play roles in the metabolism of 4-nitrophenol after oral exposure. Abu-Qare et al. (2000) also observed distribution of 4-nitrophenol into the tissue of the fetus, suggesting 4-nitrophenol crosses the placental barrier after oral exposure in rats, though no fetal toxic effects were observed due to this exposure to 4-nitrophenol.

No studies were identified that quantitatively described distribution in humans following dermal exposure to 2-, 3-, and 4- nitrophenol. No studies were identified that quantitatively described distribution in animals following dermal exposure to 2- and 3- nitrophenol.

4-nitrophenol is minimally distributed in animals after dermal exposure. Dermal application of ^{14}C-4-nitrophenol for 120 hours was used to quantify the distributions in rats, and showed that the body burden of 4-nitrophenol was minimal (0.4%), with the majority of 4- nitrophenol being excreted via urine (63%) and feces (3%) (Hughes and Hall 1997). Nearly 30% of 4-nitrophenol was washed off of the skin 24 hours after dermal application, as it had not been absorbed (Hughes and Hall 1997).

Evidence suggests there is minimal body burden following intravenous or intraperitoneal exposure as well. Qiao et al. (2000) administered 150 µg 4-nitrophenol intravenously to female weanling piglets. Qiao et al. (2000) reported an insignificant amount of 4-nitrophenol in tissues as less than 0.04% 4-nitrophenol remained in the body 96 hours after dosing. Only 2% remained in tissues after dermal application (Qiao et al. 2000). The mean residence times, determined by modeling, in plasma and peripheral tissues were, on average, longer for dermally applied 4-nitrophenol than for 4-nitrophenol administered intravenously (Qiao et al. 2000). The highest modeled tissue concentration after intravenous administration occurred two to three hours after exposure; Qiao et al. (2000) also estimated that all tissues would be cleared of 4-nitrophenol 24 to 36 hours after intravenous exposure. 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 seven days after treatment (Snodgrass 1983). Similarly, the body burden of 4-nitrophenol after intraperitoneal administration was approximately 0.4% after 120 hours 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 two days. After approximately five minutes post-dose, the plasma concentration of 4-nitrophenol was effectively 100% of the administered dose, but after 15 minutes post-dose, plasma concentrations dropped to 7% of the administered dose of 25 mg/kg/day, and around 10% of the administered dose of 30 mg/kg/day (Eichenbaum et al. 2009). The authors suggested this was evidence of extensive distribution of 4-nitrophenol outside the plasma (Eichenbaum et al. 2009).

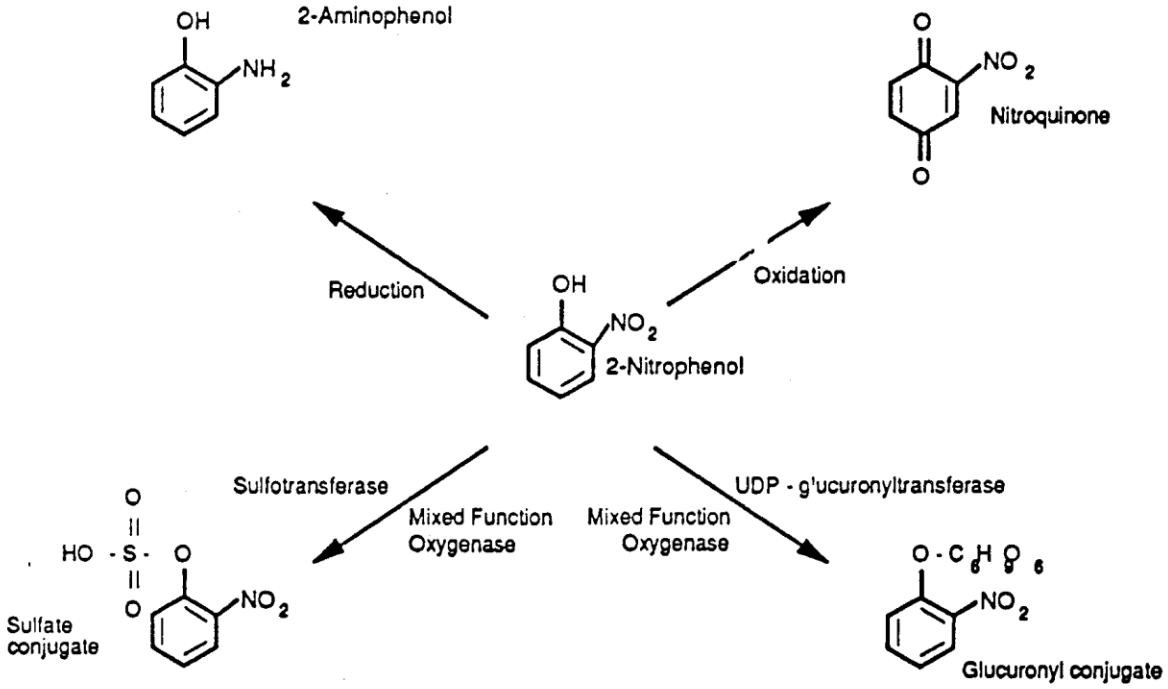
3.1.3 Metabolism

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. 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.

No studies regarding metabolism in humans following inhalation or oral exposure to 2-, 3-, and 4-nitrophenol were identified. No animal studies regarding the metabolism of 2-, 3-, and 4-nitrophenol after inhalation exposure were identified. There are a few animal studies that study the metabolism of the 2-, 3-, and 4-nitrophenols after oral 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 6-14% of the dose. Oxidation accounted for less than 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).

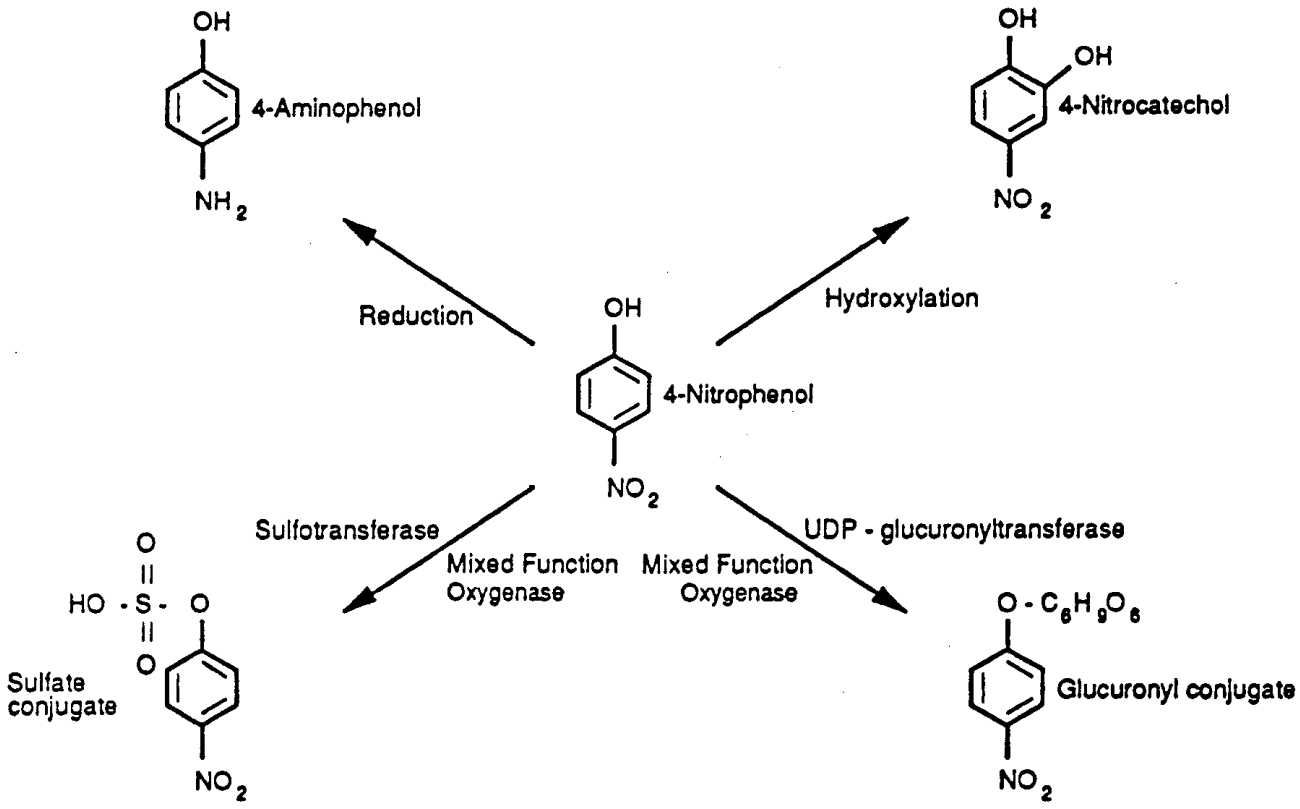
Figure 3-1. Proposed Metabolic Pathway of 2-Nitrophenol Following Oral Administration in Rats



-

Adapted from Robinson et al. 1951a

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



Adapted from Robinson et al. 1951a

No studies regarding metabolism in humans following dermal exposure to 2-, 3-, and 4- nitrophenol were identified. No animal studies regarding the metabolism of the 2- and 3- nitrophenols after dermal exposure were identified.

4- Nitrophenol is rapidly metabolized in dogs, rabbits, and pigs after dermal exposure. 4-Nitrophenol is metabolized by conjugation with glucuronic (60-80 percent) and sulfonic acid (10-20 percent) and reduction to aminophenols (10 percent); less than 1% of the dose is excreted unchanged as 4-nitrophenol (Snodgrass 1983). While the acid conjugates are excreted rapidly, reduction to aminophenols may take 48 hours (Snodgrass 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 (Snodgrass 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 1/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 one 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

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.

No studies regarding excretion in humans following inhalation, oral, or dermal exposure to 2-, 3-, and 4-nitrophenol were identified.

No animal studies regarding the excretion of the 2- and 3- nitrophenol after inhalation exposure were identified. Smith et al. (1988) discuss a decrease in urine volume after exposure to 4-nitrophenol via inhalation, but further details about excretion of the parent compound and the metabolites are not reported (Smith et al. 1988).

No animal studies with oral exposure to 2-, and 3- nitrophenol were identified. 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 four hours, and

more than 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). The authors hypothesized that the kidney and liver played an important role in the excretion of 4-nitrophenol (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. (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).

Seventy-eight and 92% of intravenously administered 4-nitrophenol was excreted within the first day after exposure in rabbits and dogs, respectively (Snodgrass 1983). Twenty-seven and 3% of topically administered 4-nitrophenol was excreted within the first day after exposure in rabbits and dogs, respectively (Snodgrass 1983). These results suggest a rapid excretion of 4-nitrophenol after intravenous exposure with little to no accumulation in the body, with a less complete excretion of the chemical after dermal exposure in these species. Similar results were seen in mice. 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). Following a single dermal dose of 160 mg/kg in mice, elimination of 4-nitrophenol was slightly slower due to a more extended dermal absorption period than the intravenous dose; estimated half-life values 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 either intravenous or dermal administration (Qiao et al. 2000). The amount recovered in urine was 96.9% for intravenous administration and 70.9% for dermal administration (Qiao et al. 2000). The excretion half-lives for 4-nitrophenol and the conjugate were 0.84 and 0.86 hours, respectively (Qiao et al. 2000). The urinary excretion rate was modeled to be three to seven times faster for the conjugate than for 4-nitrophenol (Qiao et al. 2000). Approximately 90% of the intravenous dose was excreted in urine in the first 12 hours (Qiao et al. 2000). The conjugate form comprised two thirds of the total amount in urine and 4-nitrophenol comprised the other one-third after intravenous administration (Qiao et al. 2000). More than half of the amount measured in urine 96 hours after dermal administration was the conjugate form. For both intravenous and dermal doses, less than 1% 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 on the basis of saturation of the detoxification/excretion mechanism due to bolus (gavage) administration.

3.2 CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

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

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

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

3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

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).

A recurring hematological effect that has been observed in animal studies is 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 (Nelson et al. 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 (Nelson et al. 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 (Nelson et al. 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 (Nelson et al. 2011). This permanently increases the methemoglobin levels to 15 to 30% (Nelson et al. 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 four months after birth even in genetically normal infants, leaving them more susceptible to oxidative stress and subsequently to methemoglobinemia than adults (Nelson et al. 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 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 six hours per day, five days per week for two 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).

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.

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.

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 of 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

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-aminphenol, nitroquinone, sulfate conjugates, and glucuronyl conjugate. 4-Nitrophenol is metabolized to 4-aminophenol, 4-nitrocatechol, sulfate conjugates, and glucuronyl conjugates. All of these metabolites could be potentially used to detect exposure to 2-nitrophenol and 4-nitrophenol; however, none of them have been used as such in the literature. There is no literature on metabolism of 3-nitrophenol or biomarkers that could be potentially used to indicate exposure.

No studies were identified regarding levels of 2-, 3-, and 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 2009; 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 acute 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. NHANES data (see Table 5-7) 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 of time, 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 (Beranger et al. 2018).

3.3.2 Biomarkers of Effect

No biomarkers of effect that are specific to nitrophenols have been identified. Methemoglobinemia is one sign of toxicity. Studies in animals have shown that exposure to either 2- or 4-nitrophenol by inhalation has resulted in increased methemoglobin levels (Hazleton 1984; Smith et al. 1988). However, the presence of methemoglobin in humans may be due to other confounding factors such as inherited disorders and pharmaceutical drugs, or it may be due to exposure to other substances that cause methemoglobinemia. Therefore, this effect is not specific to exposure to nitrophenols. Oral exposure to 4-nitrophenol altered the expression of cytochrome P450 and other enzymes in the small intestine in male Wistar rats (Tang et al. 2016). Due to a lack studies in females, other species, and other animal models that observe similar effects on the same enzymes, these changes cannot be conclusively identified as biomarkers of effect. 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 authors also implicate 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 this 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 end points 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-nitrophenols impaired normal

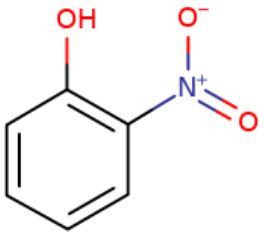
physiology, *i.e.* it generated reactive oxygen species, increased oxidative stress which lead to peroxidation of lipids, and eventually lead to membrane damage (Chen et al. 2016).

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

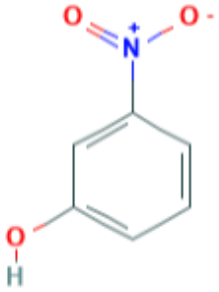
Mononitrophenols exist in three isomeric forms: 2-nitrophenol (or ortho-or o-), 3-nitrophenol (or meta- or m-), and 4-nitrophenol (or para- or p-). All three of these nitrophenols are manmade. Table 4-1 lists common synonyms, trade names, and other pertinent identification information for 2-nitrophenol, 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	Reference
Chemical Name	2-Nitrophenol	PubChem 2020b
Synonym(s) and Registered trade name(s)	O-Hydroxynitrobenzene; 2-Hydroxynitrobenzene; o-Nitrophenol; Phenol, o-nitro-; Phenol, 2-nitro	PubChem 2020b
Chemical formula	$C_6H_5NO_3$	PubChem 2020b
Chemical structure		PubChem 2020b
CAS registry number	88-75-5 (2-Nitrophenol)	PubChem 2020b

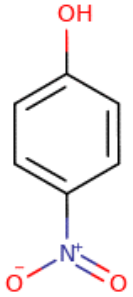
CAS = Chemical Abstracts Service

Table 4-2. Chemical Identity of 3-Nitrophenol

Characteristic	Information	Reference
Chemical Name	3-Nitrophenol	PubChem 2020c
Synonym(s) and Registered trade name(s)	M-Hydroxynitrobenzene; 3-Hydroxynitrobenzene; m-Nitrophenol; Phenol, m-nitro-; Phenol, 3-nitro-;	PubChem 2020c
Chemical formula	$C_6H_5NO_3$	PubChem 2020c
Chemical structure		PubChem 2020c
CAS registry number	554-84-7 (3-Nitrophenol)	PubChem 2020c

CAS = Chemical Abstracts Service

Table 4-3. Chemical Identity of 4-Nitrophenol

Characteristic	Information	Reference
Chemical Name	4-Nitrophenol	PubChem 2020a
Synonym(s) and Registered trade name(s)	P-Hydroxynitrobenzene; 4-Hydroxynitrobenzene; Niphen; P-Nitrophenol; Paranitrophenol; Phenol, p-nitro-; Phenol, 4-nitro-; PNP	PubChem 2020a
Chemical formula	$C_6H_5NO_3$	PubChem 2020a
Chemical structure		PubChem 2020a
CAS registry number	100-02-7 (4-Nitrophenol)	PubChem 2020a

CAS = Chemical Abstracts Service

4.2 PHYSICAL AND CHEMICAL PROPERTIES

2-Nitrophenol is a light yellow, aromatic solid. 3-Nitrophenol and 4-nitrophenol are colorless to pale yellow solids. The mononitrophenols 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). Table **4-4.**, Table **4-5.**, and Table **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	
Color	Light yellow	O'Neil 2006
Physical state	Crystalline solid	HSDB 2013
Melting point	44-45°C	O'Neil 2006
Boiling point	216°C	
Density: At 20°C/4°C	1.29 g/cu at 40°C	
Odor	Aromatic	O'Neil 2006
Odor threshold: Water Air	 10 mg/L $8x10^{-11}$ moles/cu m	 Vershueren 1983 Fazzalari 1978
Taste threshold	0.001 mg/L	Vershueren 2001
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 alcohol, ether, acetone, chlorine; freely soluble in carbon sulfide, alkali hydroxides	 Vershueren 2001 Yalkowsky et al. 2010 Vershueren 2001 Budavari 1996; Haynes 2011
Partition coefficients: Log K_{OW} Log K_{OC}	 1.79 113	 Hansch et al. 1995 EPA 2007b
Vapor pressure At 20°C	0.113 mm Hg at 25°C	Scala and Banerjee 1982
Henry's law constant	0.000013 at 20°C 0.0000163 at 25°C	Tremp et al. 1993 Harrison et al. 2002
Autoignition temperature	550°C	PubChem 2020b
Flashpoint	108°C	PubChem 2020b
Flammability limits	No data	
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	

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

Property	Information	Reference
Explosive limits	No data	

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

Property	Information	Reference
Molecular weight	139.11 g/mol	PubChem 2020c
Color	Colorless to pale yellow	USCG 1999
Physical state	Crystalline solid	USCG 1999
Melting point	96.1°C to 97.8°C	NTP 1992
Boiling point	193.9°C	NTP 1992
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/cu m	 Vershueren 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	 Yalkowsky et al. 2010 Vershueren 2001 Haynes 2011
Partition coefficients: Log K_{OW} Log K_{OC}	 2.00 72.1 L/kg	 Hansch et al. 1995 EPA 2017
Vapor pressure At 20°C	1.5 x10^{-4} mm Hg at 25°C	Barley and McFiggans 2010
Henry's law constant	2.00 e^{-09} atm-m^3/mole at 25°C	PubChem 2020c
Autoignition temperature	400°C	PubChem 2020c
Flashpoint	>100°C	PubChem 2020c
Flammability limits	No data	
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	
Explosive limits	No data	PubChem 2020c

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

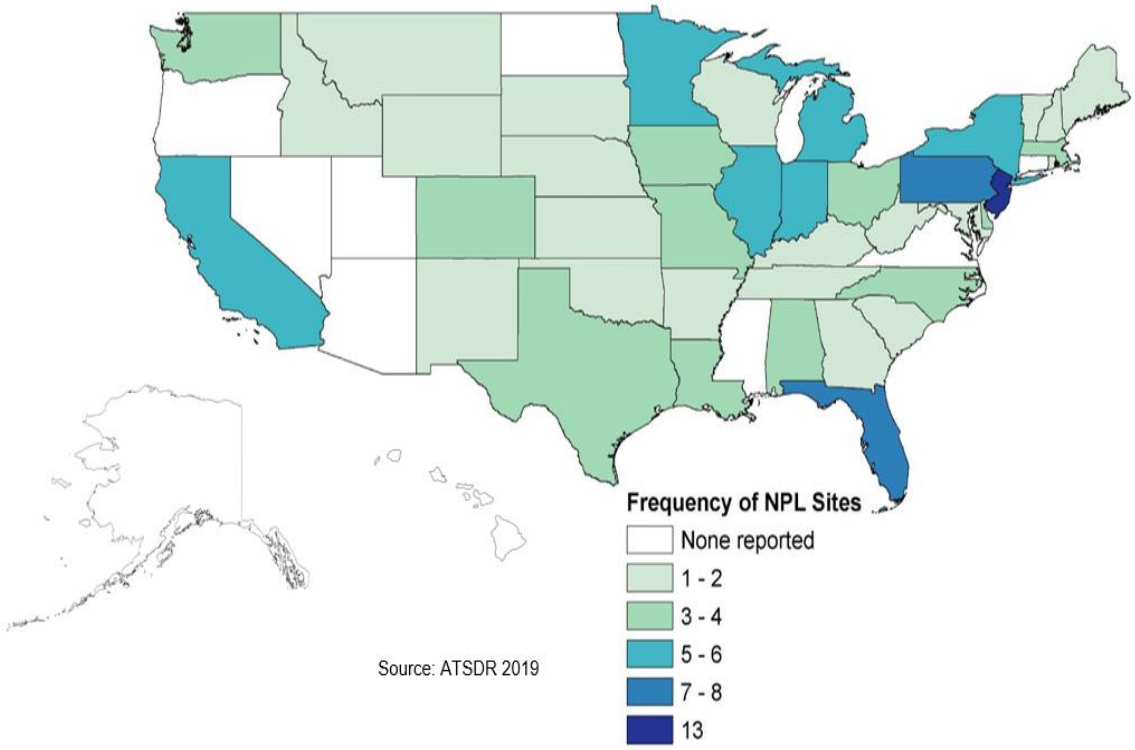
Property	Information	Reference
Molecular weight	139.11	O'Neil 2006
Color	Colorless to slightly yellow	O'Neil 2006
Physical state	Solid	HSDB 2012
Melting point	113-114°C	O'Neil 2006
Boiling point	279°C	Lewis Sr 2007
Density: At 20°C/4°C	1.479 g/cu cm	Lewis Sr 2007
Odor	Odorless	O'Neil 2006
Odor threshold: Water Air	 2.5 mg/L 2.3 mg/cu m	 Vershueren 1983
Taste threshold	43.4 mg/L	NRC 1981
Solubility: Water Organic solvent(s)	 10,000 mg/L at 15°C 15,600 at 25°C Very soluble in ethanol, ether and acetone; freely soluble in alcohol, chloroform; soluble in solution of fixed alkali hydroxides and carbonates	 Vershueren 2001 Yalkowsky et al. 2010 Haynes 2011; O'Neil 2006
Partition coefficients: Log K_{OW} Log K_{OC}	 1.91 141	 Hansch et al. 1995 EPA 2007b
Vapor pressure At 20°C	9.79×10^{-5} mm Hg	Schwarzenbach et al. 1988
Henry's law constant	1.28×10^{-8} atm-cu m/mol at 20°C	Tremp et al. 1993
Autoignition temperature	490°C	PubChem 2020a
Flashpoint	169°C	PubChem 2020a
Flammability limits	No data	
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	
Explosive limits	No data	

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Nitrophenols have been identified in at least 131 of the 1,854 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2019). However, the number of sites evaluated for nitrophenols is not known. The number of sites in each state is shown in Figure 5-1. Of these sites, all 131 are located within the United States. None are located in Puerto Rico or the Virgin Islands

Figure 5-1. Number of NPL Sites with 2-Nitrophenol, 3-Nitrophenol, and 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.
- 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 as a result of atmospheric photochemical reactions of several aromatic compounds formed from anthropogenic sources. They are also formed in vehicular exhausts as a result of 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 are also metabolites of nitrobenzene (EPA 2009). These nitrophenols are a result of an oxidation reaction during the metabolism of nitrobenzene (EPA 2009). 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 (PubChem 2020a, 2020b, 2020c). 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 21 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 1985; 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. 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 rain water 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). No other report of detection of nitrophenols in U.S. drinking water was found in the literature. 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 National Health and Nutrition Examination Survey (NHANES) measured 4-nitrophenol in 90% of urine samples of the general population, with a geometric mean value of 0.64 ug/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.

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 Table 5-1. The national aggregated production volume of 2-nitrophenol from 2011 to 2015 is between 439,164, and 1,319,387 pounds (CDR 2016). 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 1985; Lewis Sr 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 1985; Lewis Sr 2007). 3-Nitrophenol is an impurity in 4-nitrophenol and is produced as a by-product of synthesis or a degradation product (Wróbel et al. 2000).

Table 5-1. Facilities that Produce, Process, or Use 2- and 4-Nitrophenol

Facility	State[a]	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
2-Nitrophenol				
Rubicon LLC	LA	100,000	999,999	1, 5, 13
Syngenta Crop Protection LLC Saint Gabriel Facility	LA	100,000	999,999	1, 2, 3, 6
First Chemical Corp	MS	1,000	9,999	1, 5, 13
4-Nitrophenol				
Rubicon LLC	LA	10,000	99,999	1, 5, 13
Heritage Thermal Services	OH	1,000	9,999	12

[a]Post office state abbreviation 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: TRI18 2020; Data are from 2018

5.2.2 Import/Export

Syngenta Corporation in Greensboro, North Carolina reported receiving imports of 2-nitrophenol totaling 1,201,507 pounds in 2015 (CDR 2016).

5.2.3 Use

Mononitrophenol 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 (CDR 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 820-1600°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 waste water was set for electroplating plants that discharge less than 10,000 gallons of waste water 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

Reported amounts of 2- and 4-nitrophenols released to the environment by U.S. facilities are reported in Table 5-2. 3-Nitrophenol is not reported to the Toxics Release Inventory (TRI). 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).

Table 5-2. Releases to the Environment from Facilities that Produce, Process, or Use 2- and 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
2-Nitrophenol									
LA	1	0	56	6,604	1,739	No data	56	8,343	8,399
MS	2	0	0	0	No data	No data	0	3	3
Total	3	0	56	6,604	1,739	No data	56	8,346	8,402
4-Nitrophenol									
OH	1	0	0	0	0	No data	0	86	86
LA	1	0	0	0	0	No data	0	No data	0
Total	2	0	0	0	0	No data	0	No data	86

Source: TRI18 2020; Data are from 2018

RF = Reporting Facilities; UI = Underground Injection

[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 by a given facility.
[f] The sum of on-site surface water discharges, and off-site transfers to waste water treatment (metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g] The sum of on-site and off-site disposal to underground injection wells (Class I wells and Class II-V).
[h] The sum of on-site and off-site disposal to: Resource Conservation and Recovery Act (RCRA) subtitle C landfills, other landfills, RCRA subtitle C surface impoundments, other surface impoundments, land treatment, other land disposal.
[i] Includes the sum of off-site transfers to: storage only, solidification/stabilization (metals only) disposal, other off-site management, waste broker for disposal, unknown.
[j] Total on-site disposal or other releases of the chemical including emissions to air, surface water discharges, land and underground injection wells.
[k] Total amount of chemical transferred off-site for disposal or other releases, including to POTWs.

5.3.1 Air

There were no estimated releases of 2-nitrophenols to the atmosphere from 3 domestic manufacturing and processing facilities in 2018 and no releases of 4-nitrophenols from two facilities (TRI18 2020). These releases are summarized in Table 5-2.

There is no evidence of the formation of the mononitrophenols from natural sources in the environment. The primary anthropogenic source of the mononitrophenol isomers found in air is traffic activity. These nitrophenols are released from exhausts of both gasoline- and diesel-powered vehicles (Inomata et al. 2016; Inomata et al. 2015; Lu et al. 2019; Nojima et al. 1983; Rubio et al. 2019). Since the efficiencies of the incinerator/thermal processes are less than 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. 1980; Nojima et al. 1976; Rippen et al. 1987). 4-Nitrophenol is a degradation product of 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. A quantitative estimate of atmospheric release of 2- and 4-nitrophenol from any of the last three indirect pathways (photochemical formation, vehicular exhaust, insecticide use) is not available. 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 56 pounds (~0.03 metric tons) of 2-nitrophenol to surface water from three domestic manufacturing and processing facilities in 2018 accounted for about 0.67% of the estimated total environmental releases from facilities required to report to the TRI (TRI18 2020). The facilities did not report data on releases to publicly owned treatment works (POTWs) (TRI18 2020). These releases are summarized in Table 5-2. There were no estimated releases of 4-nitrophenol to surface water from two domestic manufacturing and processing facilities in 2018 (TRI18 2020). The facilities did not report data on releases to publicly owned treatment works (POTWs) (TRI18 2020). These releases are summarized in Table 5-2.

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 POTWs (EPA 1981a). In addition, 2- and 4-nitrophenol were found in treated waste waters 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

Estimated releases of 1,739 pounds (~0.8 metric tons) of 2-nitrophenol to soils from three domestic manufacturing and processing facilities in 2018 accounted for about 21% of the estimated total environmental releases from facilities required to report to the TRI (TRI18 2020). An additional 6,604 pounds (~3 metric tons), constituting about 79% of the total environmental emissions, were released via

underground injection (TRI18 2020). These releases are summarized in Table 5-2. Estimated releases of 86 pounds (~0.04 metric tons) of 4-nitrophenol to soils from two domestic manufacturing and processing facilities in 2018 accounted for about 100% of the estimated total environmental releases from facilities required to report to the TRI (TRI18 2020). No additional releases were made via underground injection (TRI18 2020). These releases are summarized in Table 5-2.

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 (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 the 4-isomer because it has a Henry's law constant value that is four orders of magnitude higher. Based on the 4-nitrophenol data given by Yoshida et al. (1983), the fraction in air is still expected to be small for 2-nitrophenol. The partitioning of a chemical from the atmosphere to land and water depends on its physical state and physico-chemical properties. For example, gravitational settling may be more important than other transport processes for partitioning of suspended particulate matter from air to land and water, whereas wet deposition via rainwater or snow may be more important for chemicals that exist in the vapor phase in air. From the vapor pressure data, both of these chemicals are expected to be present predominantly in the vapor phase in the atmosphere (Eisenreich et al. 1981), although they have been detected in particulates collected over Yokohama, Japan (Nojima et al. 1983). The intramedia 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. The partitioning of nitrophenols between water and sediment is expected to depend on the pH of the water.

Water. Because of their significant water solubilities and expected existence in the vapor phase, 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 by a few authors (Leuenberger et al. 1988; Rippen et al. 1987) supports this partitioning mechanism. The partitioning of 2-and 4-nitrophenol from water to air and different aquatic phases will depend on the volatility from water to air and the distribution between water, sediment, and biota, respectively. Experimental volatilization rates for either of the compounds 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 (H) values for these two compounds (0.000013 atm-cu m/mol at 20°C for 2-nitrophenol and $1.28x10^{-8}$ atm-cu m/mol at 20°C for 4-nitrophenol) and the volatility characteristics associated with various H values (Thomas 1982) can be used to predict that volatilization from water will not be important. 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 anion form in the environment (PubChem 2020a, 2020b, 2020c). Since ionic species do not volatilize significantly from water, the ionization may further limit volatilization (PubChem 2020a, 2020b, 2020c).

Sediment and Soil. Two sorption mechanisms may be operating. One mechanism is the normal hydrophobic sorption common to hydrophobic organic compounds, which can be correlated with organic carbon content of sediments. The other mechanism is chemical bonding (probably hydrogen bonding) between the sediment and the chemical (Boyd 1982; Isaacson 1985). The fact that sorption of 4-nitrophenol was correlated with iron oxide, clay, and silt contents of soils (Artiola-Fortuny and Fuller 1982) confirms these hypotheses. The log Koc values of 2.06-2.42 can be used to predict that 2- and 4-nitrophenol would not be sorbed appreciably to sediments. On the basis of the Koc value, the non-steady-state equilibrium model (Yoshida et al. 1983) predicts that only 4.4% of 4-nitrophenol will remain in sediment, compared to 94.6% in water. The sorption will be higher for sediments with high organic content, iron oxide, and montmorillonite or other clay minerals. Experimental data with an estuarine sediment show that once 4-nitrophenol is sorbed to reduced estuarine sediment, the desorption of the compound from sediment back to the water column will be insignificant (Siragusa and Delaune 1986).

The transport and partitioning of nitrophenols in soils will depend on their sorption and volatilization characteristics. The sorption characteristics will be similar to those described in sediments. The measured log Koc 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 1.72, respectively (Boyd 1982). Other authors have reported log Koc values in the range 2.18-2.42 for 4-nitrophenol (Hodson and Williams 1988). These Koc values indicate that nitrophenols will not strongly adsorb to soils. Although sorption of 4-nitrophenol to soil is weak, the sorption increases with the hydrogen bonding capacity of soils/sediments (Artiola-Fortuny and Fuller 1982; Isaacson 1985). Therefore, in the absence of significant degradation, nitrophenols may leach from soil and may be found in the leachate of landfills. 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 significant 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.

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 three days of exposure was 57 (Freitag et al. 1982). With 14C radiolabeled test compound, the mean plateau whole-body 14C 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 authors 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, 4-nitrophenol would bioconcentrate slightly, but the 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 free 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 greater

than 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. Photolysis experiments in water can be used to predict that photolysis of nitrophenols in air will be a significant degradation process. The rate constant for the gas-phase reaction of 2-nitrophenol with OH radicals is $9.0x10^{-13}$ cm^3 -molecule/sec at 21°C (Atkinson 1986) and $8.95x10^{-13}$ cm^3 -molecule/sec 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 $5x10^5$ radicals/cm^3 (Atkinson 1986), the atmospheric half-life of 4-nitrophenol due to this reaction is an estimated 18 days, and the reaction may not be an important fate determining process in the atmosphere.

Water. Chemical oxidation reactions of 2- and 4-nitrophenol by singlet oxygen and alkyl peroxy radicals formed as a result of sunlight-induced photochemical reactions in water are too slow to be significant (EPA 1985; Scully Jr 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 photoreacts quite rapidly in water in the presence of nitrate or nitrite (EPA 1985). This is not surprising, since nitrate and nitrite in water produce elevated concentrations of OH when irradiated by sunlight. The photolytic behavior of nitrophenols in water is well studied. The irradiation of 4-nitrophenol in neutral or acidic aqueous solution in the presence of air at wavelength 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 authors have determined the phototransformation quantum yield to be in the range $3.3x10^{-6}$ to $8.3x10^{-6}$ 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 1985). Hustert et al. (1981), on the other hand, used the EPA test procedure and determined the photolytic half-lives of 5.7 days at pH 5, 6.7 days at pH 7, and 13.7 days at pH 9.

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; Kitano 1978; 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 authors 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; Spain et al. 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 a river (Bourquin 1984; Bourquin et al. 1982); a mean of 3.2 days for five pond and river waters (Vaishnav and Korthals 1988); and a mean of less than one day for five pond and river waters based on the concentration of degrader microorganisms of 10^6 organisms/ml (Paris et al. 1983).

Compared to these fresh waters, the half-life of 4-nitrophenol in sea water may be longer, and the experimental half-life may range between 13 and 21 days (Bourquin 1984; Bourquin et al. 1982; Van Veld and Spain 1983). The rate and extent of degradation of 4-nitrophenol in natural water also depend on the initial concentration of the substance, the nature and concentration of nutrients, the activities of the organisms, and the 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 investigators 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 one week in one study (Boyd et al. 1983), and over 75% mineralized in 56 days in another (Shelton and Tiedje 1984). Under anaerobic conditions in two flooded soils, over 50% degradation of 2-nitrophenol 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 Mn (+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 Mn oxide with 4-nitrophenol was

less than 10-9 mol/L-min 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. A number of studies discussed in the following paragraph support this conclusion. Several pure cultures isolated from soils degraded nitrophenols (EPA 1985). 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 one 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 two to three 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 5-3 shows the limit of detections typically achieved by analytical analysis in environmental media. Presented in Table 5-4 is a summary of the range of concentrations detected in environmental media at NPL sites.

Table 5-3. 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	
Urine	4-nitrophenol	0.10 µg/L	CDC 2020
Soil/Sediment	2-nitrophenol	660 µg/kg	EPA 1998
	4-nitrophenol	330 µg/kg	
Groundwater	2-nitrophenol	10 µg/L	EPA 1998
	4-nitrophenol	50 µg/L	
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 5-4. 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 (mg/L)	0.01	0.0123	5.50	4	4
Soil (mg/kg)	2.83	1.98	12.1	5	5
Air (mg/m^3)	NR	NR	NR	NR	NR
3-Nitrophenol[b]					
Water (mg/L)	NR	NR	NR	NR	NR
Soil (mg/kg)	NR	NR	NR	NR	NR
Air (mg/m^3)	NR	NR	NR	NR	NR
4-Nitrophenol					
Water (mg/L)	0.016	0.0274	11.3	9	7
Soil (mg/kg)	5.14	6.51	49.8	16	15
Air (mg/m^3)	NR	NR	NR	NR	NR

[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 5 NPL sites, however no data on levels or frequency in water, air, or soil were reported in 2019 data.

NR = not reported

5.5.1 Air

Monitoring data for nitrophenols in U.S. air are limited, and much of the available data was obtained many years ago. Therefore, monitoring data for these compounds in ambient air, rainwater, and vehicular exhausts from both inside and outside of the United States are presented. 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). Nitrophenols were detected but not quantified in the urban air and rainwater of a Japanese city in 1975 (Rippen et al. 1987). Concentrations of 2-nitrophenol (less than 0.05-3.9 µg/g) and 4-nitrophenol (5.1-42 µg/g) were detected in the air particulate matter collected in a Japanese city in 1982. Under engine idling conditions, the concentrations of 2-nitrophenol and 4-nitrophenol in vehicular exhaust gases were 3.1 ppb (17.9 µg/m^3) and less than 0.5 ppb (less than 2.9 µg/m^3), respectively, for a gasoline engine (2,600 cc) and 6.4 ppb (37 µg/m^3) and 2.5 ppb (14.5 µg/m^3), respectively, for a diesel engine (7,000 cc) (Nojima et al. 1983). 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 also 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). This data is presented in Table 5-5 and summarized below.

Table 5-5. Water Monitoring Data for Nitrophenols in EPA's Water Quality Portal from 2000-2020

Type	Date(s)	Range	Mean Concentration	Source
2-Nitrophenol				
Landfill effluent	2000	Not detected	Not detected	WQP 2020 (NWIS)
Effluent	2018	Not detected	Not detected	WQP 2020 (NWIS)

Industrial Effluent	2004, 2006	<0.00037 - <0.013 µg/L	Not applicable[a]	WQP 2020 (STORET)
Stormwater	2000, 2002-2008, 2011, 2015, 2016	<0.883 – 10 µg/L	2.04 µg/L	WQP 2020 (STORET)
Surface water	2000-2020	Not detected – 5.3 µg/L	0.57 µg/L	WQP 2020 (NWIS)
Surface water	2000-2019	Not detected – 200 µg/L	3.80 µg/L	WQP 2020 (STORET)
Groundwater	2000-2020	Not detected – 0.57 µg/L	0.18 µg/L	WQP 2020 (NWIS)
Groundwater	2000-2019	Not detected – 1,000 µg/L	12.76 µg/L	WQP 2020 (STORET)
4-Nitrophenol				
Landfill effluent	2000	Not detected	Not detected	WQP 2020 (NWIS)
Effluent	2018	Not detected	Not detected	WQP 2020 (NWIS)
Industrial Effluent	2017-2018	<0.36 µg/L	Not applicable[a]	WQP 2020 (STORET)
Stormwater	2000, 2002-2008, 2011, 2015, 2016	<.883 – 50 µg/L	7.94 µg/L	WQP 2020 (STORET)
Surface water	2000-2020	Not detected – 27 µg/L	1.77 µg/L	WQP 2020 (NWIS)
Surface water	2001-2013	Not detected – 200 µg/L	5.18 µg/L	WQP 2020 (STORET)
Groundwater	2000-2020	Not detected – 12 µg/L	3.15 µg/L	WQP 2020 (NWIS)
Groundwater	2000-2015, 2017-2019	Not detected – 250 µg/L	34 µg/L	WQP 2020 (STORET)

[a]Detections were below the method detection limits.

Neither 2- or 4-nitrophenol were detected in landfill effluent sampled for the USGS National Water Information System (NWIS) in 2000 (WQP 2020). Nitrophenols were also not detected in effluent sampled for the NWIS in 2018 (WQP 2020). Based on data collected for EPA, 2-nitrophenol has been detected above the detection limit in five out of seven industrial effluent samples at various locations in the United States in 1997, 2004, and 2006; 4-nitrophenol was present below the quantification limit of 0.36 µg/L in two samples from 2017 and 2018 (WQP 2020). In the past, nitrophenols have been identified in effluents from several industries. 2-Nitrophenol has been detected in effluents from photographic and electronics industries (Bursey and Pellizzari 1983). Nitrophenols (isomer unidentified) at a concentration of 5 mg/L were detected in oil shale retort water (Dobson et al. 1985). Nitrophenols have been identified in effluents from other chemical plants as well. 4-Nitrophenol has been identified in effluent from a pesticide plant (EPA 1985). Both 2- and 4-nitrophenol were detected in the final effluent from the waste water of a petroleum industry refinery (Snider and Manning 1982). Nitrophenols have also been identified in primary and secondary effluents of municipal waste water treatment plants. For example, both nitrophenols were identified in the secondary effluent from a waste water treatment plant in

Sauget, Illinois, (Ellis et al. 1982), and 4-nitrophenol was detected in both primary and secondary effluent from a waste water treatment plant in Los Angeles, California, in secondary effluent from a waste water treatment plant in Orange County, California, and in primary effluent from a San Diego, California waste water treatment plant (Young 1978).

4-Nitrophenol was detected above the quantification limit in 31 of 34 stormwater samples from 1990 to 2020 recorded in STORET; 2-nitrophenol was detected above the quantification limit in 32 of 35 stormwater samples (WQP 2020). Concentrations in these samples ranged from 0.048-50 µg/L (4-nitrophenol) and 0.014-10 µg/L (2-nitrophenol). Both nitrophenols were analyzed in 8.1% (6,069 total samples) of surface water samples for NWIS from 1990 to 2020 (WQP 2020). Concentrations in these samples ranged from 0.08-1,900 µg/L (4-nitrophenol) and 0.02-790 µg/L (2-nitrophenol). Based on data from EPA's STORET database from 1990 to 2020, 2-nitrophenol has been detected above the detection limit in 22.2% (4,234 total samples) of surface water samples at various locations in the United States; 4-nitrophenol was detected above the detection limit in 7.69% of surface water samples (4,026 total samples) (WQP 2020). The measured concentrations of both nitrophenols in these samples were no more than 0.2 mg/L. Measurements from 1990-2001 of 2-nitrophenol in surface waters in the literature range from 0.028 to 0.43 µg/L, and from 0.011 to 88 µg/L for 4-nitrophenol (Schmidt-Bäumler et al. 1999; Vanni et al. 2001; Wennrich et al. 1995). These measurements were mostly reported in Europe. Measurements taken from 1990-2001 of 2-nitrophenol in different compartments in the atmosphere ranged from 0.2-0.3 µg/L in clouds, and 0.059-1.4 µg/L in rain (Leuenberger et al. 1985; Leuenberger et al. 1988; Levsen et al. 1990; Lüttke et al. 1999; Lüttke et al. 1997; Rippen et al. 1987). Measurements of 4-nitrophenol in different atmospheric compartments ranged from 2.2-21 µg/L in clouds, 8.1-40.2 µg/L in fog, <0.01-16 µg/ in rain, and 0.008-0.013 µg/L in snow (Harrison et al. 2005; Levsen et al. 1993; Levsen et al. 1990; Lüttke et al. 1999; Lüttke et al. 1997; Richartz et al. 1990; Rippen et al. 1987; Schüssler and Nitschke 2001; Vanni et al. 2001). 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). Neither of the nitrophenols was detected in water from Lake Erie and Lake Michigan (Great Lakes Water Quality Board 1983).

According to the NWIS database from 1990 to 2020, 2- and 4-nitrophenol have been detected in 0.5% (total samples, 3,466) and 0.1% (total samples, 3,808) of groundwater samples for the respective isomer at various locations in the United States. The concentration of 2-nitrophenol ranged from 0.03 to 0.57 µg/L, and the concentration of 4-nitrophenol ranged from 0.06 to 12 µg/L in these samples (WQP 2020). According to WQP, 2-nitrophenol was detected in 1,310 of 1,940 groundwater samples and 4-nitrophenol

was detected in 1,299 of 1,929 samples from 1990 to 2019 for STORET. Concentrations of 2-nitrophenol and 4-nitrophenol were 0-10,000 µg/L and <0.6-25,000 µg/L, respectively (WQP 2020).

4-Nitrophenol at a concentration of 0.2 mg/L was detected in the potable water supply of Ames, Iowa. 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). No other detection of any nitrophenol in U.S. drinking water was reported.

5.5.3 Sediment and Soil

Nitrophenols have been detected in soil and sediment samples taken for EPA's WQP database from 1990 to 2020. These data are described below and summarized in Table 5-6.

Table 5-6. Soil and Sediment Monitoring Data for Nitrophenols in EPA's Water Quality Portal from 2000-2020

	Date(s)	Range	Mean Concentration[b]	Source
2-Nitrophenol				
Soil	2000, 2003-2006, 2008-2009, 2011-2012, 2018	Not detected – 67,000 µg/kg	198 µg/kg	WQP 2020 (STORET)
Sediment	2000-2009, 2015, 2019	Not detected-23,200 µg/kg	1,434 µg/kg	WQP (STORET)
Leachate	2002	Not detected	Not detected	WQP 2020 (NWIS)
Leachate	2001-2006, 2008, 2011, 2012	<0.5 - <24 µg/L	Not applicable[a]	WQP 2020 (STORET)
3-Nitrophenol				
Sediment	2001, 2007, 2009-2011	Not detected – 200 µg/kg	200 µg/kg	WQP 2020 (NWIS)
4-Nitrophenol				
Soil	2000-2001, 2003-2006, 2008, 2009, 2011-2012, 2018	Not detected – 330,000 µg/kg	225.5 µg/kg	WQP 2020 (STORET)
Sediment	2000 – 2009, 2015, 2019	Not detected-289,000 µg/kg	5,758 µg/kg	WQP 2020 (STORET)
Leachate	2002	Not detected	Not detected	WQP 2020 (NWIS)

[a]Detections were below the method detection limit.
[b]The sediment concentrations are reported on a dry weight basis.

2-Nitrophenol was detected in 149 of 823 (18.1%) soil samples at concentrations ranging from less than 0.33 to 67,000 µg/kg from 1990 to 2018 (WQP 2020). 4-Nitrophenol was detected in 122 of 796 (15.3%)

soil samples from 1990 to 2018. Concentrations ranged from less than 0.03 to 330,000 µg/kg (WQP 2020). In sediment samples, 2-nitrophenol was detected in 4,625 out of 7,530 samples (61.4%) from 1990 to 2019, and 4-nitrophenol was detected in 4,927 out of 7,817 samples (63%) from 1990 to 2019. Concentrations ranged from 1.5 to 23,200 µg/kg for 2-nitrophenol and 0.0895 to 289,000 µg/kg for 4-nitrophenol (WQP 2020). 2-nitrophenol was also detected in 39 samples of leachate for WQP from 1990 to 2012. Concentrations of 2-nitrophenol in these samples were below 0.1 µg/kg (WQP 2020). Nitrophenols were not detected in any of the 34 samples of leachate analyzed for USGS's NWIS in 1995, 1999, and 2002 (WQP 2020). 3-Nitrophenol was detected in 32 of 80 sediment samples collected between 1992 and 2011 for WQP at concentrations ranging from 17 to 3,800 µg/kg (WQP 2020). 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 (Blackman Jr et al. 1985).

5.5.4 Other Media

No data in the literature demonstrated the presence of nitrophenols in foods. Nitrophenols were not included in the FDA's 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 U.S. 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. However, when spinach fields were sprayed with 0.5-1.0 pound (active ingredient) of parathion/acre, the 4-nitrophenol residues seven days following application of the pesticide at the recommended application rate did not exceed the unsprayed spinach. The source of 4-nitrophenol in unsprayed spinach was not stated. Since the recommendations for parathion application call for harvesting at least 14 days following application, 4-nitrophenol may not be found in harvested spinach (because it was not found in spinach on the 7th day following application) (EPA 1980).

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 (less than 1 µg/m^3) of 2-nitrophenol are expected to exist in the air. Nitrophenols have not been detected in drinking water and 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 these two sources, 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 2009). 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 5-7. 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. 4-Nitrophenol has been detected at concentrations of 190 to 410 µg/g creatinine in the urine of workers exposed to 25 µg/m^3 ethylparathion in air (Leng and Lewalter 1999). 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).

Table 5-7. 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) (CDC 2020)

	Survey years	Geometric mean (95% CI)	Selected Percentiles				Sample size
			50th	75th	90th	95th	
Total	2011-2012	0.64 (0.57-0.70)	0.63	1.17	2.17	3.31	2,350
	2013-2014	0.64 (0.60-0.68)	0.61	1.18	2.17	3.21	2,584
Age group							
18 to 19	2011-2012	0.61 (0.52-0.73)	0.64	1.15	1.85	2.51	376
12 to 19	2013-2014	0.66 (0.58-0.76)	0.68	1.23	1.82	2.71	415
20 to 59	2011-2012	0.64 (0.57-0.71)	0.65	1.16	2.11	3.38	1,106
	2013-2014	0.60 (0.56-0.65)	0.56	1.12	1.99	2.89	1,223
60 and older	2011-2012	0.65 (0.53-0.80)	0.61	1.34	2.65	4.10	474
	2013-2014	0.68 (0.60-0.76)	0.67	1.18	2.37	4.05	535
Sex							
Male	2011-2012	0.67 (0.61-0.73)	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 (0.52-0.69)	0.58	1.13	2.14	3.48	1,160
	2013-2014	0.62 (0.57-0.67)	0.58	1.19	2.32	3.40	1,278
Race/ethnicity							

Mexican American	2011-2012	0.62 (0.53-0.72)	0.68	1.18	1.84	2.51	285
	2013-2014	0.68 (0.59-0.79)	0.67	1.30	2.07	2.64	403
Other Hispanic	2011-2012	0.67 (0.59-0.77)	0.69	1.13	2.53	3.73	261
	2013-2014	0.70 (0.60-0.82)	0.67	1.28	2.26	3.69	234
Non-Hispanic White	2011-2012	0.62 (0.55-0.70)	0.60	1.15	2.13	3.31	752
	2013-2014	0.60 (0.57-0.64)	0.57	1.10	2.03	3.16	986
Non-Hispanic Black	2011-2012	0.70 (0.57-0.86)	0.72	1.37	2.34	3.47	642
	2013-2014	0.76 (0.70-0.83)	0.78	1.37	2.49	3.59	576
Other race	2011-2012	0.66 (0.58-0.76)	0.62	1.20	2.53	3.74	410
	2013-2014	0.73 (0.62-0.86)	0.68	1.32	2.36	4.05	385

CI = confidence interval

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 gas powered 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 to 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 to 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 (13.2 pg/mg) of the 140 pesticides and metabolites studied (Beranger 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.

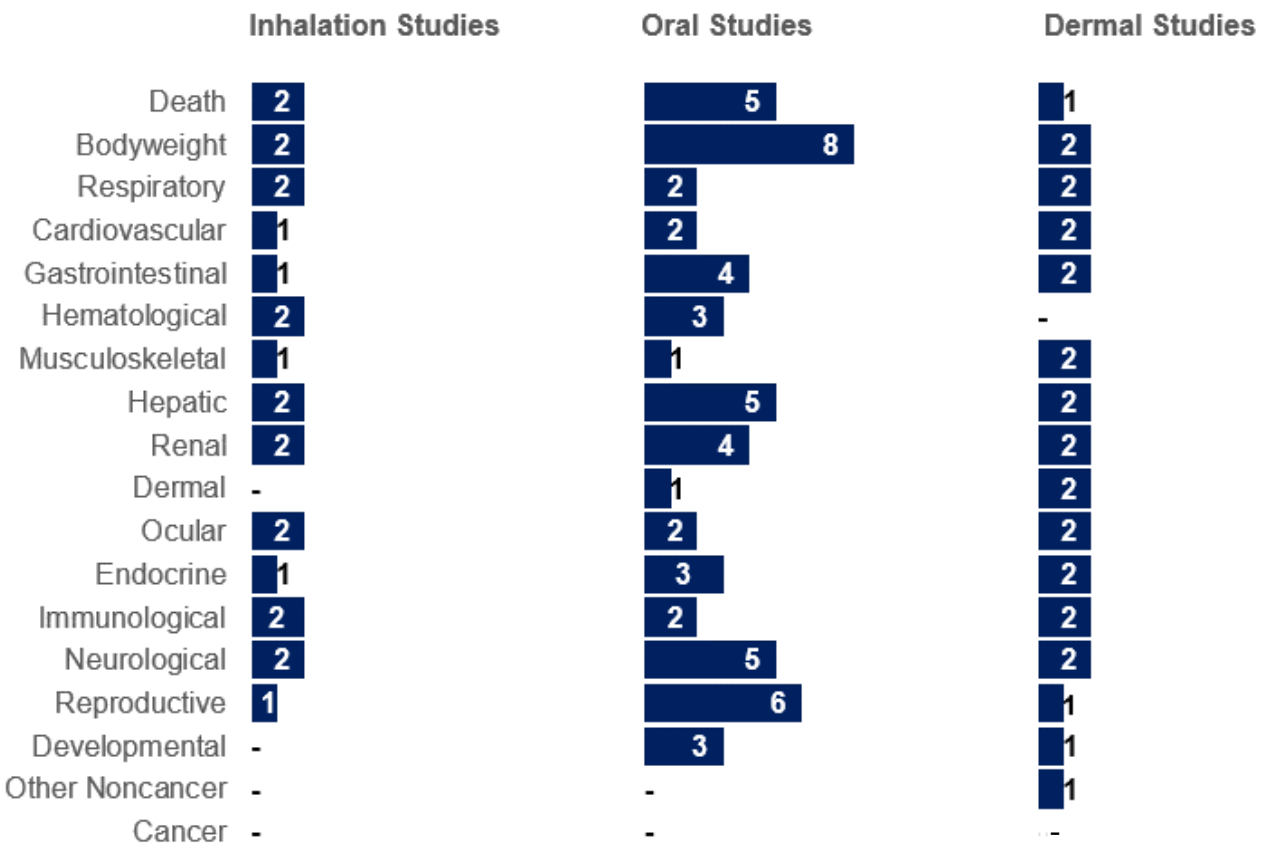
Data needs are defined as substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will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

6.1 EXISTING 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.

Figure 6-1. Summary of Existing Health Effects Studies on Exposure to 4-Nitrophenol 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 [redacted].



*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.

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.

Acute-Duration MRLs. The available acute database was inadequate for deriving oral or inhalation MRLs for 2-, 3-, or 4-nitrophenol for all routes of exposure. No adequately conducted acute-duration human or animal studies were identified for 2-nitrophenol or 3-nitrophenol. Information on 4-nitrophenol toxicity in humans is lacking, as no such studies have been conducted. Additional acute inhalation studies are needed to further investigate whether the hematological effects observed in rats can be corroborated and also can be extrapolated across species. The additional data would add further confidence in this endpoint as a viable health effect for MRL development. Additional acute oral studies on 4-nitrophenol are also needed as a 40% decrease in body weight gain was observed at the lowest oral dose associated with health effects. As a decrease in body weight gain of this magnitude is considered a serious effect, an MRL is unable to be derived for health effects at this dose level (ATSDR 2018). 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. Information on 4-nitrophenol toxicity in humans is lacking, as no such studies have been conducted. Additional intermediate inhalation studies on 4-nitrophenol are needed as the most sensitive endpoint for deriving an MRL is related to unilateral and bilateral diffused anterior capsular cataracts, which are always considered serious effects (ATSDR 2018). Additional studies are needed to characterize less serious health effects for lower-level doses. The intermediate oral database is also insufficient, as the respiratory distress that occurred at the lowest oral dose associated with health effects eventually led to death in the rats that exhibited the symptoms. 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 for lower-level doses of 4-nitrophenol. The available intermediate-duration database was inadequate for deriving an MRL for 3-nitrophenol for all routes of exposure as no adequately conducted intermediate-duration human or animal studies were identified. The available intermediate-duration database was

inadequate for deriving an MRL for 2-nitrophenol for all routes of exposure. Additional intermediate inhalation studies are needed to further investigate whether the respiratory effect of increased incidence of squamous metaplasia of the nasal epithelium observed in rats can be replicated in rats and extrapolated across species. The additional data would add further confidence in this endpoint as a viable health effect for MRL development. No adequately conducted intermediate-duration oral human or animal studies were identified.

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 respiratory effects, hematological effects, and ocular effects may be health effects of concern 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 is 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, at a relatively low dose of 25 mg/kg/day. There were a large number of 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 currently no 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.

Respiratory. There are no studies that examine respiratory endpoints in humans through any route of exposure for any duration. A data need has been identified for studies examining respiratory effects in animals after acute or chronic inhalation exposure to 2-nitrophenol. A data gap also exists regarding respiratory effects in animals after chronic inhalation exposure to 4-nitrophenol. One study examined an intermediate duration of exposure to 2-nitrophenol resulting in a significant increase in squamous metaplasia of the nasal epithelium at and above concentrations of 32.5 mg/m^3, with effectively 100% of

the rats treated at and above this level of exposure exhibiting the effect (Hazleton 1984). Additional studies of 2-nitrophenol investigating this particular respiratory health effect could allow for the confirmation of the validity of this finding across species and concentrations. No studies were identified regarding respiratory effects in animals after oral exposure of any duration to 2-nitrophenol. No studies were identified regarding respiratory effects in animals after acute or chronic oral exposure to 4-nitrophenol. Additional data is needed to provide more literature on respiratory effects after intermediate oral exposure to 4-nitrophenol. Wheezing and dyspnea were observed after oral intermediate exposure to 4-nitrophenol (Hazleton 1989), though Koizumi et al. (2001) reported no effects after a higher dose of exposure for a shorter amount of time. A data need exists to understand the cause of the respiratory effects observed at the comparatively lower concentrations in the longer duration intermediate study.

Hematological. No studies exist in the literature that examine hematological end points in humans through any route of exposure for any duration. A data need exists to better understand the effects of acute or chronic inhalation exposure to 2-nitrophenol on hematological effects in animals, as there is some evidence to suggest increases in methemoglobin are a key endpoint after relatively low levels of inhalation exposure in rats (Hazleton 1984). However, since there is only one adequately conducted study regarding the health effects of 2-nitrophenol, additional literature is needed to validate these findings in other exposure durations and animal species. An additional data need exists regarding hematological effects in animals after acute or chronic inhalation exposure to 4-nitrophenol to strengthen the database on the relationship between exposure and the presence of increased methemoglobin in multiple animal species. Currently, two separate studies in the same publication have provided evidence to suggest increased methemoglobin occurs after acute inhalation exposure to 4-nitrophenol in Albino rats (Smith et al. 1988), though it is difficult to draw conclusions given the results were elucidated from the same study. Additionally, an intermediate-duration inhalation study in Sprague-Dawley rats showed no hematological effects, albeit at lower concentrations (Hazleton 1983). Additional studies would help to identify the validity of the findings in the Smith et al. (1988) study.

Ocular. There are no studies that examine ocular endpoints in humans through any route of exposure for any duration for 2-, 3-, and 4-nitrophenol. No studies were identified regarding ocular effects in animals after acute or chronic inhalation exposure to 2-nitrophenol. Given the presence of ocular effects in inhalation studies of 4-nitrophenol, a data need exists to investigate inhalation of 2-nitrophenol at higher concentrations than those administered in Hazleton (1984). A data need has also been identified with respect to inhalation studies of 4-nitrophenol. The current database suggests that both acute and intermediate inhalation exposure to 4-nitrophenol can cause changes in ocular function at sufficient levels

of exposure, though only two studies have been conducted, and both were in rats (Smith et al 1988; Hazleton 1983). Additional studies are needed in other animals to investigate the validity of this finding in other species, as well as at levels of exposure below 30 mg/m^3. A data need also exists to understand ocular effects of 4-nitrophenol exposure dermally, as an acute-duration dermal study produced effects in rabbits when the substance was placed in the eye, however this study did not include a control group (Weeks 1992).

Mechanisms of Action. More research is needed to elucidate the mechanism of action for toxicity caused by nitrophenols.

Epidemiology and Human Dosimetry Studies. No information regarding respiratory, ocular, reproductive, endocrine, and hematological effects associated with human exposure to nitrophenols were identified. Additional studies should be conducted in humans to monitor exposure levels and health effects associated with nitrophenols.

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-nitrophenol 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.

Based on the current literature, methemoglobinemia is the predominant effect observed in animals. There is a data need to identify unique biomarkers of effect specific to nitrophenols as methemoglobinemia can be caused by exposure to other toxicants and conditions as well.

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.

Data needs related to both prenatal and childhood exposures, and developmental effects expressed whether prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above.

Limited data for exposure in humans for prenatal and childhood exposure to nitrophenols 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 understand children's susceptibility to nitrophenol exposure and subsequent health effects.

Physical and Chemical Properties.

The physical and chemical properties of 2-nitrophenol 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. Production methods for nitrophenols are known and there does not appear to be a need for further information. According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The TRI, which contains this information, became available in 2001. This database is updated yearly and should provide a list of industrial production facilities and emissions.

Use. 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 (CDR 2016). Additional data on the uses of nitrophenols are not needed.

Release. TRI contains data on releases to air, water, and soil from facilities that produce nitrophenols. Additional data is 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.

Disposal. 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.

Regulatory Information. 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 (see Section 5.4.2), 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-, and 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-, or 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 is 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 (Table 5-5). The levels of 4-nitrophenols in other tissues in the general population are unknown. There is no data available on levels 2- and 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.

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. Nitrophenols have not been classified for carcinogenicity and have also not been assigned exposure limits by OSHA or NIOSH. 4-nitrophenol is regulated in water by EPA.

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. The databases for 2-, 3-, and 4-nitrophenol were all considered inadequate for the derivation of MRLs for any exposure route and duration.. See Section 1.3 and Appendix A for more detailed information on the topic of MRLs for nitrophenols.

Table 7-1. Regulations and Guidelines Applicable to Nitrophenols

Agency	Description	Information	Reference
	Air		
EPA	RfC[a]		IRIS 1991
	4-nitrophenol	No data	
	Subchronic provisional RfC		EPA 2007a
	2-nitrophenol	0.0005 mg/m^3	
	Chronic provisional RfC		
	2-nitrophenol	No data	
WHO	Air quality guidelines	No data	WHO 2005
	Water & Food		
EPA	Drinking water standards		EPA 2018
	1-day health advisory for a 10-kg child		
	4-nitrophenol	0.8 mg/L	
	10-day health advisory for a 10-kg child		
	4-nitrophenol	0.8 mg/L	
	DWEL[b]		
	4-nitrophenol	0.3 mg/L	
	National primary drinking water regulations		
	MCL	No data	
	Public health goal	No data	
	RfD		IRIS 1991
	4-nitrophenol	No data	
WHO	Drinking water quality guideline	Not established	WHO 2017
FDA	Substances Added to Food (EAFUS)	No data	FDA 2020
	Cancer		
HHS	Carcinogenicity classification	No Data	NTP 2016
EPA	Carcinogenicity classification		IRIS 1991
	4-nitrophenol	Not evaluated	
IARC	Carcinogenicity classification	No Data	IARC 2020

Table 7-1. Regulations and Guidelines Applicable to Nitrophenols

Agency	Description	Information	Reference
	Occupational		
OSHA	PEL (8-hour TWA) for general industry, shipyards and construction	No Data	OSHA 2020
	STEL (15 minutes)	No Data	OSHA 2020
NIOSH	REL (up to 10-hour TWA)	No Data	NIOSH 2020
	Emergency Criteria		
AIHA	ERPGs		AIHA 2019
	ERPG-1	No Data	
	ERPG-2	No Data	
	ERPG-3	No Data	
EPA	AEGLS-air	No data	AEGLs 2018
DOE	PACs-air		DOE 2018
	2-Nitrophenol		
	PAC-1	2.1 mg/m^3	
	PAC-2	23 mg/m^3	
	PAC-3	140 mg/m^3	
	3-Nitrophenol		
	PAC-1	2.8 mg/m^3	
	PAC-2	31 mg/m^3	
	PAC-3	180 mg/m^3	
	4-Nitrophenol		
	PAC-1	0.69 mg/m^3	
	PAC-2	7.6 mg/m^3	
	PAC-3	46 mg/m^3	

[a]RfC: An EPA work group decided that the available 4-nitrophenol health effects data was insufficient to determine an RfC. This determination was reviewed and confirmed in 2001.
[b]DWEL: Drinking Water Equivalent Level; A lifetime exposure concentration protective of adverse, non-cancer health effects that assumes all of the exposure to a contaminant is from a drinking water source.

AEGL = acute exposure guideline levels; AIHA = American Industrial Hygiene Association; HHS = Department of Health and Human Services; DOE = Department of Energy; DWEL = drinking water equivalent level; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; ERPG = emergency response planning guidelines; FDA = Food and Drug Administration; IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; MCL = maximum contaminant level; 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

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APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

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

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

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

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.

Table of Contents

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2-Nitrophenol
CAS Numbers: 88-75-5
Date: April 2022
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Acute

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

Rationale for Not Deriving an MRL: An MRL has not been 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): Melanie Buser, MPH

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2-Nitrophenol
CAS Numbers: 88-75-5
Date: April 2022
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Intermediate

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

Rationale for Not Deriving an MRL: An MRL has not been derived for intermediate inhalation exposure (15-364 days) to 2-nitrophenol. The most sensitive endpoint for deriving an intermediate inhalation MRL is related to increased incidence of squamous metaplasia of the nasal epithelium observed in both male and female rats at and above 32.5 mg/m^3 with a NOAEL of 5 mg/m^3 (Hazleton 1984). However, Hazleton (1984) is the only study to evaluate the toxicity of 2-nitrophenol following intermediate inhalation exposure. Although the Hazleton (1984) is considered to be a well-conducted study, the study on its own is not strong enough to support the derivation of an MRL. There is evidence for other respiratory effects such as decreased lung weight after intermediate inhalation exposure to 4-nitrophenol (Smith et al. 1988); however, this other observed respiratory effect is more of a systemic effect, rather than the localized portal of entry effect observed in Hazleton (1984). There are also other system respiratory effects that have been observed after oral exposure to 4-nitrophenol such as wheezing and dyspnea (Branch and Stout 1983a Hazleton 1989), but these effects were observed for a different route of exposure. Additionally, as these other respiratory effects were observed after inhalation exposure to a differing form of the chemical, we are unable to use these studies as corroborating evidence for a provisional intermediate duration inhalation MRL for 2-nitrophenol. This lack of supporting literature precludes the derivation of an MRL for this route and duration. The relevant NOAELs and LOAELs are presented below 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					
Rat Sprague-Dawley	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 = $Intermittent\ dose \times \frac{Exposure\ hours}{24\ hours} \times \frac{Exposure\ days}{7\ days}$

Agency Contacts (Chemical Managers): Melanie Buser, MPH.

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2-Nitrophenol
CAS Numbers: 88-75-5
Date: April 2022
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Chronic

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

Rationale for Not Deriving an MRL: A provisional MRL has not been 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): Melanie Buser, MPH.

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2-Nitrophenol
CAS Numbers: 88-75-5
Date: April 2022
Profile Status: Draft for Public Comment
Route: Oral
Duration: Acute

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

Rationale for Not Deriving an MRL: A provisional MRL has not been derived for acute oral exposure (≤14 days) to 2-nitrophenol. Monsanto (1990) was the only adequately conducted study identified for acute oral exposure to 2-nitrophenol. The only observed health effects after acute oral exposure to 2-nitrophenol in Monsanto (1990) are reproductive effects of a 92% increase in resorptions and a 68% increase in post-implantation losses, which were observed in rats at 1,000 mg/kg/day. Because increased post-implantation losses are always considered a serious effect, this precludes the derivation of a provisional acute duration oral MRL (ATSDR 2018).

Agency Contacts (Chemical Managers): Melanie Buser, MPH.

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2-Nitrophenol
CAS Numbers: 88-75-5
Date: April 2022
Profile Status: Draft for Public Comment
Route: Oral
Duration: Intermediate

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

Rationale for Not Deriving an MRL: A provisional MRL has not been derived for intermediate duration oral exposure (15-364 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): Melanie Buser, MPH.

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2-Nitrophenol
CAS Numbers: 88-75-5
Date: April 2022
Profile Status: Draft for Public Comment
Route: Oral
Duration: Chronic

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

Rationale for Not Deriving an MRL: A provisional MRL has not been derived for chronic duration oral 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): Melanie Buser, MPH.

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 3-Nitrophenol
CAS Numbers: 554-84-7
Date: April 2022
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Acute

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

Rationale for Not Deriving an MRL: A provisional MRL has not been derived for acute duration inhalation exposure (≤14 days) to 3-nitrophenol. No adequately conducted studies were identified that investigated health effects of 3-nitrophenol for this route and duration.

Agency Contacts (Chemical Managers): Melanie Buser, MPH.

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 3-Nitrophenol
CAS Numbers: 554-84-7
Date: April 2022
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Intermediate

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

Rationale for Not Deriving an MRL: A provisional MRL has not been derived for intermediate duration inhalation exposure (15-364 days) to 3-nitrophenol. No adequately conducted studies were identified that investigated health effects of 3-nitrophenol for this route and duration.

Agency Contacts (Chemical Managers): Melanie Buser, MPH.

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 3-Nitrophenol
CAS Numbers: 554-84-7
Date: April 2022
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Chronic

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

Rationale for Not Deriving an MRL: A provisional MRL has not been derived for chronic duration inhalation exposure (≥365 days) to 3-nitrophenol. No adequately conducted studies were identified that investigated health effects of 3-nitrophenol for this route and duration.

Agency Contacts (Chemical Managers): Melanie Buser, MPH.

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 3-Nitrophenol
CAS Numbers: 554-84-7
Date: April 2022
Profile Status: Draft for Public Comment
Route: Oral
Duration: Acute

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

Rationale for Not Deriving an MRL: A provisional MRL has not been derived for acute duration oral exposure (≤14 days) to 3-nitrophenol. No adequately conducted studies were identified that investigated health effects of 3-nitrophenol for this route and duration.

Agency Contacts (Chemical Managers): Melanie Buser, MPH.

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 3-Nitrophenol
CAS Numbers: 554-84-7
Date: April 2022
Profile Status: Draft for Public Comment
Route: Oral
Duration: Intermediate

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

Rationale for Not Deriving an MRL: A provisional MRL has not been derived for intermediate duration oral exposure (15-364 days) to 3-nitrophenol. No adequately conducted studies were identified that investigated health effects of 3-nitrophenol for this route and duration.

Agency Contacts (Chemical Managers): Melanie Buser, MPH.

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 3-Nitrophenol
CAS Numbers: 554-84-7
Date: April 2022
Profile Status: Draft for Public Comment
Route: Oral
Duration: Chronic

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

Rationale for Not Deriving an MRL: A provisional MRL has not been derived for chronic duration oral exposure (≥365 days) to 3-nitrophenol. No adequately conducted studies were identified that investigated health effects of 3-nitrophenol for this route and duration.

Agency Contacts (Chemical Managers): Melanie Buser, MPH.

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 4-Nitrophenol
CAS Numbers: 100-02-7
Date: April 2022
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Acute

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

Rationale for Not Deriving an MRL: A provisional MRL has not been derived for acute duration inhalation exposure to 4-nitrophenol. The most sensitive endpoint for deriving an acute duration inhalation MRL is related to increased methemoglobin observed in rats at 112 mg/m^3 with a NOAEL of 26 mg/m^3 (Smith et al. 1988). The increase in methemoglobin at 112 mg/m^3 returned to normal levels after 14 days of recovery. Increases in methemoglobin lower oxygen carrying and delivery capacity, which can cause hypoxia. High levels of methemoglobin may be associated with cyanosis and fatigue, weakness, dyspnea, headache, and dizziness. It is estimated that rats have two to five times as much methemoglobin reductase activity, or the enzyme responsible for controlling the amount of methemoglobin in blood, than humans (Bloom and Brandt 2019), which could mean that humans would potentially be more sensitive to 4-nitrophenol toxicity than the rats observed in the Smith et al. (1988) study. An increasing dose-response was also observed for this endpoint in Smith et al. (1988) with higher level exposures of 294 and 2,133 mg/m^3 in males. Females demonstrated increased methemoglobin levels at 2,133 mg/m^3.

However, Smith et al. (1988) is the only study to evaluate the toxicity of 4-nitrophenol following acute duration inhalation exposure. Although the Smith et al. (1988) is considered to be an adequately-conducted study, the study on its own is not strong enough to support the derivation of an MRL. The experiments contained within Smith et al. (1988) were analyzed for risk of bias within the context of performing the systematic literature review in Appendix C and were judged to have low to moderate confidence that the true effect is reflected in the relationships portrayed. These confidence ratings suggest that the Smith et al. (1988) study is not adequate to serve as the basis for an MRL without additional support from other studies. Hazleton (1983) observed a statistically significant increase in methemoglobin compared with controls in an intermediate-duration inhalation study to 4-nitrophenol in the 5 mg/m^3 concentration group; however, there was not a similar increase in the higher concentration group. Evidence for an increase in methemoglobin was also observed in Hazleton (1984) after intermediate duration inhalation exposure to 2-nitrophenol; however, we are unable to use this as corroborating evidence for 4-nitrophenol given the differing form of the chemical. This lack of supporting literature precludes the derivation of a provisional MRL for this route and duration. The relevant NOAELs and LOAELs are presented below in Table A-2.

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					
Rat Albino	2 weeks 5 days/week	294 M	2,133 M	Methemoglobin increased by 665% (from 0.2% to 1.53%) after 10 days	Smith et al. 1988

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
	6 hours/day			of exposure. After 14 days of recovery, levels of erythrocytes, hemoglobin, and methemoglobin remained elevated by 7%, 7.5% and 250% respectively. One rat was cyanotic after the first exposure.	
Rat Albino	2 weeks 5 days/week 6 hours/day	26 M	112 M	200% increase in methemoglobin (from 0.5% to 1.5%) compared to control after 10 exposures and returned to normal after a 14 day recovery period	Smith et al. 1988

Agency Contacts (Chemical Managers): Melanie Buser, MPH

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 4-Nitrophenol
CAS Numbers: 100-02-7
Date: April 2022
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Intermediate

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

Rationale for Not Deriving an MRL: A provisional MRL has not been derived for intermediate duration inhalation exposure (15-364 days) to 4-nitrophenol. Hazleton (1983) was the only adequately conducted study identified for intermediate duration inhalation exposures to 4-nitrophenol. The only observed health effect after intermediate inhalation exposure to 4-nitrophenol in Hazleton (1983) is unilateral and bilateral diffused anterior capsular cataracts, which was observed in rats at 30 mg/m^3. Because cataracts are always considered a serious effect, this precludes the derivation of a provisional intermediate duration inhalation MRL (ATSDR 2018).

Agency Contacts (Chemical Managers): Melanie Buser, MPH.

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 4-Nitrophenol
CAS Numbers: 100-02-7
Date: April 2022
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Chronic

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

Rationale for Not Deriving an MRL: A provisional MRL has not been derived for chronic duration inhalation exposure (≥365 days) to 4-nitrophenol. No adequately conducted studies were identified that investigated health effects of 4-nitrophenol for this route and duration.

Agency Contacts (Chemical Managers): Melanie Buser, MPH

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 4-Nitrophenol
CAS Numbers: 100-02-7
Date: April 2022
Profile Status: Draft for Public Comment
Route: Oral
Duration: Acute

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

Rationale for Not Deriving an MRL: A provisional MRL has not been derived for acute duration oral exposure to 4-nitrophenol. Tang et al. (2016) showed hepatic, gastrointestinal, renal, and endocrine health effects at 200 mg/kg/day, and Li et al. (2017) also showed hepatic health effects at 200 mg/kg/day. However, the Tang et al. (2016) study additionally observed a serious LOAEL of a 40% decrease in body weight gain at this same dose of 200 mg/kg/day, and the Li et al. (2017) additionally observed a serious LOAEL based on a 25% decrease in body weight at this same dose. Therefore, any MRL must be below 200 mg/kg/day to avoid this serious effect. As no other adequately conducted studies exist with observed health effects at acute duration oral doses of 4-nitrophenol below 200 mg/kg/day, we are unable to derive an MRL. A summary of select NOAELs/LOAELs is presented in Table A-3.

Table A-3. Summary of Relevant NOAEL and LOAEL Values Following Acute Duration Oral Exposure to 4-Nitrophenol

Species	Duration/ route	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Hepatic effects					
Rat Wistar	Once (G)		200 M	The central vein of the hepatic lobule was detached, and the hepatocytes were disordered (not otherwise described)	Li et al. 2017
Rat Wistar	3 days (G)		200 M	Hepatic sinusoid was wider compared to the control group, and the hepatocytes were disordered (not otherwise described)	Li et al. 2017
Rat Wistar	3 days (GO)		200 M	12% decrease in relative liver weight	Tang et al. 2016
Gastrointestinal effects					
Rat Wistar	Once		200 M	Damage to the intestinal mucosal goblet cells and caused necrosis of intestinal epithelial cells (not otherwise described)	Tang et al. 2016
Rat Wistar	3 days (GO)		200 M	Damage to the intestinal mucosal goblet cells and caused necrosis of intestinal epithelial cells (not otherwise described)	Tang et al. 2016
Renal effects					
Rat Wistar	3 days (GO)		200 M	14% increase in relative kidney weight	Tang et al. 2016

Table A-3. Summary of Relevant NOAEL and LOAEL Values Following Acute Duration Oral Exposure to 4-Nitrophenol

Species	Duration/ route	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Endocrine effects					
Rat Wistar	3 days (GO)		200 M	41% increase in relative adrenal gland weight	Tang et al. 2016
Body weight effects					
Rat Wistar	3 days (GO)		200 M*	40% decrease in body weight gain	Tang et al. 2016
Rat Wistar	3 days		200 M*	25% decrease in body weight	Li et al. 2017

* indicates that the LOAEL represents a serious LOAEL, thus an acute duration oral MRL cannot be derived

Agency Contacts (Chemical Managers): Melanie Buser, MPH.

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 4-Nitrophenol
CAS Numbers: 100-02-7
Date: April 2022
Profile Status: Draft for Public Comment
Route: Oral
Duration: Intermediate

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

Rationale for Not Deriving an MRL: A provisional MRL has not been derived for intermediate duration oral exposure to 4-nitrophenol. Although rats exposed to 70 mg/kg/day daily for 13 weeks showed signs of respiratory distress, such as wheezing and dyspnea in Hazelton et al. (1989), the death of a female rat occurred prior to the end of the study in the 25 mg/kg/day dose group. Since death is always considered a serious effect, this precludes the derivation of an intermediate duration oral MRL at this dose (ATSDR 2018). Table A-4 presents the relevant NOAELs/LOAELs for this route and duration.

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

Species	Duration/ route	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Respiratory effects					
Rat Sprague-Dawley	13 weeks 7 days/week (GW)	25	70	Wheezing, dyspnea (not otherwise described)	Hazleton (1989)
Death effects					
Rat Sprague-Dawley	13 weeks 7 days/week (GW)		25 F*	1/20 females died	Hazleton (1989)
Rat Sprague-Dawley	13 weeks 7 days/week (GW)		70 M*	1/20 males died	Hazleton (1989)

* indicates that the LOAEL represents a serious LOAEL, and thus an intermediate duration oral MRL cannot be derived

Agency Contacts (Chemical Managers): Melanie Buser, MPH.

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 4-Nitrophenol
CAS Numbers: 100-02-7
Date: April 2022
Profile Status: Draft for Public Comment
Route: Oral
Duration: Chronic

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

Rationale for Not Deriving an MRL: A provisional MRL has not been derived for chronic duration oral exposure (≥365 days) to 4-nitrophenol. No adequately conducted studies were identified that investigated health effects of 4-nitrophenol for this route and duration.

Agency Contacts (Chemical Managers): Melanie Buser, MPH.

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 was 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
Drosophila (for genotoxicity studies)
In vitro assay (for genotoxicity and for supporting data for other endpoints)
Route of exposure
Inhalation
Oral
Dermal (or ocular)
Parenteral (these studies will be considered supporting data)
Health outcome
Death
Systemic effects
Respiratory effects
Cardiovascular effects
Gastrointestinal effects
Hematological effects
Musculoskeletal effects
Hepatic effects
Renal effects
Endocrine effects
Dermal effects
Ocular effects
Body weight effects
Metabolic effects
Other systemic effects
Immunological effects
Neurological effects
Reproductive effects
Developmental effects
Genotoxicity
Cancer

B.1.1 Literature Search

The current literature search was intended to update the existing toxicological profile for nitrophenols (ATSDR 1992), thus, the literature search was restricted to studies published between January 1990 to June 2020. The following main databases were searched in June 2020:

- PubMed
- MEDLINE
- Science Direct
- Scopus

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

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, 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-2. 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	Chemical	Query String
MEDLINE 06/05/2020	2-Nitrophenol	(MH "2-Nitrophenol") OR "2-Nitrophenol" OR "O-Nitrophenol" OR "2-Hydroxynitrobenzene" OR "Phenol, 2-Nitro-" OR "O-Hydroxynitrobenzene" OR "Phenol, O-Nitro" OR "O-Nitrofenol" OR "2-Nitro-Phenol" OR "Phenol, Nitro-" OR "O-Nitrofenol" OR "Nitro Phenol" OR "Hydroxy(2-Hydroxyphenyl)Oxoammonium" OR "Ortho-Nitrophenol" OR "2-Hydroxynitrobenzene]" OR "O-Nitro-Phenol" OR "O-Nitrophenol" OR "2-Nitro Phenol" OR "Hydroxynitrobenzene" OR "Nitrophenolate" OR "Atonik" OR RN (88-75-5) Limiters: Date of Publication: 19900101-20200605
	3-Nitrophenol	(MH "3-Nitrophenol") OR "3-Nitrophenol" OR "M-Nitrophenol" OR "3-Hydroxynitrobenzene" OR "Phenol, 3-Nitro-" OR "m-Hydroxynitrobenzene" OR "Phenol, m-Nitro" OR "m-Nitrofenol" OR "meta-Nitrophenol" OR "3-nitro-phenol" OR "m-Nitrofenol" OR "1-Hydroxy-3-nitrobenzene" OR "1-Hydroxy-3-nitrobenzene" OR "3-nitro phenol" OR "2- m-Nitrophenol" OR RN (554-84-7) Limiters: Date of Publication: 19900101-20200605
	4-Nitrophenol	(MH "4-Nitrophenol") OR "4-Nitrophenol" OR "p-Nitrophenol" OR "Phenol, 4-Nitro -" OR "Niphen" OR "Paranitrophenol" OR "4-Hydroxynitrobenzene" OR "; p-Hydroxynitrobenzene" OR "Phenol, p-Nitro-" OR "para-Nitrophenol" OR "Mononitrophenol" OR "Paranitrofenol" OR "Paranitrofenolo" OR "p-Nitrofenol" OR "4-Nitrofenol" OR "P-Nitrofenol OR "Paranitrofenol " OR "4-Nitrofenol " OR "Paranitrofenolo" OR "PNP" OR "Paranitrophenol" OR "1-Hydroxy-4-Nitrobenzene" OR "P-Nitrophenolate" OR "4-Nitro-Phenol" OR "4-Nitrobenzen-1-Olate" OR "4-Nitrophenolate(1-)" OR "P-Nitro Phenol" OR "4-Notrophenol" OR "4-Nitryl Phenol" OR "4- nitrophenol" OR "4-nitro phenol" OR "P-Nitrophenolic Acid" OR "HONP" OR "4-Nitrophenolic Acid" OR "P-Nitrophenol Solution" OR "Phenol,4-Nitro" OR "P-Nitrophenolic Acid Ion" OR "Para Nitro Phenol" RN "P-Nitrophenolic Acid(1-)" OR"4-Nitrobenzen-1-Olic Acid" OR"4-Nitrophenolic Acid(1-)" OR "1-Hydroxy- 4-Nitrobenzol" OR (100-02-7) Limiters: Date of Publication: 19900101-20200605

Table B-2. Database Query Strings

Database	Chemical	Query String
PubMed 06/05/2020	2-Nitrophenol	((“2-nitrophenol”[MeSH Terms]) OR ([Text Word](“2-Nitrophenol” OR “O-Nitrophenol” OR “2-Hydroxynitrobenzene” OR “Phenol, 2-Nitro-” OR “O-Hydroxynitrobenzene” OR “Phenol, O-Nitro” OR “O-Nitrofenol” OR “2-Nitro-Phenol” OR “Phenol, Nitro-” OR “O-Nitrofenol” OR “Nitro Phenol” OR “Hydroxy(2-Hydroxyphenyl)Oxoammonium” OR “Ortho-Nitrophenol” OR “2-Hydroxynitrobenzene” OR “O-Nitro-Phenol” OR “O-Nitrophenol” OR “2-Nitro Phenol” OR “Hydroxynitrobenzene” OR “Nitrophenolate” OR “Atonik”))) OR “88-75-5”[EC/RN Number] Limited 1990 – present
	3-Nitrophenol	((“3-nitrophenol”[MeSH Terms]) OR ([Text Word] (“3-Nitrophenol” OR “M-Nitrophenol” OR “3-Hydroxynitrobenzene” OR “Phenol, 3-Nitro-” OR “m-Hydroxynitrobenzene” OR “Phenol, m-Nitro” OR “m-Nitrofenol” OR “meta-Nitrophenol” OR “3-nitro-phenol” OR “m-Nitrofenol” OR “1-Hydroxy-3-nitrobenzene” OR “1-Hydroxy-3-nitrobenzene” OR “3-nitro phenol” OR “2- m-Nitrophenol” OR))) “554-84-7”[EC/RN Number]
	4-Nitrophenol	((“4-Nitrophenol”[MeSH Terms]) OR ([Text Word](“4-Nitrophenol” OR “p-Nitrophenol” OR “Phenol, 4-Nitro -” OR “Niphen” OR “Paranitrophenol” OR “4-Hydroxynitrobenzene” OR “p-Hydroxynitrobenzene” OR “Phenol, p-Nitro-” OR “para-Nitrophenol” OR “Mononitrophenol” OR “Paranitrofenol” OR “Paranitrofenolo” OR “p-Nitrofenol” OR “4-Nitrofenol” OR “P-Nitrofenol” OR “Paranitrofenol” OR “4-Nitrofenol” OR “Paranitrofenolo” OR “PNP” OR “Paranitrophenol” OR “1-Hydroxy-4-Nitrobenzene” OR “P-Nitrophenolate” OR “4-Nitro-Phenol” OR “4-Nitrobenzen-1-Olate” OR “4-Nitrophenolate(1-)” OR “P-Nitro Phenol” OR “4-Notrophenol” OR “4-Nitryl Phenol” OR “4- nitrophenol” OR “4-nitro phenol” OR “P-Nitrophenolic Acid” OR “HONP” OR “4-Nitrophenolic Acid” OR “P-Nitrophenol Solution” OR “Phenol,4-Nitro” OR “P-Nitrophenolic Acid Ion” OR “Para Nitro Phenol” RN “P-Nitrophenolic Acid(1-)” OR“4-Nitrobenzen-1-Olic Acid” OR“4-Nitrophenolic Acid(1-)” OR “1-Hydroxy-4-Nitrobenzol”))) OR “100-02-7”[EC/RN Number] Limited 1990 – present
Science Direct 06/05/2020	2-Nitrophenol	“2-Nitrophenol” OR “O-Nitrophenol” OR “2-Hydroxynitrobenzene” OR “Phenol, 2-Nitro-” OR “O-Hydroxynitrobenzene” OR “Phenol, O-Nitro” OR “O-Nitrofenol” OR “2-Nitro-Phenol” OR “Phenol, Nitro-” OR “O-Nitrofenol” OR “Nitro Phenol” OR “Hydroxy(2-Hydroxyphenyl)Oxoammonium” OR “Ortho-Nitrophenol” OR “2-Hydroxynitrobenzene” OR “O-Nitro-Phenol” OR “O-Nitrophenol” OR “2-Nitro Phenol” OR “Hydroxynitrobenzene” OR “Nitrophenolate” OR “Atonik” OR 88-75-5” Limited 1990 - present
	3-Nitrophenol	“3-nitrophenol” OR “M-Nitrophenol” OR “3-Hydroxynitrobenzene” OR “Phenol, 3-Nitro-” OR “m-Hydroxynitrobenzene” OR “Phenol, m-Nitro” OR “m-Nitrofenol” OR “meta-Nitrophenol” OR “3-nitro-phenol” OR “m-Nitrofenol” OR “1-Hydroxy-3-nitrobenzene” OR “1-Hydroxy-3-nitrobenzene” OR “3-nitro phenol” OR “2- m-Nitrophenol” OR “554-84-7” Limited 1990 - present
	4-Nitrophenol	“4-Nitrophenol” OR “P-Nitrophenol” OR “p-Nitrophenol” OR “Phenol, 4-Nitro -” OR “Niphen” OR “Paranitrophenol” OR “4-Hydroxynitrobenzene” OR “p-Hydroxynitrobenzene” OR “Phenol, p-Nitro-” OR “para-Nitrophenol” OR

Table B-2. Database Query Strings

Database	Chemical	Query String
		"Mononitrophenol" OR "Paranitrofenol" OR "Paranitrofenolo" OR "p-Nitrofenol" OR "4-Nitrofenol" OR "P-Nitrofenol" OR "Paranitrofenol" OR "4-Nitrofenol" OR "Paranitrofenolo" OR "PNP" OR "Paranitrophenol" OR "1-Hydroxy-4-Nitrobenzene" OR "P-Nitrophenolate" OR "4-Nitro-Phenol" OR "4-Nitrobenzen-1-Olate" OR "4-Nitrophenolate(1-)" OR "P-Nitro Phenol" OR "4-Notrophenol" OR "4-Nitryl Phenol" OR "4- nitrophenol" OR "4-nitro phenol" OR "P-Nitrophenolic Acid" OR "HONP" OR "4-Nitrophenolic Acid" OR "P-Nitrophenol Solution" OR "Phenol,4-Nitro" OR "P-Nitrophenolic Acid Ion" OR "Para Nitro Phenol" RN "P-Nitrophenolic Acid(1-)" OR"4-Nitrobenzen-1-Olic Acid" OR"4-Nitrophenolic Acid(1-)" OR "1-Hydroxy- 4-Nitrobenzol" OR "100-02-7" Limited 1990 – present
Scopus 06/05/2020	2-Nitrophenol	"2-Nitrophenol" OR "O-Nitrophenol" OR "2-Hydroxynitrobenzene" OR "Phenol, 2-Nitro-" OR "O-Hydroxynitrobenzene" OR "Phenol, O-Nitro" OR "O-Nitrofenol" OR "2-Nitro-Phenol" OR "Phenol, Nitro-" OR "O-Nitrofenol" OR "Nitro Phenol" OR "Hydroxy(2-Hydroxyphenyl)Oxoammonium" OR "Ortho-Nitrophenol" OR "2-Hydroxynitrobenzene" OR "O-Nitro-Phenol" OR "O-Nitrophenol" OR "2-Nitro Phenol" OR "Hydroxynitrobenzene" OR "Nitrophenolate" OR "Atonik" OR 88-75-5" Limited 1990 – present
	3-Nitrophenol	"3-nitrophenol" OR "M-Nitrophenol" OR "3-Hydroxynitrobenzene" OR "Phenol, 3-Nitro-" OR "m-Hydroxynitrobenzene" OR "Phenol, m-Nitro" OR "m-Nitrofenol" OR "meta-Nitrophenol" OR "3-nitro-phenol" OR "m-Nitrofenol" OR "1-Hydroxy-3-nitrobenzene" OR "1-Hydroxy-3-nitrobenzene" OR "3-nitro phenol" OR "2- m-Nitrophenol" OR "554-84-7" Limited 1990 - present
	4-Nitrophenol	"4-Nitrophenol" OR "P-Nitrophenol" OR "p-Nitrophenol" OR "Phenol, 4-Nitro -" OR "Niphen" OR "Paranitrophenol" OR "4-Hydroxynitrobenzene" OR "p-Hydroxynitrobenzene" OR "Phenol, p-Nitro-" OR "para-Nitrophenol" OR "Mononitrophenol" OR "Paranitrofenol" OR "Paranitrofenolo" OR "p-Nitrofenol" OR "4-Nitrofenol" OR "P-Nitrofenol" OR "Paranitrofenol" OR "4-Nitrofenol" OR "Paranitrofenolo" OR "Paranitrophenol" OR "1-Hydroxy-4-Nitrobenzene" OR "P-Nitrophenolate" OR "4-Nitro-Phenol" OR "4-Nitrobenzen-1-Olate" OR "4-Nitrophenolate(1-)" OR "P-Nitro Phenol" OR "4-Notrophenol" OR "4-Nitryl Phenol" OR "4- nitrophenol" OR "4-nitro phenol" OR "P-Nitrophenolic Acid" OR "HONP" OR "4-Nitrophenolic Acid" OR "P-Nitrophenol Solution" OR "Phenol,4-Nitro" OR "P-Nitrophenolic Acid Ion" OR "Para Nitro Phenol" RN "P-Nitrophenolic Acid(1-)" OR"4-Nitrobenzen-1-Olic Acid" OR"4-Nitrophenolic Acid(1-)" OR "1-Hydroxy- 4-Nitrobenzol" OR "100-02-7" Limited 1990 – present

The June 2020 results were:

- Number of records identified from the sources (after duplicate removal): 14,561
- Number of records identified from other strategies: 14
- Total number of records to undergo literature screening: 14,575

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

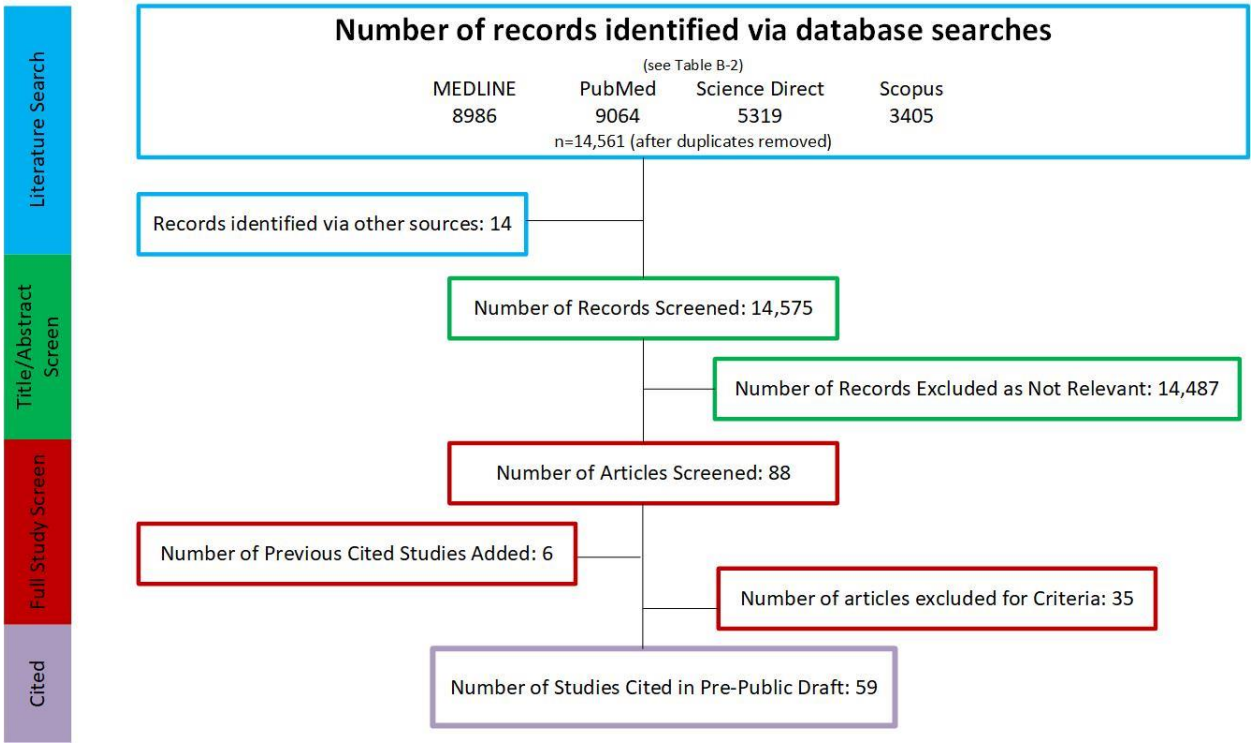
Title and Abstract Screen. Within the reference library, titles and abstracts were screened manually by a single reviewer for relevance. Studies that were considered relevant (see Table B-1 for inclusion criteria) were moved to the second step of the literature screening process. Studies were excluded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

- Number of titles and abstracts screened: 14,575
- Number of studies considered relevant and moved to the next step: 88

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: 88
- Number of studies cited in the pre-public draft of the toxicological profile: 59
- Total number of studies cited in the profile: 59

Figure B-1. May 2020 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 B-1. Data from human and laboratory animal studies were considered relevant for addressing this objective. No relevant human studies that examined the health effects of exposure to nitrophenols were identified. Data from animal studies are presented and discussed in this appendix.

C.2 LITERATURE SEARCH AND SCREEN FOR HEALTH EFFECTS STUDIES

A literature search and screen was conducted to identify studies examining the health effects of 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 literature search to update the existing toxicological profile for nitrophenols (ATSDR 1992) was restricted to studies published between 1990 and 2020. See Appendix B for the databases searched and the search strategy.

A total of 14,561 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, 14,575 records were reviewed; 88 studies were considered to meet the health effects inclusion criteria in Table B-1 and were moved to the next step in the process.

Full Text Screen. In the second step in the literature screening process for the systematic review, a full text review of the 74 health effects studies identified in the updated literature was performed. Additionally, 14 studies cited in the LSE tables for the existing profile were included in the full text screen, bringing the total

number of studies for the qualitative review to 88. Of the 88 studies undergoing full text screen, 35 studies did not meet the inclusion criteria; some of the excluded studies were used as background information on toxicokinetics or mechanisms of action or were relevant to other sections of the toxicological profile.

C.3 EXTRACT DATA FROM HEALTH EFFECTS STUDIES

Relevant data extracted from the individual studies selected for inclusion in the systematic review were collected in ATSDR's EZtox Database (for toxicological studies). A summary of the type of data extracted from each toxicological study is presented in Table C-1. For references that included more than one experiment or species, data extraction records were created for each experiment or species.

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 2-2 and 2-3, respectively).

No relevant human studies that examined the health effects of exposure to 2-, 3-, and 4- nitrophenol were identified. In animal studies, the health effects of 2-nitrophenol were examined in a single acute inhalation study. No adequately conducted animal studies examining the health effects of 3-nitrophenol exposure through any route were identified. Therefore, the systematic review completed in this section only includes health effect studies on 4-nitrophenol.

Table C-1. 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

C.4 IDENTIFY POTENTIAL HEALTH EFFECT OUTCOMES OF CONCERN

Overviews of the potential health effect outcomes for 4-nitrophenol identified in animal studies are presented in Table C-2.

No relevant human studies that examined the health effects of exposure to nitrophenols were identified. Animal studies examined a comprehensive set of end points following inhalation, oral, or dermal exposure. The available literature examined most systemic endpoints and reported respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, dermal, ocular, body weight, and metabolic effects. Additionally, a few animal studies reported reproductive and developmental effects. Hematological (alterations in levels of methemoglobin), respiratory (changes in lung weight, wheezing and dyspnea), and ocular (occurrence of cataracts) effects were observed at different doses. Studies examining these potential outcomes were carried through to Steps 4–8 of the systematic review.

Table C-2. Overview of the Health Outcomes for 4-Nitrophenol Evaluated in Animal Studies

	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Endocrine	Dermal	Ocular	Body Weight	Metabolic	Other	Immunological	Neurological	Reproductive	Developmental	Cancer
Inhalation Studies																		
Acute Duration	1			1		1	1			1	1			1	1			
	1			1		1	1			1	1			1	1			
Intermediate Duration	1	1	1	1	1	1	1	1		1	1			1	1	1		
	1	0	0	1	0	0	0	0		1	0			0	0	0		
Chronic Duration																		
Oral Studies																		
Acute Duration			2	2		4	2	1		1	7			1	3	3	3	
			2	0		3	1	1		0	4			0	0	0	0	
Intermediate Duration	1	1	1	1	1	1	1	1	1	1	2				1	2	1	
	1	0	0	0	0	1	1	0	0	0	0				0	0	0	
Chronic Duration																		
Dermal Studies																		
Acute Duration																		
Intermediate Duration	3	3	3	3	3	3	3	3	3	3	3			3	3	3	3	
	0	0	0	0	0	0	0	0	2	0	1			0	2	0	0	
Chronic Duration	1	1	1		1	1	1	1	1	1	1		1	1	1			
	0	0	0		0	0	0	0	0	0	0		0	0	0			

Number of Studies examining end point	0	1	2	3	4	5 9	≥10	
Number of studies reporting outcome	0	1	2	3	4	5 9	≥10	

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 animal experimental studies are presented in Table C-3. No relevant human studies that examined the health effects of exposure to nitrophenols were identified. 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-3. 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?
Other bias
Did the study design or analysis account for important confounding and modifying variables?

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.

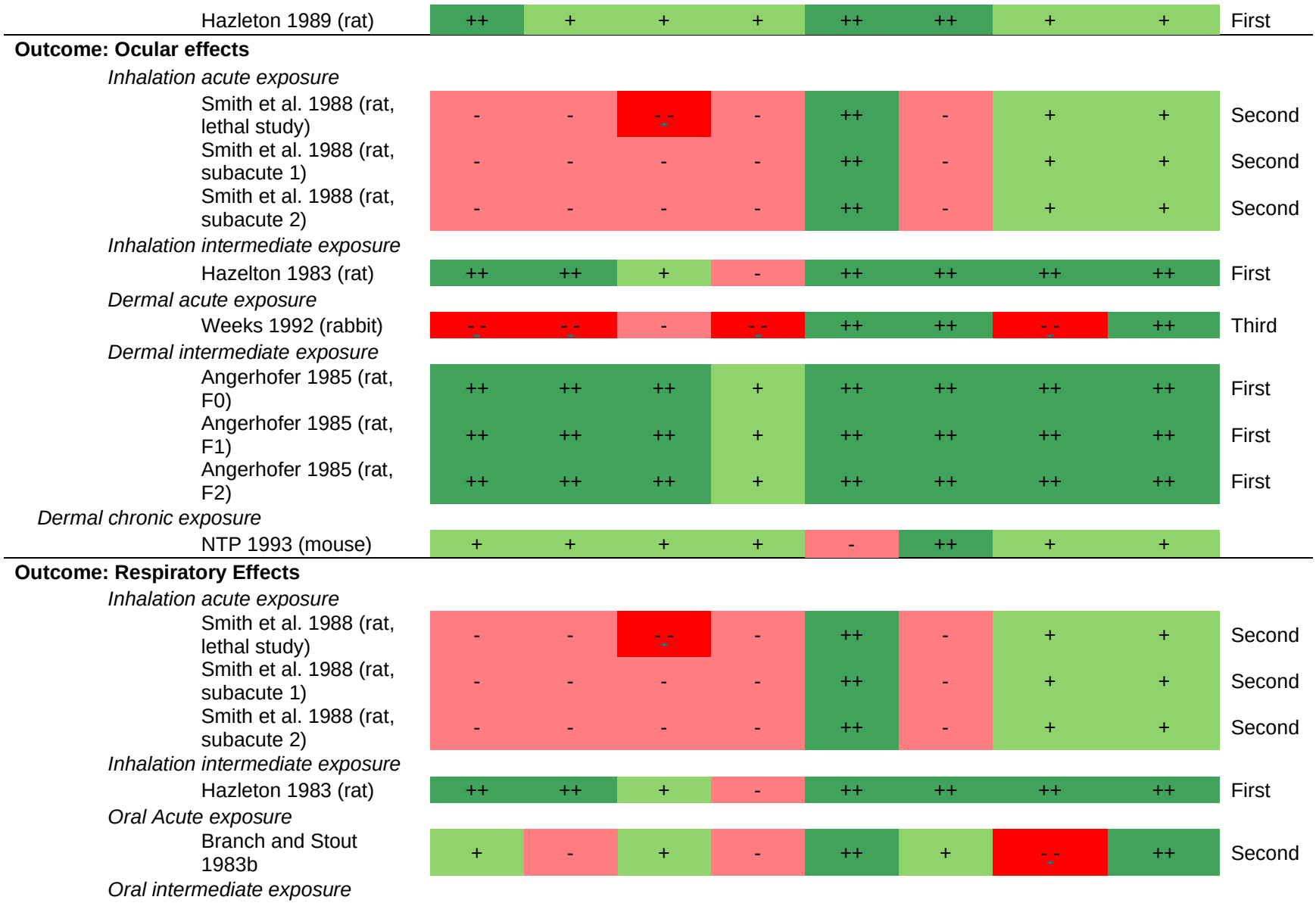
Second Tier. A study was placed in the second tier if it did not meet the criteria for the first or third tiers.

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 animal experimental studies of nitrophenols health effects are presented in Table C-4.

Table C-4. 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
Outcome: Hematological 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
Oral acute exposure									
Abu-Qare et al. 2000 (rat)	-	-	-	-	++	++	++	++	First
Oral intermediate exposure									


Hazleton 1989 (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
Hazelton 1983 (rat) ++ ++ + - ++ ++ ++ ++ First
Dermal acute exposure
Weeks 1992 (rabbit) - - - - - - ++ ++ - - ++ Third
Dermal intermediate exposure
Angerhofer 1985 (rat, F0) ++ ++ ++ + ++ ++ ++ ++ First
Angerhofer 1985 (rat, F1) ++ ++ ++ + ++ ++ ++ ++ First
Angerhofer 1985 (rat, F2) ++ ++ ++ + ++ ++ ++ ++ First
Dermal chronic exposure
NTP 1993 (mouse) + + + + - ++ + +
Outcome: Respiratory 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
Oral Acute exposure
Branch and Stout 1983b + - + - ++ + - - ++ Second
Oral intermediate exposure

Hazelton 1989 (rat)	++	+	+	+	++	++	+	+	First
Koizumi et al. 2001 (rat, dose finding)	++	+	+	+	++	+	+	-	First
Koizumi et al. 2001 (rat, low dose)	++	+	+	+	++	+	+	-	First
Koizumi et al. 2001 (rat, high dose)	++	+	+	+	++	+	+	-	First
Dermal intermediate exposure									
Angerhofer 1985 (rat, F0)	++	++	++	+	++	++	++	++	First
Angerhofer 1985 (rat, F1)	++	++	++	+	++	++	++	++	First
Angerhofer 1985 (rat, F2)	++	++	++	+	++	++	++	++	First
Dermal chronic exposure									
NTP 1993 (mouse)	+	+	+	+	-	++	+	+	First

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

Confidences in the bodies of human and animal evidence were evaluated independently for each potential outcome. ATSDR did not evaluate the confidence in the body of evidence for carcinogenicity; rather, the Agency defaulted to the cancer weight-of-evidence assessment of other agencies including DHHS, EPA, and IARC. The confidence in the body of evidence for an association or no association between exposure to 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 in Distiller, which were customized for epidemiology, human controlled exposure, or experimental animal study designs. Separate questionnaires were completed for each outcome assessed in a study. The key features for experimental animal studies are presented in Table C-5 No relevant human studies that examined the health effects of exposure to nitrophenols were identified. 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-5. 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 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 animal experimental studies are presented in Table C-6.

A summary of the initial confidence ratings for each outcome is presented in Table C-7. 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-7.

Table C-6. Presence of Key Features of Study Design for 4-Nitrophenol - Experimental Animal Studies

Reference	Key features				Initial study confidence
	Concurrent Control Group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	
Outcome: Hematological effects					
Inhalation acute exposure					
Smith et al. 1988 (rat, lethal study)	No	Yes	Yes	No	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	Yes	Yes	Yes	High
Oral acute exposure					
Abu-Qare et al. 2000 (rat)	Yes	No	Yes	No	Low
Oral intermediate exposure					
Hazleton 1989 (rat)	Yes	Yes	Yes	Yes	High
Outcome: Ocular effects					
Inhalation acute exposure					
Smith et al. 1988 (rat, lethal study)	No	Yes	Yes	No	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	Yes	Yes	Yes	High
Dermal acute exposure					
Weeks 1992 (rabbit)	No	Yes	Yes	No	Moderate
Dermal intermediate exposure					

Table C-6. Presence of Key Features of Study Design for 4-Nitrophenol - Experimental Animal Studies

Reference	Key features				Initial study confidence
	Concurrent Control Group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	
Angerhofer 1985 (rat, F0)	Yes	Yes	Yes	Yes	High
Angerhofer 1985 (rat, F1)	Yes	Yes	Yes	Yes	High
Angerhofer 1985 (rat, F2)	Yes	Yes	Yes	Yes	High
Dermal chronic exposure					
NTP 1993 (mouse)	Yes	Yes	Yes	Yes	High
Outcome: Respiratory effects					
Inhalation acute exposure					
Smith et al. 1988 (rat, lethal study)	No	Yes	Yes	No	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	Yes	Yes	Yes	High
Oral acute exposure					
Branch and Stout 1983b (rat)	No	Yes	Yes	No	Moderate
Oral intermediate exposure					
Hazleton 1989 (rat)	Yes	Yes	Yes	Yes	High
Koizumi et al. 2001 (rat, dose finding)	Yes	No	Yes	Yes	Moderate
Koizumi et al. 2001 (rat, low dose)	Yes	No	Yes	Yes	Moderate
Koizumi et al. 2001 (rat, high dose)	Yes	No	Yes	Yes	Moderate
Dermal intermediate exposure					
Angerhofer 1985 (rat, F0)	Yes	Yes	Yes	Yes	High
Angerhofer 1985 (rat, F1)	Yes	Yes	Yes	Yes	High
Angerhofer 1985 (rat, F2)	Yes	Yes	Yes	Yes	High
Dermal chronic exposure					
NTP 1993 (mouse)	Yes	Yes	Yes	Yes	High

Table C-7 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)	Low	Moderate
Smith et al. 1988 (rat, subacute 1)	Moderate	
Smith et al. 1988 (rat, subacute 2)	Moderate	
Inhalation intermediate exposure		
Hazleton 1983 (rat)	High	High
Oral acute exposure		
Abu-Qare et al. 2000 (rat)	Low	Low
Oral intermediate exposure		
Hazleton 1989 (rat)	High	High
Outcome: Ocular effects		
Inhalation acute exposure		
Smith et al. 1988 (rat, lethal study)	Low	Moderate
Smith et al. 1988 (rat, subacute 1)	Moderate	
Smith et al. 1988 (rat, subacute 2)	Moderate	
Inhalation intermediate exposure		
Hazleton 1983 (rat)	High	High
Dermal acute exposure		
Weeks 1992 (rabbit)	Moderate	Moderate
Dermal intermediate exposure		
Angerhofer 1985 (rat, F0)	High	High
Angerhofer 1985 (rat, F1)	High	
Angerhofer 1985 (rat, F2)	High	
Dermal chronic exposure		
NTP 1993 (mouse)	High	High
Outcome: Respiratory effects		
Inhalation acute exposure		
Smith et al. 1988 (rat, lethal study)	Low	Moderate
Smith et al. 1988 (rat, subacute 1)	Moderate	
Smith et al. 1988 (rat, subacute 2)	Moderate	
Inhalation intermediate exposure		
Hazleton 1983 (rat)	High	High
Oral acute exposure		
Branch and Stout 1983b (rat)	Moderate	Moderate
Oral intermediate exposure		
Hazleton 1989 (rat)	High	High
Koizumi et al. 2001 (rat, dose finding)	Moderate	
Koizumi et al. 2001 (rat, low dose)	Moderate	

Table C-7 Initial Confidence Rating for 4-Nitrophenol Health Effects Studies

	Initial study Confidence	Initial Confidence Rating
Koizumi et al. 2001 (rat, high dose)	Moderate	
Dermal intermediate exposure		
Angerhofer 1985 (rat, F0)	High	
Angerhofer 1985 (rat, F1)	High	High
Angerhofer 1985 (rat, F2)	High	
Dermal chronic exposure		
NTP 1993 (mouse)	High	High

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-8. 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-9.

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

- **Risk of bias.** Evaluation of whether there is substantial risk of bias across most of the studies examining the outcome. This evaluation used the risk of bias tier groupings for individual studies examining a particular outcome (Table C-4). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for risk of bias:
    - No downgrade if most studies are in the risk of bias first tier
    - Downgrade one confidence level if most studies are in the risk of bias second tier
    - Downgrade two confidence levels if most studies are in the risk of bias third tier

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

- **Indirectness.** Evaluation of four factors that can affect the applicability, generalizability, and relevance of the studies:
    - Relevance of the animal model to human health—unless otherwise indicated, studies in rats, mice, and other mammalian species are considered relevant to humans
    - Directness of the endpoints to the primary health outcome—examples of secondary outcomes or nonspecific outcomes include organ weight in the absence of histopathology or clinical chemistry findings in the absence of target tissue effects
    - Nature of the exposure in human studies and route of administration in animal studies—inhalation, oral, and dermal exposure routes are considered relevant unless there are compelling data to the contrary
    - Duration of treatment in animal studies and length of time between exposure and outcome assessment in animal and prospective human studies—this should be considered on an outcome-specific basis

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

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

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

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

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

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

- **Dose response.** Evaluation of the dose-response relationships measured within a study and across studies. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:

  - Upgrade one confidence level for evidence of a monotonic dose-response gradient
  - Upgrade one confidence level for evidence of a non-monotonic dose-response gradient where there is prior knowledge that supports a non-monotonic dose-response and a non-monotonic dose-response gradient is observed across studies

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

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

The results of this assessment are presented in Table C-8 with the final confidence in the body of literature by endpoint presented in Table C-9.

Table C-8. 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			
Animal Studies	High	-1 Indirectness, -1 Imprecision	Moderate
Outcome: Ocular Effects			
Animal Studies	High	-1 Indirectness, -1 Imprecision	Moderate
Outcome: Respiratory Effects			
Animal Studies	High	-1 Unexplained inconsistency, -1 Indirectness, -1 Imprecision	Low

Table C-9. Confidence in the Body of Evidence for 4-Nitrophenol

Outcome	Confidence in Body of Evidence	
	Human studies	Animal Studies
Hematological Effects	No data	Moderate
Respiratory Effects	No data	Moderate
Ocular Effects	No data	Low

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-10.

Table C-10. 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
Respiratory Effects	No data		No data
Ocular Effects	No data		No data
Animal studies			
Hematological Effects	Moderate	Health Effect	Moderate

Respiratory Effects	Moderate	Health Effect	Moderate
Ocular Effects	Moderate	Health Effect	Low

C.8 INTEGRATE EVIDENCE TO DEVELOP HAZARD IDENTIFICATION CONCLUSIONS

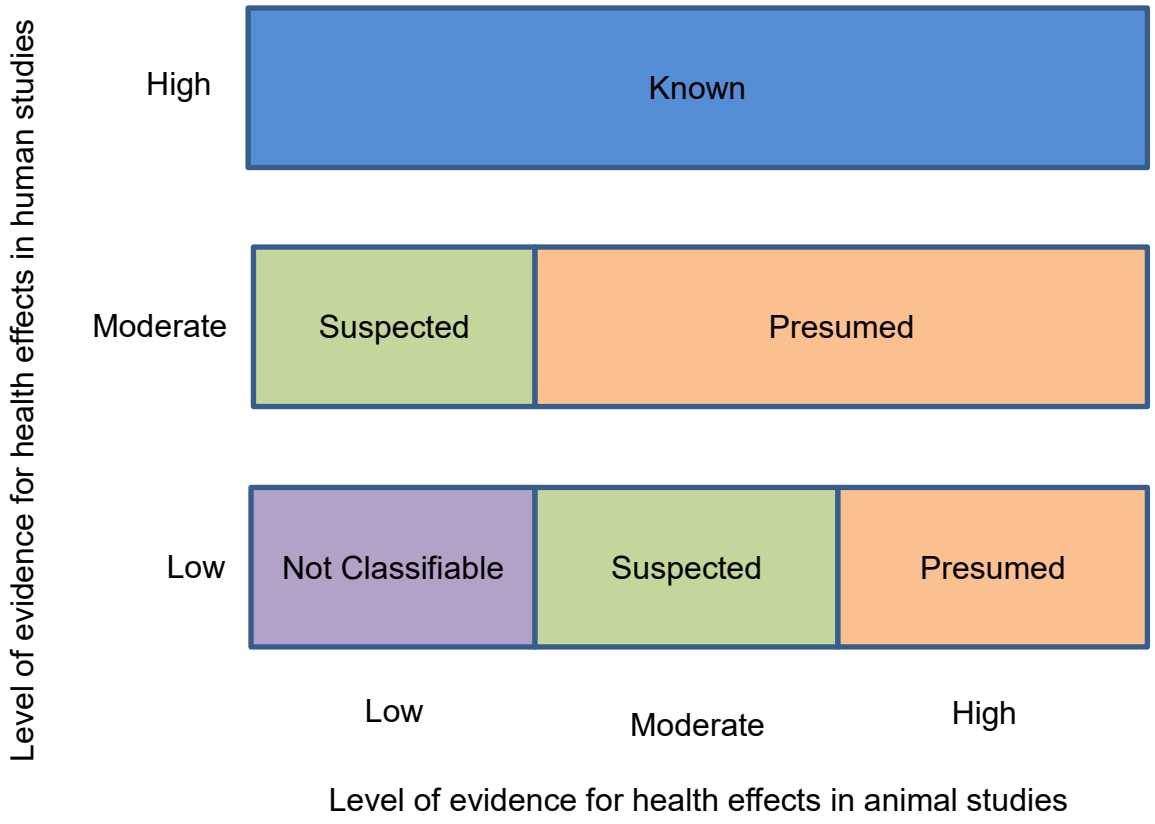
The final step involved the integration of the evidence streams for the human studies and animal studies to allow for a determination of hazard identification conclusions. For health effects, there were four hazard identification conclusion categories:

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

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

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

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-11.

Suspected Health Effects

- Hematological effects

- No human data that examined effects of 4-nitrophenol exposure on hematological endpoints were available.
- Moderate evidence in animal studies exists based on a study by Smith et al. (1988), where increases in methemoglobin occurred after acute inhalation exposures at higher concentrations (Smith et al. 1988). Additional studies found no changes in hematological endpoints after intermediate inhalation exposure (Hazleton 1983), but this difference in effect is potentially due to exposure at comparatively lower concentrations than those used in Smith et al. (1988). No hematological effects were observed after acute and intermediate oral exposure to 4-nitrophenol (Abu-Qare et al. 2000; Hazleton 1989).
- Based on moderate evidence from animal studies and an absence of human studies, increased methemoglobin is classified as a suspected health effect.

- Respiratory effects
  - No human data that examined effects of 4-nitrophenol exposure on respiratory endpoints were available.
  - Moderate evidence is available from acute inhalation exposure in animal studies (Smith et al. 1988). Smith et al. 1988 showed alterations in lung weight after acute inhalation exposure to 4-nitrophenol at higher concentrations (Smith et al. 1988). Intermediate inhalation exposure to 4-nitrophenol showed no effect on respiratory endpoints (Hazleton 1983).
  - Dyspnea was observed after an acute oral study of 4-nitrophenol in rats, but this study did not include a control group (Branch D. and Stout 1983b). There is moderate evidence for wheezing and dyspnea occurring after oral intermediate exposure to 4-nitrophenol (Hazleton 1989), though Koizumi et al. (2001) reported no effects after a higher dose of exposure for a shorter amount of time.
  - Based on moderate evidence from animal studies and an absence of human studies, the respiratory endpoint of dyspnea should be classified as a suspected health effect.

Not Classifiable

- Ocular effects
  - No human data that examined effects of 4-nitrophenol exposure on ocular end points were available.
  - Low evidence from animal studies that examine acute and intermediate inhalation exposure of 4-nitrophenol show changes in ocular function, including corneal opacity and irritation, as well as unilateral and bilateral diffused anterior capsular cataracts (Hazleton 1983; Smith et al. 1988). A 4-nitrophenol acute dermal exposure study that had no control group observed severe conjunctival irritation and corneal opacity, along with irritation and visible destruction of the iris (Weeks 1992), though chronic dermal exposure showed no effects (NTP 1993). No ocular effects were observed in the only oral study that examined ocular endpoints after exposure to 4-nitrophenol. (Angerhofer 1985; NTP 1993).
  - Based on low evidence from animal studies and an absence of human studies, ocular endpoints are not classifiable as a health effect.

Table C-11. Hazard Identification Conclusions for 4- Nitrophenol

Outcome	Hazard identification

Hematological effects	Suspected health effect
Respiratory effects	Suspected health effect
Ocular effects	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 two years. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Aida et al. 1992).

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

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

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

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

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

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

FIGURE LEGEND

See Sample LSE Figure (page D-6)

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

(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)

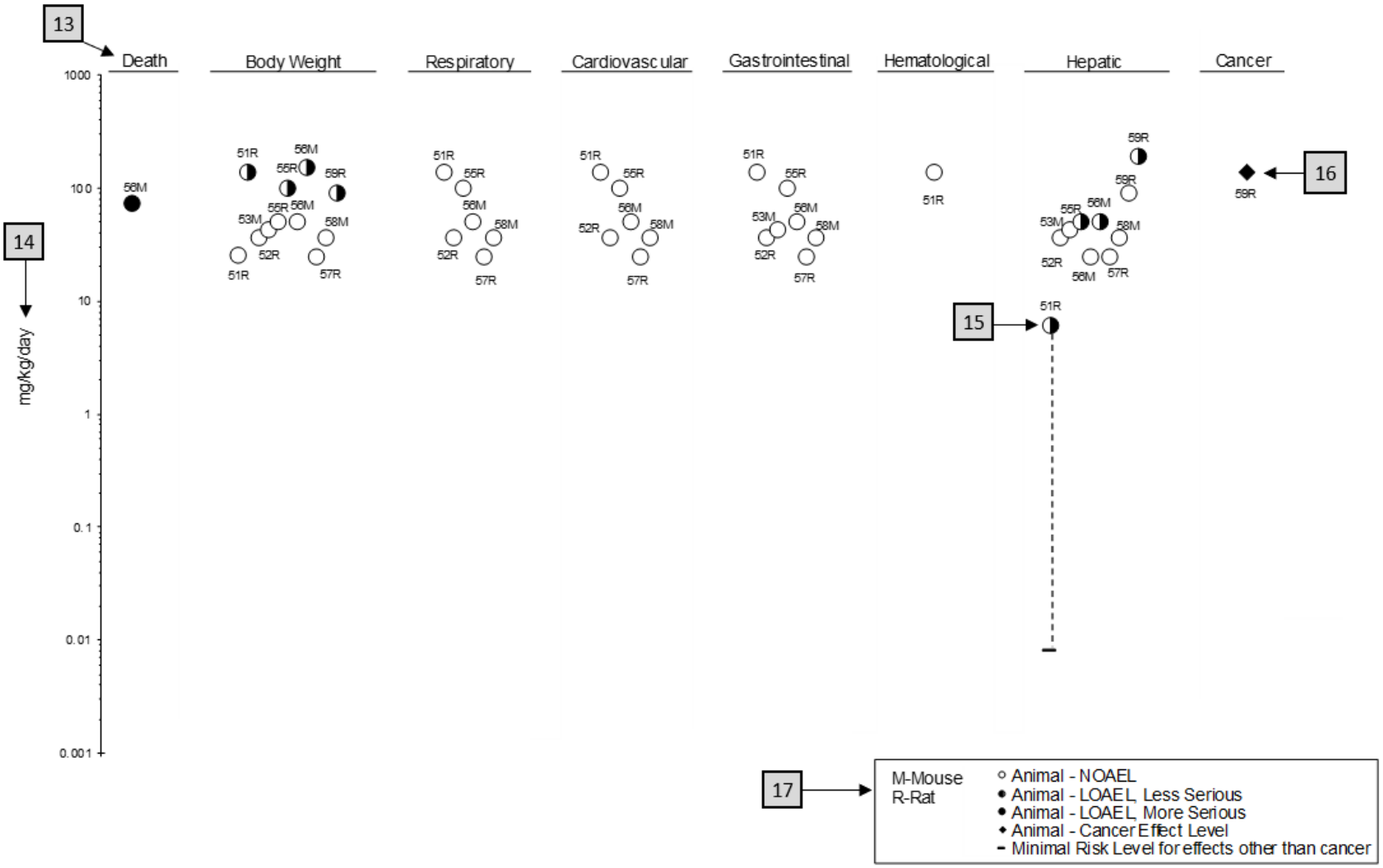
Figure key[a] (3)	Species (strain) No./group (4)	Exposure parameters (5)	Doses (mg/kg/day) (5)	Parameters monitored (6)	Endpoint (7)	NOAEL (mg/kg/day) (8)	Less serious LOAEL (mg/kg/day) (9)	Serious LOAEL (mg/kg/day) (9)	Effect
CHRONIC EXPOSURE (2)									
51	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0,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

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

(11) [b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.1 mg/kg/day based on the $BMDL_{05}$ of 10 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

[c]Used to derive a chronic-duration oral MRL of 0.008 mg/kg/day based on the $BMDL_{10}$ of 0.78 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

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



APPENDIX E. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

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

Primary Chapters/Sections of Interest

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

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

Pediatrics:

Section 3.2 Children and Other Populations that are Unusually Susceptible

Section 3.3 Biomarkers of Exposure and Effect

ATSDR Information Center

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

The following additional materials are available online:

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

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

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

Other Agencies and Organizations

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

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

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

Clinical Resources (Publicly Available Information)

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

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

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

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

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

APPENDIX F. GLOSSARY

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

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

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

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

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

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

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

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

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

Carcinogen—A chemical capable of inducing cancer.

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

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

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

Ceiling Value—A concentration that must not be exceeded.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Physiologically Based Pharmacokinetic (PBPK) Model—A type of physiologically based dose-response model that is comprised of a series of compartments representing organs or tissue groups with

realistic weights and blood flows. These models require a variety of physiological information, including tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as blood:air partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

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

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

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

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation RfC is expressed in units of mg/m3 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
AKP	aryl hydrocarbon receptor
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
Cre	creatinine
CWA	Clean Water Act
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DWEL	drinking water exposure level
EAFUS	Everything Added to Food in the United States
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
ER α	Estrogen receptor α
ER β	Estrogen receptor β
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 level/limit
REL-C	recommended exposure level-ceiling value
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SD	standard deviation
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase (same as aspartate aminotransferase or AST)
SGPT	serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT)
SIC	standard industrial classification
SMR	standardized mortality ratio
sRBC	sheep red blood cell
STEL	short term exposure limit
TBIL	total bilirubin
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
q1*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result