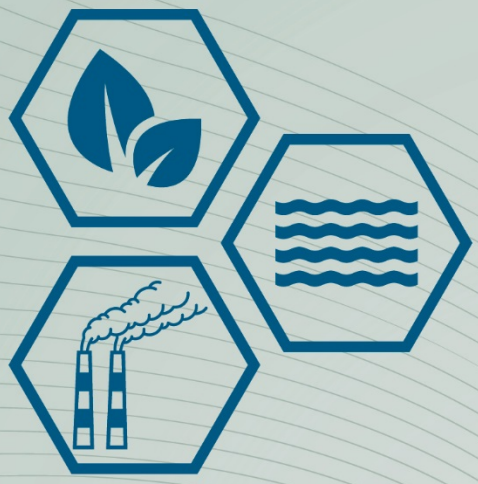

Toxicological Profile for Dinitrocresols

January 2018

ATSDR
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.

Each profile includes the following:

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

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

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

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public.

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

Patrick N. Breysse, Ph.D., CIH
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Agency for Toxic Substances and Disease Registry
Centers for Disease Control and Prevention

*Legislative Background

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

VERSION HISTORY

Date	Description
August 1995	Draft for public comment toxicological profile released
October 2009	Addendum to the toxicological profile released
January 2018	Update of data in Chapters 2, 3, and 7

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CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

ATSDR's *Toxicological Profile for Dinitrocresols* was released in 1995. In order to update the literature in this profile, ATSDR conducted a literature search focused on health effects information as described in Appendix B. Chapters 2 and 3 were revised to reflect the most current health effects data. In some cases, other sections of the profile were updated as needed or for consistency with the updated health effects data. However, the focus of the update to this profile is on health effects information.

Dinitrocresols are a group of organic chemicals that can contain up to 18 individual compounds. 4,6-Dinitro-*o*-cresol (DNOC) is the most commercially important dinitrocresol. DNOC is a yellow solid with no smell; it dissolves slightly in water. DNOC in water and soil does not easily evaporate to air. DNOC was primarily used to protect fruit trees and other food crops from insect damage. However, the U.S. Environmental Protection Agency (EPA) has cancelled its registration as a pesticide. In the 1930s, DNOC was used in pills for reducing weight. It is no longer used for this purpose because of bad effects on health. The most likely source of exposure for the general population is from contaminated drinking water. Populations living near sites containing DNOC wastes may be exposed by breathing contaminated air as well.

1.2 SUMMARY OF HEALTH EFFECTS

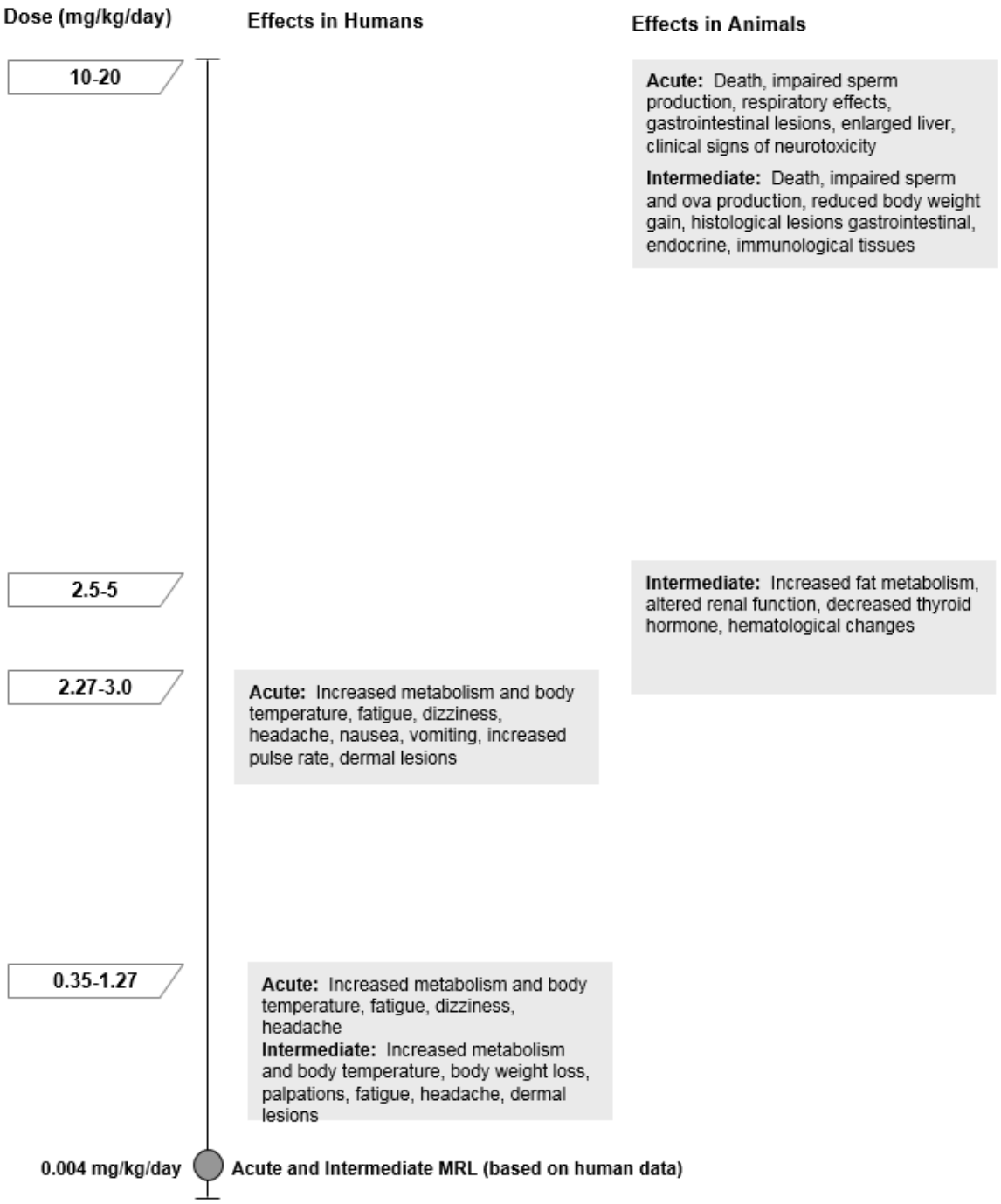
DNOC uncouples oxidative phosphorylation, resulting in energy being given off as heat and manifested as hyperthermia. In an attempt to reduce body temperature, the body increases respiratory rate and heart rate as part of a compensatory mechanism. The most significant and sensitive effects resulting from acute, intermediate, or chronic exposure are related to increased basal metabolic rates in humans. Overexposure to DNOC has resulted in death in humans and animals.

Increased pulse rate, respiratory rate, and profuse sweating were commonly seen in humans and animals exposed to DNOC. Neurological signs such as lethargy, depression, and peripheral neuritis have occurred in humans exposed to DNOC. Maculopapular urticarial eruptions were also observed in humans after oral exposure; this effect was not seen in animals. DNOC has been associated with cataract formation in humans. Cataract formation is an important reason why the government and the medical community stopped use of DNOC and dinitrophenol for weight loss in humans. A limited number of animal studies reported DNOC-induced effects on sperm and lack of corpora lutea production. There are no reliable

human data regarding DNOC-induced reproductive or developmental effects. No data were located regarding potential for DNOC to cause cancer in humans or animals. However, clastogenicity has been demonstrated in both *in vivo* and *in vitro* human and animal test systems.

As illustrated in Figure 1-1, the most sensitive effects following oral exposure are cardiovascular, metabolic, immunological (dermal allergic reactions), and neurological effects.

Figure 1-1. Health Effects Found in Animals and Humans Following Oral Exposure to Dinitrocresols



1.3 MINIMAL RISK LEVELS (MRLs)

As presented in Figure 1-2, limited inhalation data from animals indicate metabolic and hematological systems as particularly sensitive targets of DNOC toxicity. However, the available information is considered insufficient to derive inhalation MRLs for DNOC. As presented in Figure 1-3, available oral data from humans identify metabolism, neurological, cardiovascular, and immunological systems as the most sensitive targets of DNOC toxicity; laboratory animal data generally support the findings in humans. The MRL values for acute- and intermediate-duration oral exposure to DNOC are summarized in Table 1-1 and discussed in greater detail in Appendix A.

Figure 1-2. Summary of Sensitive Targets of Dinitrocresols – Inhalation

The hematological and metabolic systems are the most sensitive target of dinitrocresols.
Based on the lowest LOAELs (mg/m^3) among health effects in animals; no human data were identified.

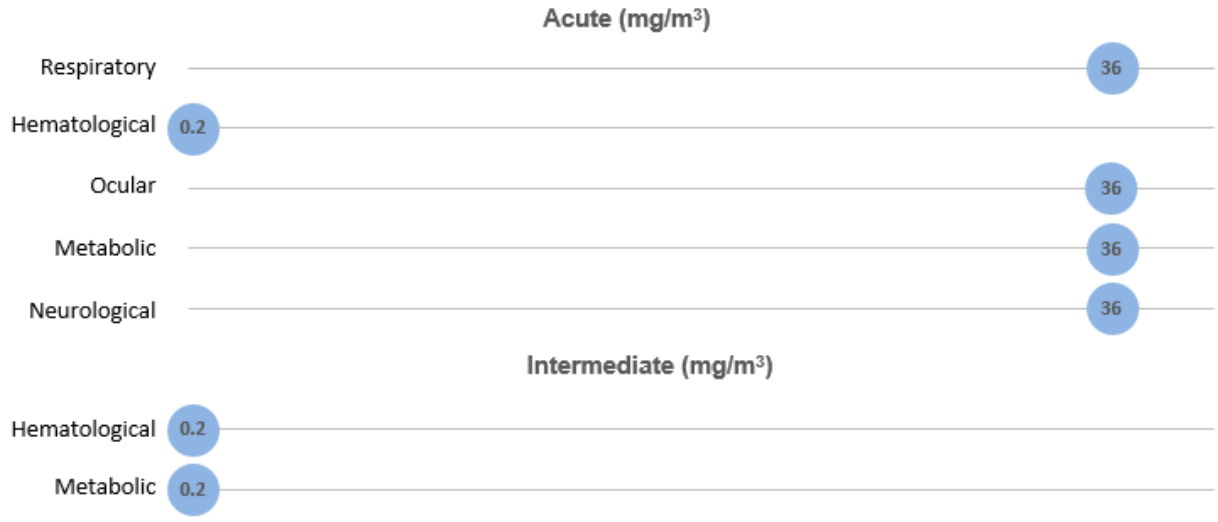


Figure 1-3. Summary of Sensitive Targets of Dinitrocresols – Oral

Metabolism, cardiovascular system, immunological system, and nervous system are the most sensitive targets of dinitrocresols

Numbers in triangles and circles are the lowest LOAELs (mg/kg/day) among health effects in humans and animals, respectively

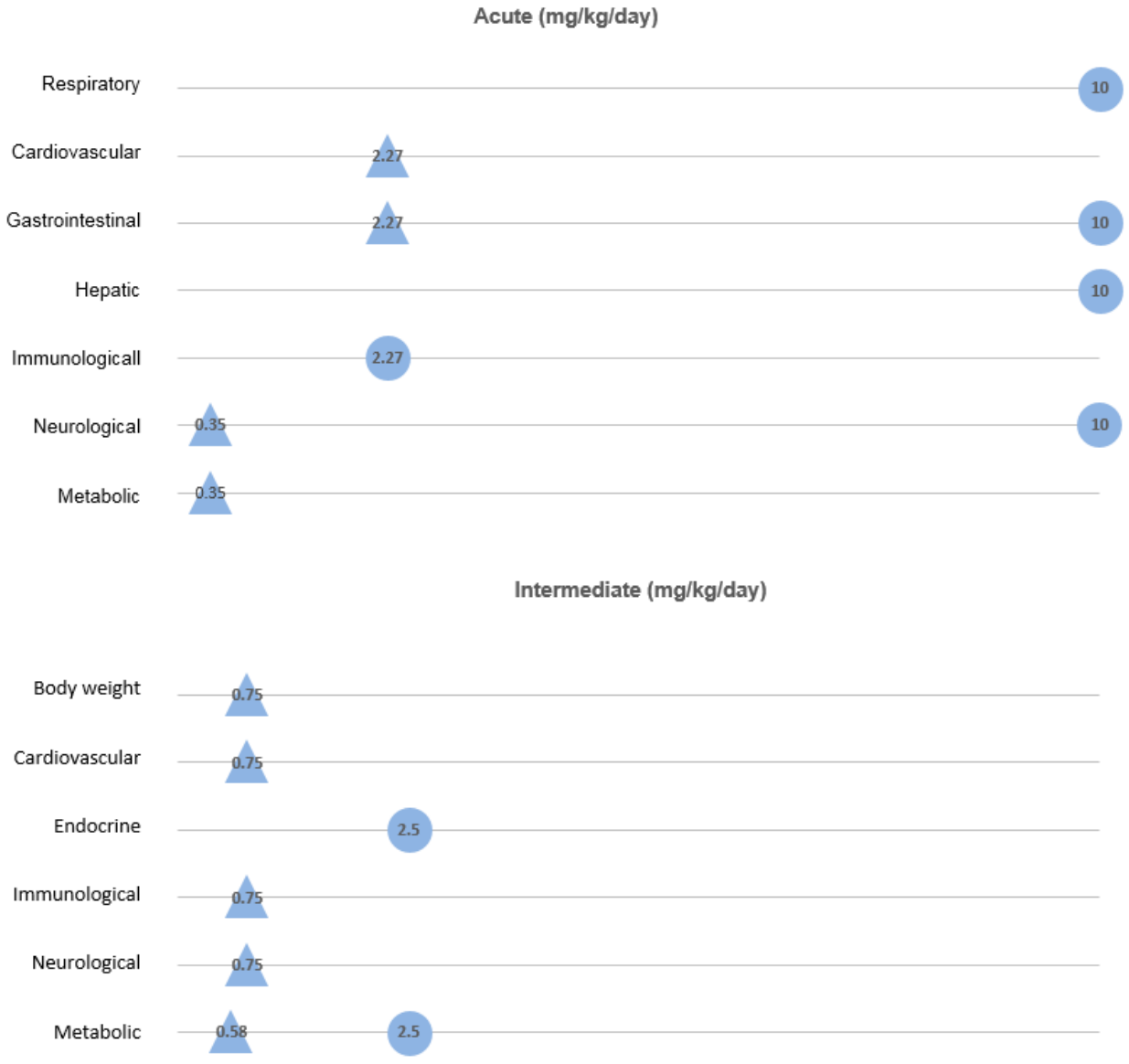


Table 1-1. Minimal Risk Levels (MRLs) for Dinitrocresols[a]

Exposure duration	MRL	Critical effect	Point of departure	Uncertainty factor	Reference
Inhalation exposure (ppm)					
Acute	Insufficient data for MRL derivation				
Intermediate	Insufficient data for MRL derivation				
Chronic	Insufficient data for MRL derivation				
Oral exposure (mg/kg/day)					
Acute[b]	0.004	Neurological effects	0.35 (LOAEL)	100	Plotz 1936
Intermediate[b]	0.004	Neurological effects	0.35 (LOAEL)	100	Plotz 1936
Chronic	Insufficient data for MRL derivation				

[a]See Appendix A for additional information.
[b]MRL derived for 4,6-dinitro-*o*-cresol.

LOAEL = lowest-observed-adverse-effect level

CHAPTER 2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of dinitrocresols. 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.

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 dinitrocresols, but may not be inclusive of the entire body of literature.

Inhalation studies (animals), oral studies (controlled human and animal), and dermal studies (controlled human and animal) are presented in Table 2-1 and Figure 2-2, Table 2-2 and Figure 2-3, and Table 2-3, respectively.

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 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 C). This guide should aid in the interpretation of the tables and figures for LSEs and MRLs.

Studies regarding toxic effects of dinitrocresols conducted by the inhalation, oral, or dermal routes of exposure almost exclusively employed 4,6-dinitro-*o*-cresol (DNOC). Therefore, the focus of this profile is on 4,6-dinitro-*o*-cresol. DNOC is the most industrially and toxicologically important isomer since it is used as a pesticide and was used in the past as a weight-reducing drug. It should be noted that in the United Kingdom, 4,6-dinitro-*o*-cresol (or more correctly 2-methyl-4,6-dinitrophenol) was often called 3,5-dinitro-*o*-cresol, which is not to be confused with genuine 3,5-dinitro-*o*-cresol (or more correctly 2-methyl-3,5-dinitrophenol) (King and Harvey 1953a).

As described in detail in Section 2.21 (Mechanisms of Action), DNOC-induced acute toxic effects are related to DNOC acting directly on cell metabolism and interfering with oxidative phosphorylation.

The health effects of DNOC have been evaluated in human and animal studies. As illustrated in Figure 2-1, most of the health effects data come from acute- or intermediate-duration oral studies in animals. In addition to the studies summarized in Figure 2-1, 23 studies examined DNOC lethality following inhalation, oral, or dermal exposure. Only one study evaluated immunological endpoints; developmental endpoints were evaluated in only one other study.

The available human and animal data suggest the following sensitive targets of toxicity:

- **Metabolic Endpoint:** Increased basal metabolic rate and accompanying increases in body temperature and blood sugar, as well as decreased activity of selected enzymes have been reported in humans and animals exposed to DNOC by inhalation or oral routes.

- **Neurological Endpoint:** Lethargy, dizziness, twitching, ataxia, salivation, and/or sluggishness in DNOC-exposed humans and animals

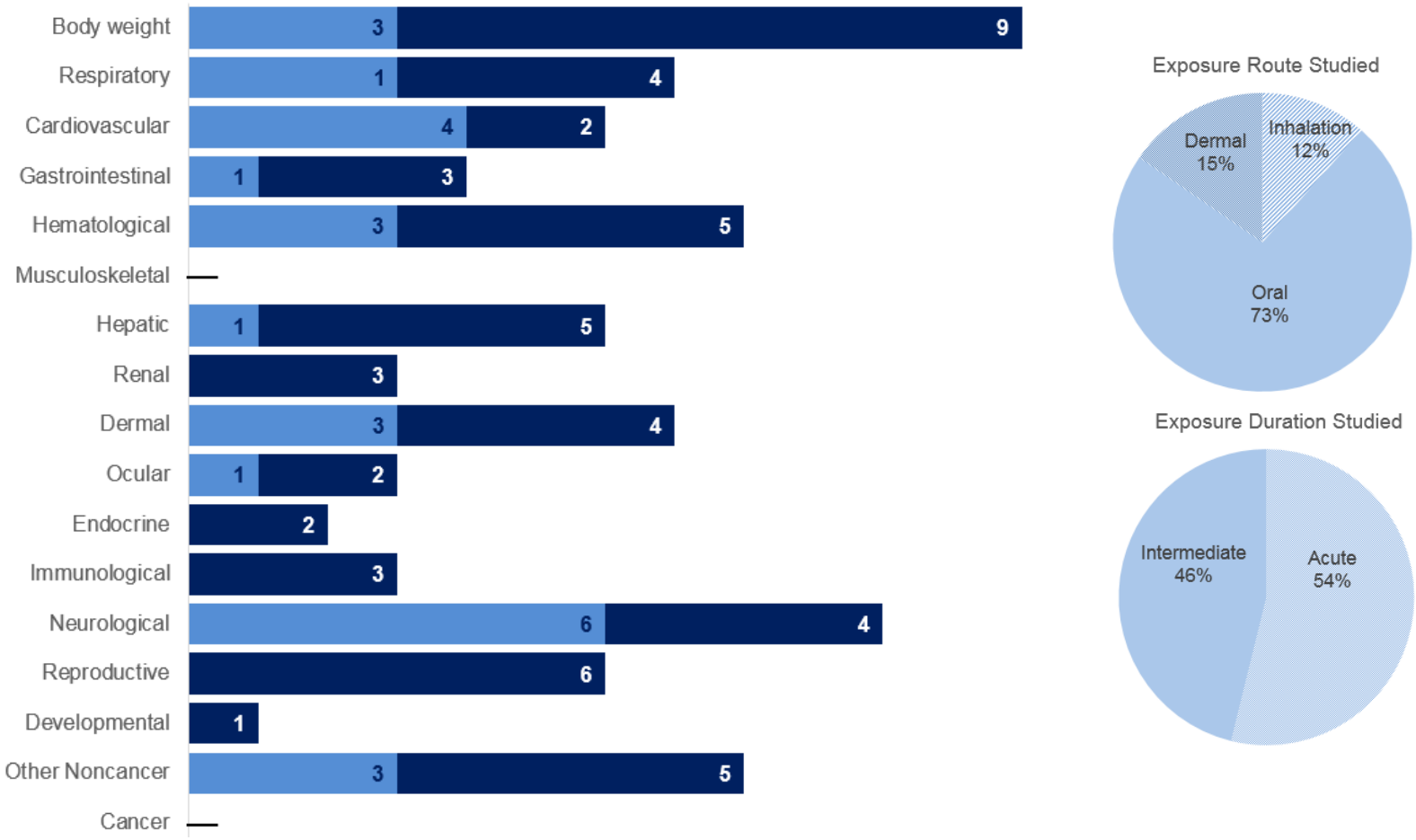
- **Cardiovascular Endpoint:** Increased pulse rate, palpitations, swelling of fingers and hands in humans

- **Immunological Endpoint:** Urticarial eruptions on skin (an allergic response) following oral exposure in humans

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

Body weight, hematological, neurological, and other noncancer effects of dinitrocresols were the most widely examined potential toxicity outcomes

More studies evaluated health effects in humans than humans (counts represent studies examining endpoint)



*Includes studies discussed in Chapter 2. A total of 28 studies (including those finding no effect) have examined toxicity; most animal studies examined multiple endpoints.

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Exposure levels (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effect
ACUTE EXPOSURE									
1	Cat (NS) 3 or 6 (sex NS)	4 hours; liquid aerosol (head-only)	0.4, 1.4, 40, 100	BI, BW, CS, HE, LE	Death			40	1/3 cats died at 40 mg/m^3; 2/6 cats died at 100 mg/m^3
					Resp	1.4		40	Dyspnea in 1/3 cats (followed by death) at 40 mg/m^3; dyspnea in 3/6 cats at 100 mg/m^3
					Hemato	1.4		40	Decreases in hemoglobin and RBCs, increased leukocytes
					Neuro	1.4		40	Sluggishness, loss of muscle tone at 40 mg/m^3 in the cat that subsequently died; sluggishness, salivation, loss of appetite, tremors, ataxia at 100 mg/m^3
					Other noncancer (metabolic)	1.4		40	Increased body temperature, decreased catalase and peroxidase activities, increased blood sugar
Burkatskaya 1965b 4,6-DNOC									
2	Cat (NS) 3 or 6 (sex NS)	4 hours; solid aerosol (head-only)	36, 60, 100	BI, BW, CS, HE, LE	Death			100	2/6 died (one each on postexposure days 6 and 11)
					Resp		36		Dyspnea, sneezing, nasal secretions
					Hemato		36		Accelerated erythrocyte sedimentation rate, decreases in hemoglobin and RBCs, increased leukocytes
					Ocular		36		Lacrimation and blepharospasm
					Neuro			36	Twitching, tremors, ataxia, sluggishness, salivation
					Other noncancer (metabolic)	1.4	36		Increased body temperature, increased blood sugar, decreased catalase and peroxidase activities
Burkatskaya 1965b 4,6-DNOC									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Exposure levels (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effect
3	Rat (albino and hooded); Number and sex NS	4–5 hours	100	BI, BW, CS, HE, LE	Resp		100		10% increase in respiration rates 16 hours after exposure
					Neuro		100		Lethargy
					Other noncancer (metabolic)		100		0.7°C increase in body temperatures 16 hours after exposure
King and Harvey 1953a 4,6-DNOC									
INTERMEDIATE EXPOSURE									
4	Cat (NS); 3 (sex NS)	1 month 4 hours/day liquid aerosol (head-only)	2.0	BI, BW, CS, HE, LE	Death			2.0	Death of 2/3 cats
					Bd Wt		2.0		Depressed body weight
					Hemato		2.0		Accelerated erythrocyte sedimentation rate, decreased hemoglobin and RBCs, increased leukocytes, alterations in differential WBC count
					Other noncancer (metabolic)		2.0		Increased body temperature, increased blood sugar, decreased catalase and peroxidase activities
Burkatskaya 1965b 4,6-DNOC									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Exposure levels (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effect
5	Cat (NS); 3 (sex NS)	2–3 months 4 hours/day solid aerosol (head-only)	0.2	BI, BW, CS, HE, LE	Hemato		0.2		Accelerated erythrocyte sedimentation rate, decreased hemoglobin and RBCs, increased leukocytes
					Other noncancer (metabolic)		0.2		Increased body temperature, increased blood sugar, decreased catalase and peroxidase activities
Burkatskaya 1965b 4,6-DNOC									

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

Bd Wt or BW = body weight; BI = biochemical changes; CS = clinical signs; DNOC = dinitrocresol; HE = hematology; Hemato = hematological; LE = lethality; LOAEL= lowest-observed-adverse-effect level; Neuro = neurological NOAEL = no-observed-adverse-effect level; NS = not specified; RBC = red blood cell; Resp = respiratory; WBC = white blood cell

Figure 2-2. Levels of Significant Exposure to Dinitrocresols – Inhalation

Acute (≤14 days)

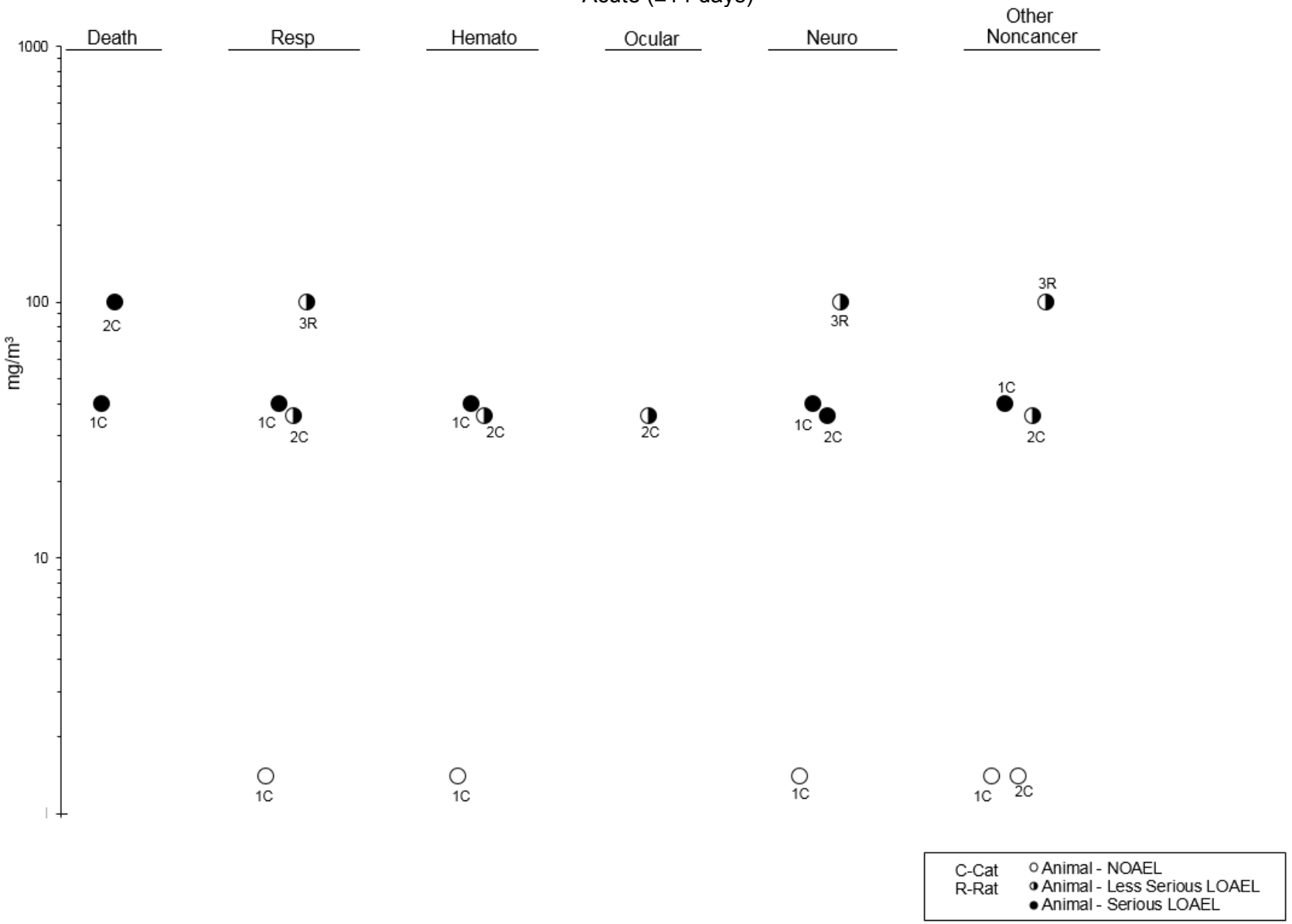


Figure 2-2. Levels of Significant Exposure to Dinitrocresols – Inhalation
Intermediate (15-364)

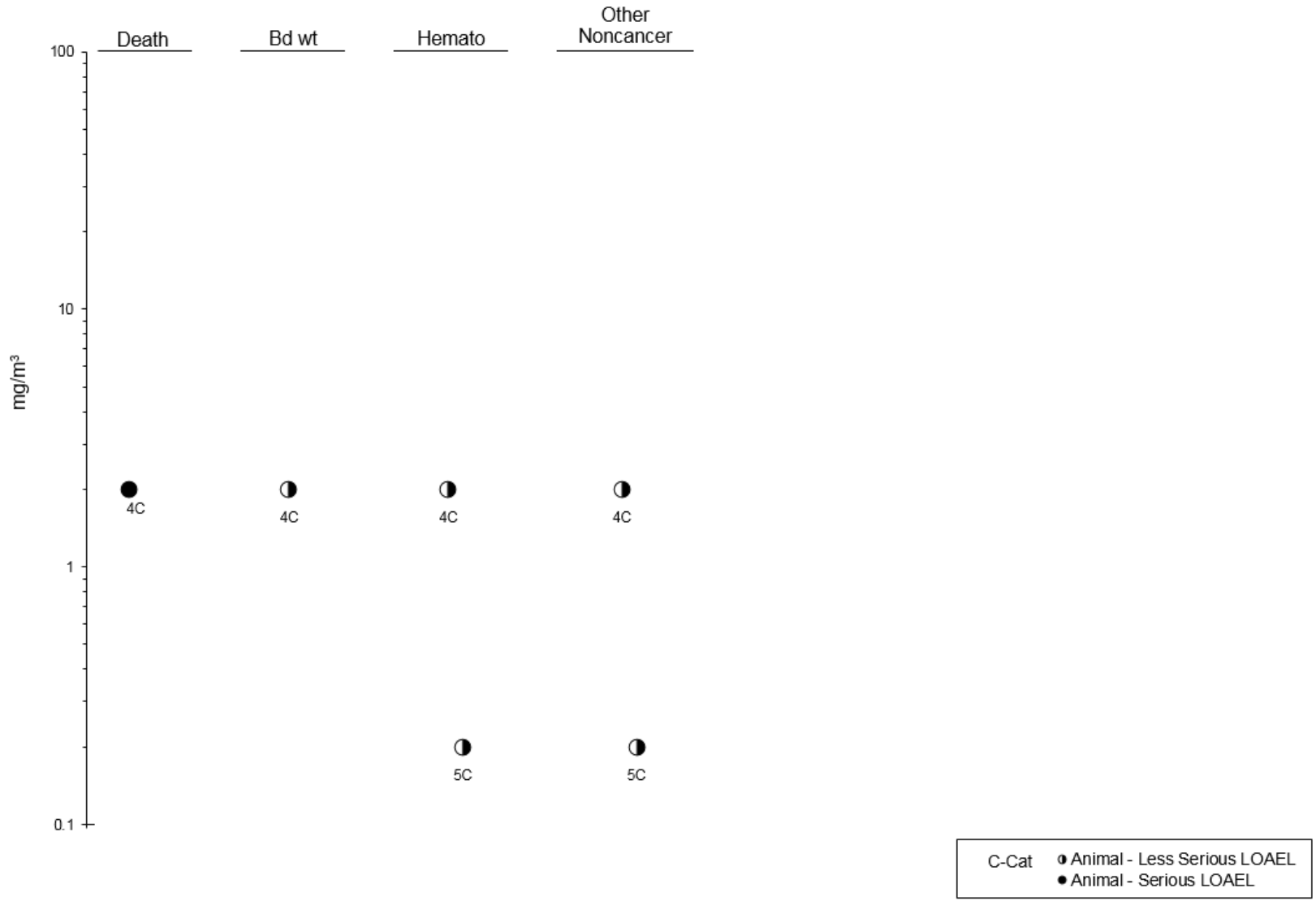


Table 2-2. Levels of Significant Exposure to Dinitrocresols – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
ACUTE EXPOSURE									
1	Human; number and sex NS	1–4 days 1 time/day (C)	3	CS, HE	Neuro		3		Lethargy, headache, loss of appetite
					Other noncancer (metabolic			3	>50% increase in basal metabolic rate, sweating
Dodds and Robertson 1933 4,6-DNOC									
2	Human 1 F	11 d 1 time/day (C)	2.27 (TWA)	CS, HE	Cardio		2.27 F		Pulse rate 90/minute; swelling of fingers and hands
					Gastro		2.27 F		Nausea, vomiting
					Hemato	2.27 F			
					Hepatic	2.27 F			
					Immuno		2.27 F		Maculopapular eruption on skin
					Neuro		2.27 F		Drowsiness, headache, ringing in ears
Gordon and Wallfield 1935 4,6-DNOC									
3	Human 5 M	5–7 days 1 time/day (C)	0.92–1.27	BW, CS, HE	Bd Wt	1.27 M			
					Resp	1.27 M			
					Cardio	1.27 M			
					Hemato	1.27 M			
					Immuno	1.27 M			
					Neuro		1.27		Malaise, lassitude, headache
Harvey et al. 1951 4,6-DNOC									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
4	Human 1 M	3–5 days 1 time/day (C)		BI, CS	Neuro		0.35[b] M		Fatigue, dizziness
					Other noncancer (metabolic)		0.35 M		Increased perspiration and fatigue, elevated temperature (38.2°C)
Plotz 1936 4,6-DNOC									
5	Rat (NS) 10–30 M	Once (G)	18, 27, 36, 45, 90	CS, LE	Death			27 M	3/10 died, 100% mortality at higher doses; dose adjusted for DNOC content in sodium DNOC
					Resp	27 M		36 M	Dyspnea, asphyxia convulsions
					Hemato	27 M		36 M	Cyanosis
					Neuro	18 M		27 M	Depression
Ambrose 1942 Sodium 3,5-DNOC									
6	Rat (white)	Once (G)	NS	LE	Death			25	LD_{50}
Ben-Dyke et al. 1970; Jones et al. 1968 4,6-DNOC									
7	Rat (white)	Once (GO)	NS	LE	Death			30	LD_{50}
Dow Chemical Co. 1950 4,6-DNOC									
8	Rat (NS)	Once (GO)	NS	LE	Death			50	100% mortality
Dow Chemical Co. 1940 4,6-DNOC									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
9	Rat (NS) 10–12 (sex NS)	Once (GW)	5, 10, 20, 30, 40, 50, 60, 70	LE	Death			20 40	6/12 deaths at 37–40°C 2/12 deaths at 20–22°C
King and Harvey 1953a 4,6-DNOC									
10	Rat (NS) 6 (sex NS)	10 days 1 time/day (GW)	5, 10, 25	BW, CS, LE	Death			25	3/6 deaths
					Bd Wt	25			
King and Harvey 1953a 4,6-DNOC									
11	Rat (albino) 12 (sex NS)	4–10 days (F)		LE	Death			60	4/12 died
Parker et al. 1951 2,4-DNOC									
12	Rat (NS) 20 (sex NS)	Once (GO)	10, 20, 30, 40, 50	LE	Death			20	Deaths at 20, 30, 40, and 50 mg/kg/day were 3/20, 9/20, 15/20, and 20/20, respectively
Spencer et al. 1948 4,6-DNOC									
13	Rat (Jcl:SD) 6 M	5 days 1 time/days	0, 4, 7.5. 15	BW, CS, HP, LE, OF, OW	Death			15	5/12 died prior to cessation of dosing
					Bd Wt	15			
					Repro	7.5		15	At 14 days following cessation of dosing, 21% decreased sperm motility and 31% decreased percentage of normal sperm
Takahashi et al. 2004 4-6-DNOC									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
14	Rat (Jcl:SD) 24 or 36 M	5 days 1 time/day	0, 10, 15	BW, CS, HP, LE, OF, OW	Bd Wt	15			
					Repro	10	15		Up to 35% decreased percentage of normal sperm
Takahashi et al. 2006 4-6-DNOC									
15	Mouse (white) 12, 20, or 30 (sex NS)	Once (GW)	10, 15, 20, 25, 30, 35	CS, GN, LE	Death			10	Deaths among 10, 15, 20, 25, 30, and 35 mg/kg/day dose groups were 3/30, 6/12, 16/30, 9/12, 29/30, and 20/20, respectively
					Resp			10	Dyspnea, hemothorax
					Gastro			10	Coagulative necrosis in stomach mucosa; catarrhal inflammation of small intestine
					Hepatic			10	Enlarged liver with foci of hemorrhage and necrosis
					Neuro			10	Severe agitation, muscle twitches, prostration
Arustamyan 1972 4,6-DNOC									
16	Mouse (white) number and sex NS	Once (GW)	NS	LE	Death			16.4	LD_{50}
Arustamyan 1972 4,6-DNOC									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
17	Mouse (C3H, C57BL/6) 6 M	5 days 1 time/day (GW)	0, 3, 6, 12	HP, OF, OW	Repro	12 M			No effects on sperm parameters or testicular weights at 35 days following cessation of dosing
Quinto et al. 1989 4,6-DNOC									
18	Mouse (DBA and CFLP) 13–20 F	GDs 11–14 1 time/day (GW)	0, 8	DX	Develop	8			
Nehez et al. 1987 4,6-DNOC									
19	Chicken	Once (GO)	2.48–59.45	CS, OP	Ocular		2.48		Cataract formation in 4–5 hours posttreatment; earlier onset of cataracts at higher dose levels
					Other noncancer (metabolic)		2.48		Decreased body temperature; at 4 mg/kg, increased oxygen uptake
Buschke 1947 4,6-DNOC									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
INTERMEDIATE EXPOSURE									
20	Human	14–63 days 1 time/day (C)	0.8–1.42 (average 1.05)	BI, BW, CS	Bd Wt		1.05		Weight loss of 0.45 kg/week
					Cardio	1.05			
					Neuro		1.05		Lethargy, depression
					Other noncancer (metabolic)			1.05	34–77% increase in basal metabolic rate, excessive thirst and perspiration, 40°C body temperature
Ibrahim et al. 1934 4,6-DNOC									
21	Human 2 M, 1 F, 1 NS	4–11 weeks 1 time/day (C)	0.58, 0.75, 1.0, 1.5	BI, BW, CS	Bd Wt		0.75		Decrease in body weight of 0.6 kg/week
					Cardio		0.75		Palpitations
					Immuno		0.75		Urticarial eruptions
					Neuro		0.75		Headache, lassitude
					Other noncancer (metabolic)		0.58		2°F average increase in body temperature
Plotz 1936 4,6-DNOC									
22	Rat (Wistar) 5–10 M	105 days (F)	0, 0.36, 0.81, 1.62, 3.6, 7.6, 18	BW, FI, GN, HP	Bd Wt	7.6 M	18 M		15% depressed body weight gain
Ambrose 1942 Sodium 3,5-DNOC									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
23	Rat (Wistar) 10 M, 10 F	90 days (F)	0, 2.5, 5, 10, 20	BC, BI, BW, CS, FI, HE, HP, LE, OW, UR	Death			20	5/20 deaths at highest dose level
					Cardio	20			
					Gastro	10	20		Histopathologic alterations in salivary glands and fundus
					Hemato	2.5	5		Increases in hemoglobin, hematocrit, and MCH/MCV
					Hepatic	10	20		Increased serum ALT
					Renal	2.5	5		Increased blood urea nitrogen, decreased urinary creatinine
					Endocr		2.5		Decreased thyroid hormones at 2.5 mg/kg; histopathologic adrenal and pancreatic lesions at 20 mg/kg
					Immuno	10		20	Atrophy or under-development of thymus, spleen, lymph nodes; decreased circulating lymphocytes
					Neuro	5	10		Increased relative brain weight (magnitude not specified)
					Repro	10		20	No corpora lutea in ovaries; juvenile uteri; aspermatogenesis
					Other noncancer (metabolic)		2.5		Decreased carbohydrate and increased fat metabolism (magnitude not specified)

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
Den Tonkelaar et al. 1983 **4,6-DNOC**									
24	Rat (white) 20-22 M	77–182 days (F)	0, 1, 2.5, 5, 10, 25	BC, BW, FI, HE, HP, LE, OW	Bd Wt	10 M	25 M		18% decreased body weight, depletion of body fat
					Resp	25 M			
					Cardio	25 M			
					Gastro	25 M			
					Hepatic	25 M			
					Renal	10 M	25 M		Increased blood urea nitrogen
					Ocular	25 M			
					Immuno	10 M	25 M		Hemosiderosis and congestion of the spleen
					Repro	25 M			
Spencer et al. 1948 **4,6-DNOC**									
25	Rat (white) NS F	6 months 1 time/day (G)	0, 2, 5, 10	BI, BW, CS, GN	Bd Wt	5 F	10 F		10–18% reduced body weight gain
					Hepatic	5 F	10 F		Fatty degeneration
Vashakidze 1967 **4,6-DNOC**									
26	Rat (white) 6 M	3 weeks (F)	1.25, 5, 20	BW, FI, GN, HE, HP, LE, OW	Hemato	20 M			
					Hepatic	20 M			
					Renal	20 M			
					Endocr	20 M			
					Immuno	20 M			
					Repro	20 M			
Vos et al. 1983 **4,6-DNOC**									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
27	Mouse (white) 6 NS	32 days 1 time/day (GW)	3	BW, CS, LE	Death			3	100% mortality
Arustamyan 1972 4,6-DNOC									

[a]The number corresponds to entries in Figure 2-3.
[b]Used to derive both an acute and an intermediate MRL of 0.004 mg/kg/day; dose divided by an uncertainty factor of 100 (10 for use of a LOAEL and 10 for human variability).

ALT = alanine transaminase; BC = serum (blood) chemistry; BI = biochemical changes; Bd Wt or BW = body weight; (C) = capsule; Cardio = cardiovascular; CS = clinical signs; Develop = developmental; DNOC = dinitrocresol; DX = developmental; Endocr = endocrine; (F) = feed; F = female(s); FI = food intake; (G) = gavage; Gastro = gastrointestinal; GD = gestation day; GN = gross necropsy; (GO) = gavage in oil vehicle; (GW) = gavage in water vehicle; HE = hematology; Hemato = hematological; HP = histopathology; Immuno = immunological; LD_{50} = lethal dose, 50% kill; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; MRL = minimal risk level; Neuro = neurological; NOAEL = no-observed- adverse-effect level; NS = not specified; OF = organ function; OP = ophthalmology; OW = organ weight; Resp = respiratory; Repro = reproductive; TWA = time-weighted average; UR = urinalysis

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

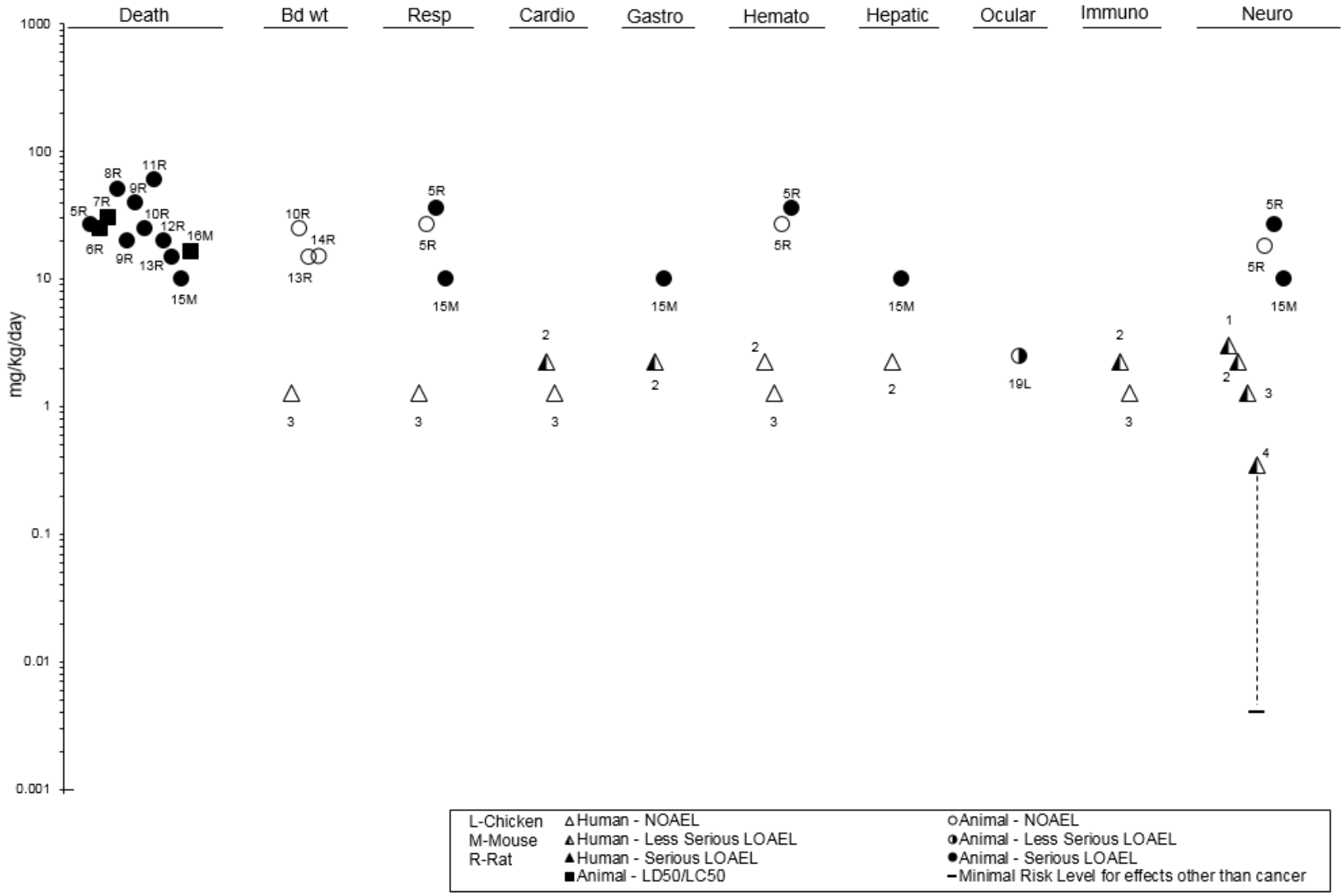


Figure 2-3. Levels of Significant Exposure to Dinitrocresols – Oral
Acute (≤14 days)

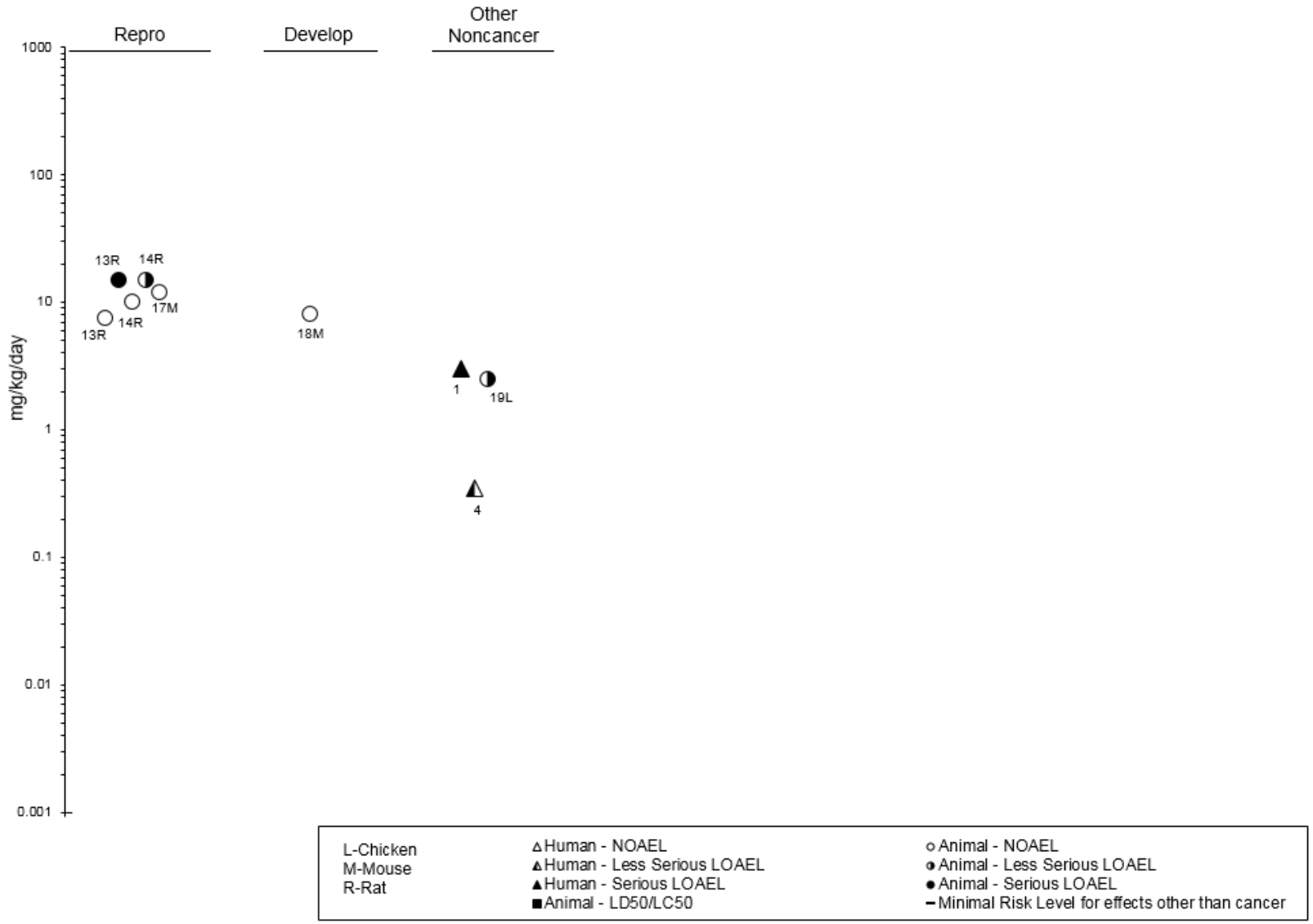


Figure 2-3. Levels of Significant Exposure to Dinitrocresols – Oral
Intermediate (15-364 days)

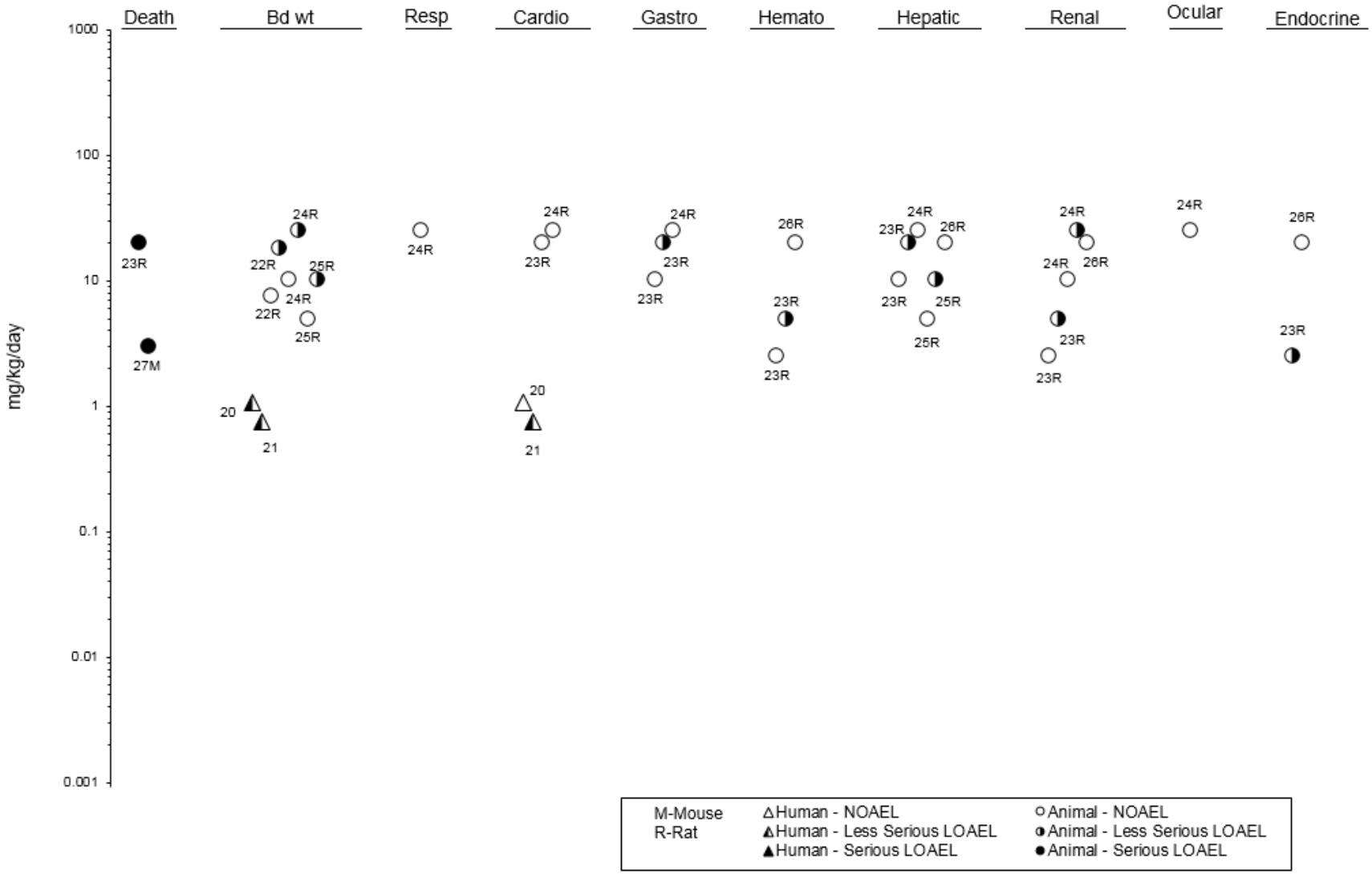


Figure 2-3. Levels of Significant Exposure to Dinitrocresols – Oral
Intermediate (15-364 days)

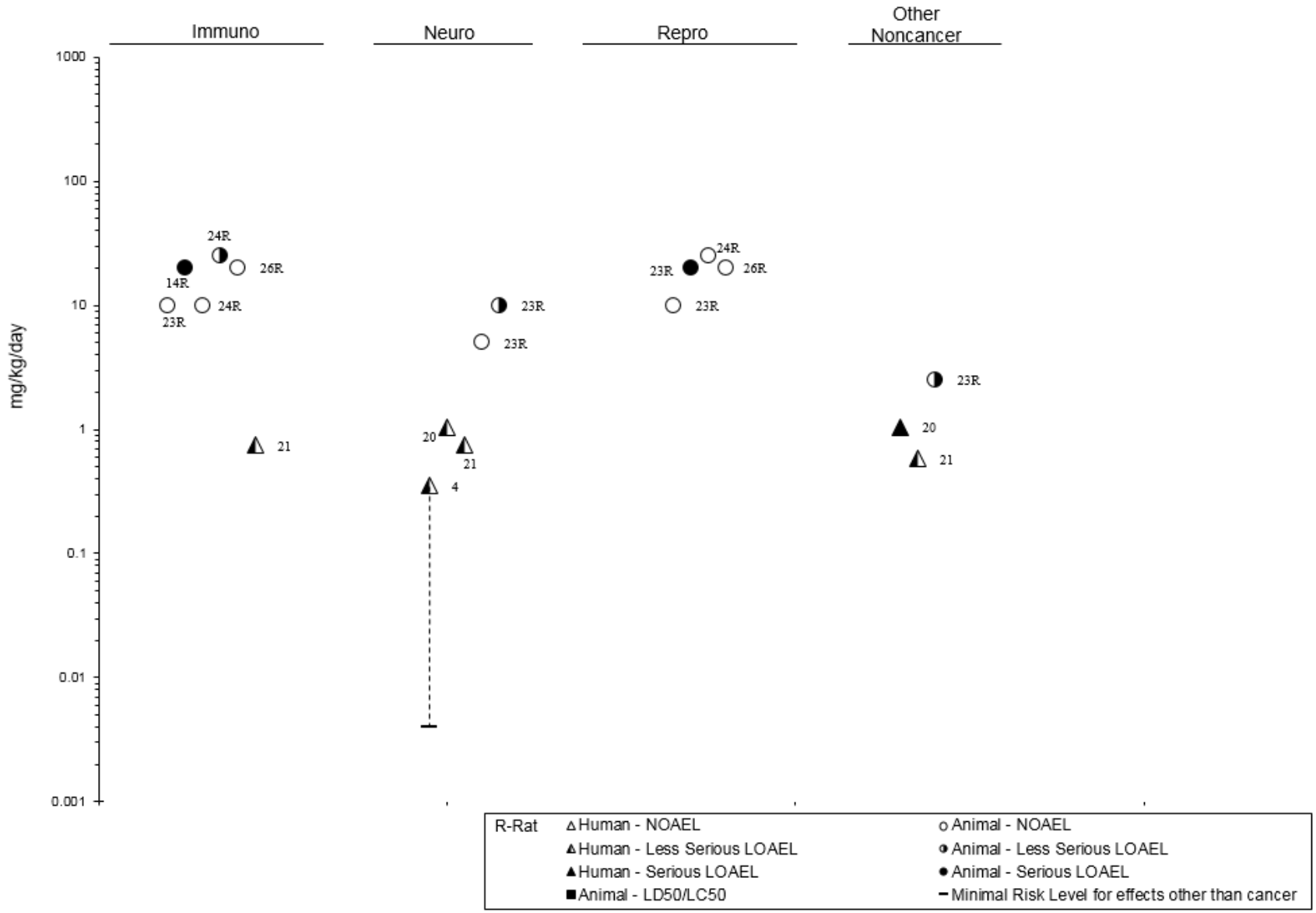


Table 2-3. Levels of Significant Exposure to Dinitrocresols – Dermal

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effect
ACUTE EXPOSURE								
Human 443–492	Once	0.5 or 1%	CS	Dermal	1%			No evidence of dermal irritation
Lisi et al. 1987								
Rat (NS); number and sex NS	Once	NS	LE	Death			200 mg/kg	LD_{50}
Ben-Dyke et al. 1970; Jones et al. 1968 4,6-DNOC								
Mouse (white); number and sex NS	Once	NS	CS, GN, LE	Death			186.7 mg/kg	LD_{50}
Arustamyan 1972 4,6-DNOC								
Rabbit (NS); number and sex NS	Once	NS	LE	Death			1,000 mg/kg	LD_{50}
Burkatskaya 1965b 4,6-DNOC								
Rabbit (NS); number and sex NS	Once	NS	LE	Death			1,671 mg/kg	LD_{50}
ERM Program Management Co. 1992 4,6-DNOC								
Rabbit (NS); number and sex NS	Once	NS	LE	Death			1,732 mg/kg	LD_{50}
ERM Program Management Co. 1992 2,6-DNPC								
Rabbit (white); number and sex NS	Up to 7 days, 1 time/day	3 or 4%	CS, LE	Death			3%	Death of unspecified number of animals
				Dermal		3%		Slight skin irritation
Spencer et al. 1948 4,6-DNOC								

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

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effect
Guinea pig 5 (sex NS)	Once	0, 100, 200, 300, 400, 500 mg/kg	LE	Death			300 mg/kg	Deaths were 0/5, 0/5, 1/5, 3/5, and 5/5 at 100, 200, 300, 400, and 500 mg/kg, respectively
Spencer et al. 1948 **4,6-DNOC**								
INTERMEDIATE EXPOSURE								
Human	30 days, 1 time/day			Dermal	1.8%			
Ambrose 1942 **Sodium 3,5-DNOC**								
Rat	30 days, 1 time/day		BW	Bd Wt	1.8%			
				Dermal	1.8%			No signs of dermal irritation
Ambrose 1942 **Sodium 3,5-DNOC**								
11 Rabbit	30 days, 1 time/day	0, 1.8%	BW, CS	Bd Wt	1.8%			
				Dermal	1.8%			No signs of dermal irritation
Ambrose 1942 **Sodium 3,5-DNOC**								
12 Rabbit	4 weeks, 5 days/week, 1 time/day	5%	CS, LE	Dermal		5%		Slight skin irritation
Spencer et al. 1948 **4,6-DNOC**								

Bd Wt or BW = body weight; CS = clinical signs; DNOC = dinitrocresol; DNPC = dinitro-*p*-cresol; GN = gross necropsy; LD_{50} = lethal dose, 50% kill; LE = lethality; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; NS = not specified

2.2 DEATH

Information regarding death of humans is limited to case reports of suspected inhalation, oral, and/or dermal exposure to DNOC. A spray operator who inhaled a dense DNOC mist for an unspecified time died after lapsing into a coma while being treated in a hospital (van Noort et al. 1960). In a survey of 133 spray operators who applied DNOC to cereal crops 5 days/week for 6 weeks, 4 developed signs of acute poisoning (not otherwise specified), one of whom died (Bidstrup et al. 1952). The amount or concentration of inhaled DNOC was not reported in the survey. Another spray operator was found dead after drinking an unknown amount of DNOC in water from a contaminated fresh water tank (Bidstrup and Payne 1951). The worker had also been exposed to DNOC aerosols for 3 weeks prior to death. A patient died <14 hours after admission to a hospital and <48 hours after the onset of signs and symptoms of DNOC toxicity (Steer 1951). The patient had sprayed DNOC for an unspecified, but apparently acute, time period. Although the yellow staining of the skin suggests dermal exposure, the patient may also have inhaled DNOC aerosols. A 4-year-old boy died 3.5 hours after 12,500 mg of DNOC was accidentally applied as an ointment to a skin rash (Buchinskii 1974). Because DNOC was applied to the rash rather than intact healthy skin, considerable amounts of DNOC were rapidly absorbed. No supporting data from human studies regarding dermal exposure to DNOC were located to suggest whether this dose would have been fatal if applied to intact skin. Two of three employees died after spraying 2% DNOC for 2 consecutive days (Buzzo and Guatelli 1949). Although inhalation may have contributed to total exposure, the yellow staining of the skin and the fact that no appropriate precautions were taken to minimize dermal exposure suggest that exposure was mainly dermal. One industrial and five agricultural workers, who were thought to be dermally exposed to unknown doses of DNOC for 2–8 weeks, died after brief periods of illnesses related to DNOC exposure (Bidstrup and Payne 1951). Because of the intense heat and discomfort, protective clothing was often discarded. This suggests that most of the DNOC was absorbed dermally, although limited amounts of DNOC aerosols may have also been inhaled.

Deaths were reported in cats exposed (head only) to DNOC liquid or solid aerosols for 4 hours at 40 and/or 100 mg/m^3, and in other cats exposed to DNOC liquid aerosol 4 hours/day for 1 month at 2 mg/m^3 (Burkatskaya 1965a). Mortality was reported following single or repeated oral dosing of rats or mice in the range of 10–50 mg/kg (Ambrose 1942; Arustamyan 1972; Ben-Dyke et al. 1970; Den Tonkelaar et al. 1983; Dow Chemical Co. 1940, 1950; Jones et al. 1968; King and Harvey 1953a; Spencer et al. 1948; Takahashi et al. 2004). Treatment of mice with 3 mg/kg/day DNOC resulted in 100% mortality within 8–32 days when the vehicle was water and within 9–38 days when the vehicle was oil (Arustamyan 1972). Environmental temperatures influenced the mortality rate among rats

orally dosed with DNOC (King and Harvey 1953a). Six of 12 rats died after receiving 20 mg/kg at 37–40ºC, while only 2 of 12 rats died after receiving twice the dose (40 mg/kg) at almost half the temperature (20–22ºC). Therefore, increased environmental temperatures increased the toxicity of DNOC in rats. Because DNOC uncouples oxidative phosphorylation, an increase in heat production and body temperature occurs. Elevated environmental temperatures lower the rate of heat dissipation and further exacerbate the signs of DNOC toxicity, which may become fatal. In attempts to produce cataracts in ducks and chickens, a diet of 2,500 ppm DNOC resulted in 56% mortality among a group of ducklings (Spencer et al. 1948), and a dose of 4.95 mg/kg resulted in death of an unspecified number of chickens (Buschke 1947).

Reported acute dermal LD_{50} values for dinitrocresols are 200–600 mg/kg for rats (Ben-Dyke et al. 1970; Jones et al. 1968), 186.7 mg/kg for mice (Arustamyan 1972), and 1,000–1,732 mg/kg for rabbits (Burkatskaya 1965b; ERM Program Management Co. 1992). Death was noted in 1/5, 3/5, and 5/5 guinea pigs administered DNOC at 300, 400, and 500 mg/kg, respectively to a shaved area of the abdomen (Spencer et al. 1948). An unspecified number of rabbits died after seven applications of 3% solution of DNOC in 95% alcohol to the ear and shaven abdomen (Spencer et al. 1948).

2.3 BODY WEIGHT

DNOC was once used to treat obesity, but this practice has been discontinued due to recognized toxic effects. Body weight was not affected in humans who ingested 0.92–1.27 mg/kg/day for 5–7 days (Harvey et al. 1951). However, a patient's weight was reduced by 15 kg after ingesting an unknown amount of DNOC for 3 years (Quick 1937). The average weight lost by 15 patients was 0.45 kg/week after they had ingested an average of 1.05 mg/kg/day DNOC for 14–63 days (Ibrahim et al. 1934). About 9.1 kg was the maximum weight loss during a 2-month period of DNOC therapy. DNOC did not cause a rise in blood glucose nor did it cause the appearance of ketones in the urine. A decrease in body weight was also observed in only one of four patients who received 0.75 mg/kg/day DNOC for 6 weeks for weight reduction purposes (Plotz 1936).

DNOC also causes decreases in body weight gain in animals. Significant decreases in body weight gain were observed in rats that received 10 or 25 mg/kg/day for 10 days, but the decrease amounted to only 2 and 5%, respectively (King and Harvey 1953a). Growth was inhibited by 15% in rats fed a diet providing 18 mg/kg/day DNOC as the sodium salt for 105 days (Ambrose 1942), by 18% in rats fed a diet providing 25 mg/kg/day DNOC for 77–182 days (Spencer et al. 1948), and by 10–18% in rats given

10 mg/kg/day DNOC by gavage for 6 months (Vashakidze 1967). Despite the decrease in growth rate, food consumption was increased in one study (Ambrose 1942). Depletion of adipose tissue was also observed at the end of the 182-day study in rats that received 25 mg/kg/day (Spencer et al. 1948). Ten daily doses of 5 mg/kg/day did not appear to alter the growth rate of the animals. No change in body weight gain was observed in rats fed diets providing doses of 15 mg/kg/day for 18 weeks (Parker et al. 1951) or other rats administered DNOC by gavage for 5 days at up to 15 mg/kg/day and observed for up to 14 days posttreatment (Takahashi et al. 2004, 2006). No changes in body weight were observed after 1.8% DNOC as the sodium salt was applied daily to the depilated dorsal surface of 10 rats or 6 rabbits for 30 days (Ambrose 1942).

2.4 RESPIRATORY

Respiratory effects have been observed in both humans and animals following exposure to DNOC. In most human cases, exposure likely involved inhalation and dermal exposure. Effects such as dyspnea, elevated respiration rate, and shallow breathing have been observed in individuals exposed to DNOC during production, mixing, and/or spray operations (Bidstrup and Payne 1951; Buzzo and Guatelli 1949; Hunter 1950; Pollard and Filbee 1951; Steer 1951; van Noort et al. 1960). Two hours after 12,500 mg of DNOC in a fatty ointment was applied to a skin rash, an increase in respiratory rate and moist rales were observed in a young boy who subsequently died (Buchinskii 1974). Autopsy and histological examination revealed severe capillary hyperemia in the lungs and pulmonary edema. Congestion, edema, and hemorrhage were observed in an employee who had accidentally ingested an unknown amount of DNOC and subsequently died (Bidstrup and Payne 1951).

Respiratory rates were increased in rats exposed to 100 mg/m^3 DNOC for 4 hours and remained elevated 20 hours following cessation of exposure (King and Harvey 1953a). Dyspnea, sneezing, and/or nasal secretions were observed in cats exposed to liquid aerosol of DNOC at 36 mg/m^3 or as a dust at 40 mg/m^3 for 4 hours (Burkatskaya 1965a). Signs of respiratory distress (dyspnea and asphyxial convulsions) were observed prior to death in rats given single oral doses of 36–90 mg/kg DNOC (Ambrose 1942) as the sodium salt. Mice that received single oral doses in the range of 10–35 mg/kg DNOC became dyspneic within 60–80 minutes (Arustamyan 1972). Necropsy revealed bloody fluid in the thoracic cavity of some mice. A single oral dose of 25 mg/kg DNOC caused accelerated heavy breathing and dyspnea in cats within the first hour (Burkatskaya 1965b). These signs persisted for 4 days after the exposure. No histopathological lesions were observed in lungs from rats fed diets providing daily doses in the range of l–25 mg/kg/day DNOC for 77–182 days (Spencer et al. 1948).

2.5 CARDIOVASCULAR

Elevated pulse rates have been observed in humans exposed to DNOC by inhalation and/or dermal routes. A male factory worker who had been employed for 17 days pouring DNOC powder had a pulse rate of 130 beats per minute; the employee also reported that he had periodically inhaled DNOC aerosols (Hunter 1950). A pulse rate of 100 beats per minute, a blood pressure of 155/70 mm Hg, and a normal electrocardiogram were found for an employee who was involved with mixing DNOC, refilling sprayer tanks with DNOC, and occasionally spraying DNOC for 5 weeks (Pollard and Filbee 1951). Within 2 hours after 12,500 mg of DNOC in a fatty ointment was applied to a skin rash in a young boy who subsequently died, the pulse rate was elevated and thready, and heart sounds were muffled (Buchinskii 1974). Histological examination at autopsy showed severe hemorrhage and capillary hyperemia in the myocardium. Because DNOC was applied to the rash rather than intact healthy skin, absorption of DNOC was facilitated. The amount of DNOC applied to intact skin required to produce these effects is not known. Elevated pulse rate and subsequent cardiac fibrillation were observed in a spray operator exposed to DNOC for an unspecified, but apparently short, time period (Steer 1951). The pulse was also elevated in three employees who were exposed primarily by the dermal route to 10% DNOC for 2 consecutive days (Buzzo and Guatelli 1949). One industrial and five agricultural workers, who were likely exposed via inhalation and/or dermal routes to unknown doses of DNOC for 2–8 weeks, had elevated pulse rates and cyanosis at the hospital; all six workers died (Bidstrup and Payne 1951). Increased pulse rate and heart palpitations were also observed in employees who sprayed DNOC for 14 days to 4 months (van Noort et al. 1960).

Cardiovascular effects appear to be secondary to cellular anoxia, but do not appear to be consistent signs of DNOC exposure in humans. However, elevated pulse rates, tachycardia, and palpitations were observed in several patients. Although the basal metabolic rate was increased, the cardiovascular system was not affected after volunteers ingested 3 mg/kg/day DNOC for 4 days (Dodds and Robertson 1933) or 0.92–1.27 mg/kg/day for 5–7 days (Harvey et al. 1951). Changes in blood pressure and pulse rate were regarded as not significant. A pulse rate of 90 beats per minute (insignificant increase over the 72-beat norm) was observed in a girl who ingested a time-weighted average (TWA) dose of 2.27 mg/kg/day DNOC for 11 days for purposes of weight reduction (Gordon and Wallfield 1935). Edema of the fingers and hands was also observed, possibly suggestive of circulatory dysfunction. No changes in pulse or blood pressure were observed in two humans who received oral DNOC doses in the range of 0.5–1.0 mg/kg/day for 40–48 days (Dodds

and Robertson 1933). The cardiovascular system in 15 patients was not affected after they had ingested an average of 1.05 mg/kg/day DNOC for 14–63 days (Ibrahim et al. 1934). A patient who received 0.75 mg/kg/day DNOC orally for 8 weeks, followed by 1.0 mg/kg/day DNOC, experienced marked palpitations (Plotz 1936). Tachycardia was periodically observed in a young woman who had ingested one capsule per day of an unspecified dose of DNOC for the first 6 months for weight reduction therapy, but had periodically ingested two capsules per day for an unspecified period (Quick 1937). The patient maintained this regimen for about 3 years.

Limited information was located regarding cardiovascular effects in laboratory animals exposed to DNOC. In intermediate-duration feeding studies, absolute heart weights were significantly ($p<0.05$) decreased in rats given diets providing 210 mg/kg/day (Den Tonkelaar et al. 1983; Spencer et al. 1948). Relative heart weight was increased (Den Tonkelaar et al. 1983). However, no histopathological lesions were observed in heart tissue in either study. The toxicological significance of the heart weight changes is not clear.

2.6 GASTROINTESTINAL

Gastrointestinal effects such as nausea and vomiting have been reported among individuals exposed to DNOC by inhalation, oral, and/or dermal routes (Buchinskii 1974; Gordon and Wallfield 1935; van Noort et al. 1960). In cases that culminated in death, lesions in gastric and or intestinal mucosa were noted at autopsy (Bidstrup and Payne 1951; Buchinskii 1974).

Vomiting was reported to occur within 60–80 minutes in mice administered 10–35 mg/kg DNOC by gavage (Arustamyan 1972). Necropsy examination revealed lesions in gastric mucosa. The small intestine in similarly treated mice also showed catarrhal inflammation over its entire length. No histopathological lesions were observed in the stomach tissue from rats fed diets providing daily doses in the range of 1–25 mg/kg/day DNOC for 77–182 days; the presence of food may have prevented the irritating effects of DNOC in the stomach (Spencer et al. 1948). A reduced number of hydrochloric acid releasing cells in the fundus of the stomach and smaller acini and no granules in the salivary glands were observed in rats receiving DNOC from the diet for 90 days at 20 mg/kg/day (Den Tonkelaar et al. 1983).

2.7 HEMATOLOGICAL

Unspecified hemorrhagic irregularities and irregular bleeding were observed in some field workers exposed to DNOC for about 8 hours (Varnai and Kote 1969). An increased red bone marrow at distal

ends of the femur and failure of blood to clot were observed in a spray operator exposed to DNOC for an unspecified, but apparently short, time period (Steer 1951). At autopsy, red bone marrow (further described as anoxemic) was found throughout the femoral shaft of an agricultural worker who died after being exposed to unknown levels of DNOC for 2–8 weeks (Bidstrup and Payne 1951). No abnormal hematological parameters were observed in an employee involved with mixing DNOC, refilling sprayer tanks with DNOC, and occasionally spraying DNOC for 5 weeks (Pollard and Filbee 1951). Reticulocyte numbers were unchanged and Heinz bodies were not observed in volunteers who ingested 0.92–1.27 mg/kg/day for 5–7 days (Harvey et al. 1951). Hematological parameters were also within normal limits in a girl who ingested a TWA dose of 2.27 mg/kg/day DNOC for 11 days for treatment of obesity (Gordon and Wallfield 1935).

In the only study located regarding hematological effects in animals after inhalation exposure to DNOC, significantly decreased hemoglobin content and red blood cell counts were observed in cats exposed to an aerosol of DNOC dust at 36 mg/m^3 or DNOC solution (mist) at 40 mg/m^3 for 4 hours (Burkatskaya 1965a). In addition, accelerated erythrocyte sedimentation rates and increased leukocyte counts were found in the cats exposed to the dust. Accelerated erythrocyte sedimentation rate, decreased hemoglobin and red blood cells, increased leukocytes, and alterations in differential white blood cell count were observed when the cats were exposed to DNOC mist at 2 mg/m^3 for 1 month; these effects (with the exception of differential white blood cell count) were also observed in cats exposed to DNOC dust at 0.2 mg/m^3 for 2 or 3 months. In the latter experiment, the hematological changes occurred within 1–2 weeks of exposure to the aerosol and were not aggravated with subsequent exposure to DNOC.

Increases in hemoglobin, hematocrit, and the ratio of mean corpuscular volume to mean corpuscular hemoglobin (MCV/MCH) were reported in rats given 5, 10, or 20 mg/kg/day DNOC orally for 90 days; the highest dose also resulted in increased erythrocyte count and decreased total leukocyte and lymphocyte counts (Den Tonkelaar et al. 1983). Hemosiderosis and congestion of the spleen were observed in rats fed diets providing 25 mg/kg/day of DNOC for 77–182 days; however, there were no differences in hematological parameters such as erythrocyte count, hemoglobin concentration, total leucocyte count, differential count, or bone marrow counts, and no evidence of histopathologic lesions in bone marrow (Spencer et al. 1948). Total leukocyte and differential leukocyte counts were not affected in rats given daily doses in the range of 1.25–20 mg/kg/day for 3 weeks (Vos et al. 1983). Cyanosis was observed in rats administered DNOC (as the sodium salt) once by gavage at doses in the range of 36–90 mg/kg (Ambrose 1942). This condition is most probably related to the dyspnea and asphyxial convulsions observed in the affected rats.

2.8 MUSCULOSKELETAL

Limited information was located regarding musculoskeletal effects in humans or animals exposed to DNOC. Only one of four employees complained of pain in the calf muscle after being exposed to a dense DNOC mist for an acute duration (van Noort et al. 1960). Shortly before death, muscular rigidity and loss of motor function were observed in two individuals who had sprayed 10% DNOC for 2 consecutive days (Buzzo and Guatelli 1949). Continuous involuntary contraction of leg muscles and pain in calf muscles were observed in a spray operator exposed to a dense DNOC mist for an acute period (van Noort et al. 1960). Exposure to an aerosol of DNOC in solution at 40 mg/m^3 for 4 hours resulted in loss of muscle tone in cats, which may have been representative of a neurological effect (Burkatskaya 1965a).

2.9 HEPATIC

DNOC is a yellow compound that stains human (Hunter 1950) and animal (Ambrose 1942) skin on contact. Absorption of DNOC by any route and subsequent distribution to tissues resulted in a characteristic yellow staining of visceral organs and tissues including the conjunctiva and sclera of the eye (Ibrahim et al. 1934; Pollard and Filbee 1957), blood serum, skeletal tissues, and urine (Ambrose 1942). The yellow staining of the skin and sclera of patients exposed to DNOC prompted physicians to test for liver effects. Results for the icteric index and the Van den Bergh tests have been consistently negative (Dodds and Robertson 1933; Gordon and Wallfield 1935; Plotz 1936), indicating that the yellow color was not due to liver damage.

However, there is some evidence of DNOC-induced hepatotoxicity. Congestion of the liver was observed in an agricultural worker who had sprayed DNOC for 3 weeks and died after accidentally ingesting an unknown amount of DNOC (Bidstrup and Payne 1951). Severe capillary hyperemia was observed in the liver of a young boy who died after 12,500 mg of DNOC was accidentally applied to a skin rash (Buchinskii 1974). Unspecified liver damage and enlarged livers were observed in several agricultural workers who were exposed to DNOC for 8 hours (Varnai and Kote 1969). Congested livers were generally observed in one industrial and five agricultural workers, who died after being exposed to unknown levels of DNOC for 2–8 weeks (Bidstrup and Payne 1951). No evidence of liver damage was observed in a girl who ingested a TWA dose of 2.27 mg/kg/day DNOC for 11 days for treatment of obesity (Gordon and Wallfield 1935).

Results from two animal studies indicated that DNOC may cause hepatic pathology; data from several other studies demonstrated that DNOC may cause changes in liver weight without evidence of histopathology. Enlarged dark brown livers with petechial hemorrhages and necrotic foci were observed in mice that received single gavage doses in the range of 10–35 mg/kg DNOC (Arustamyan 1972). Fatty degeneration of unspecified parenchymatous organs was observed in rats given daily gavage doses of 10 mg/kg/day DNOC for 6 months (Vashakidze 1967). In intermediate-duration feeding studies, no histological evidence of liver pathology was found in rats fed diets providing 25 mg/kg/day DNOC (Den Tonkelaar et al. 1983; Spencer et al. 1948; Vos et al. 1983). The method of administration (i.e., gavage versus dietary) may partly account for the different results for hepatic pathology in the intermediate-duration gavage study and the intermediate-duration feeding studies. Absolute liver weights were significantly decreased in rats receiving DNOC from the diet at 10–20 mg/kg/day (Den Tonkelaar et al. 1983; Spencer et al. 1948), and relative liver weights were increased in rats receiving 5–20 mg/kg/day (Den Tonkelaar et al. 1983; Vos et al. 1983). Two rats had greatly increased levels of serum alanine aminotransferase (ALT) at 20 mg/kg/day, and liver activity of glucose-6-phosphatase dehydrogenase (G6PDH) was decreased at 5 mg/kg/day (Den Tonkelaar et al. 1983). As DNOC is an uncoupler of oxidative phosphorylation (see Section 2.21), reduced G6PDH activity can be explained by a decrease in adenosine triphosphate (ATP) formation and the subsequent formation of glucose-6-phosphate during oxidative phosphorylation.

2.10 RENAL

Available information regarding DNOC-induced renal effects is limited. An elevated blood urea nitrogen (BUN) level was observed in an individual who mixed DNOC, refilled sprayer tanks, and occasionally sprayed DNOC for 5 weeks (Pollard and Filbee 1951). Cloudy swelling of the kidney was observed at autopsy in a DNOC spray operator who died after accidentally ingesting an unknown amount of DNOC from a water tank (Bidstrup and Payne 1951). Severe capillary hyperemia was observed in the kidney of a young boy who died after 12,500 mg of DNOC in an ointment was accidentally applied to a skin rash (Buchinskii 1974). Unspecified kidney damage was observed in several agricultural workers exposed to DNOC for 8 hours (Varnai and Kote 1969). Congested kidneys and cloudy swelling of the renal tubules were generally observed in one industrial and five agricultural workers, who died after being exposed to unknown levels of DNOC for 2–8 weeks (Bidstrup and Payne 1951).

In intermediate-duration feeding studies of rats, absolute kidney weights were decreased (Den Tonkelaar et al. 1983; Spencer et al. 1948) and relative kidney weights were increased at doses of 10 or

20 mg/kg/day, respectively; no histological evidence of renal pathology was found at doses ≤25 mg/kg/day (Den Tonkelaar et al. 1983; Spencer et al. 1948; Vos et al. 1983). BUN was increased in rats fed diets providing daily doses of 25 mg/kg/day for 77–182 days (Spencer et al. 1948). BUN was also increased at doses of 5, 10, and 20 mg/kg/day in a 90-day oral study; urinalysis revealed that urinary protein was decreased at 10 and 20 mg/kg/day, urinary glucose increased at 20 mg/kg/day, and urinary creatinine decreased at 5, 10, and 20 mg/kg/day (Den Tonkelaar et al. 1983). The elevated urine glucose was considered due to elevated blood glucose and the inhibitory effect of DNOC on oxidative phosphorylation and subsequent ATP-dependent active transport in the proximal tubules of the kidney.

2.11 DERMAL

As noted in Section 2.9, DNOC is a yellow compound that stains human (Hunter 1950; Pollard and Filbee 1951; van Noort et al. 1960) and animal (Ambrose 1942) skin on contact. Whereas the yellow staining of the skin may be unsightly, such cosmetic effects are not regarded as adverse. However, oral doses of DNOC may cause urticarial eruptions (allergic reaction) in humans. See Section 2.14 (Immunological) for discussion of urticarial eruptions in humans following oral exposure to DNOC.

Dermal exposure to DNOC does not appear to cause local irritation of the skin of humans. DNOC was not a dermal irritant ≤48 and 72 hours after concentrations of 0.5 or 1.0% were diluted in water and applied to the upper back of agricultural workers, former agricultural workers, and other humans (Lisi et al. 1987). No signs of local irritation or evidence of systemic toxicity were observed after 1.8% DNOC as the sodium salt was applied daily to the shaved armpits and to the anterior cubital surface of each arm of two humans for 30 days (Ambrose 1942).

DNOC is generally not irritating to the skin of animals. No signs of local irritation or evidence of systemic toxicity were observed after 1.8% DNOC as the sodium salt was applied daily to the depilated dorsal surface of 10 rats or 6 rabbits for 30 days (Ambrose 1942). However, slight skin irritation was observed only on the abdomen after DNOC was applied to both the abdomen and the ears of rabbits daily, for 1–7 days or for 5 days/week for 4 weeks (Spencer et al. 1948).

2.12 OCULAR

Despite the occurrence of a yellow pigmentation of the conjunctiva in humans who had ingested 3 mg/kg/day DNOC for 4 days (Dodds and Robertson 1933) or 0.92–1.27 mg/kg/day for 5–7 days (Harvey et al. 1951), no adverse ocular effects were observed. A similar observation was made for a

DNOC spray operator who had accidentally ingested an unknown dose of DNOC (Bidstrup and Payne 1951). A yellow tinge to the sclera was also observed in a 14-year-old girl who ingested a TWA dose of 2.27 mg/kg/day DNOC for 11 days for the treatment of obesity (Gordon and Wallfield 1935). A yellow pigmentation of the conjunctiva occurred in all 15 patients who had ingested an average of 1.05 mg/kg/day DNOC for 14–63 days (Ibrahim et al. 1934). A yellow tinge of the sclera was also observed in two of four patients who received 0.75 mg/kg/day DNOC for 6–11 weeks (Plotz 1936). Although the yellow staining of the skin and sclera may be unsightly, such cosmetic effects are not regarded as adverse. An 8-hour dermal exposure to DNOC was reported to have caused unspecified visual disturbances in several agricultural workers (Varnai and Kote 1969).

DNOC did not cause any signs of ocular irritation ≤24 hours after 5 drops of 0.9% DNOC as the sodium salt was instilled into the conjunctival sac of six rabbits (Ambrose 1942). Blepharospasm and excessive lacrimation were observed in cats exposed to 36 or 60 mg/m^3 DNOC dust for 4 hours (Burkatskaya 1965a). Since these effects were not reported in cats similarly exposed to a mist of DNOC in solution, they were probably due to a direct irritating effect of the dust particles on the eyes, rather than to DNOC.

Ingestion of an unspecified dose of DNOC for 3 years was associated with a pearly swollen cataract of the left eye of a woman (Quick 1937). The right eye, which had punctate central lenticular opacity, eventually became blind 1 month after the cataract was diagnosed. Because dinitrophenolic compounds have been known to be cataractogenic in humans, attempts have been made to a find a suitable animal model to study this phenomenon (Spencer et al. 1948). Cornea1 opacity and cataracts were not observed in rats fed diets providing doses in the range of l–25 mg/kg/day for 77–182 days. However, cataract formation was observed in ducklings fed a diet of 1,200 ppm DNOC for l–2 days (doses in mg/kg/day were not reported). Administration of a single oral dose of DNOC in the range of 2.48–59.45 mg/kg to chickens produced cataracts within l–5 hours (Buschke 1947). The cataract formation was considered related to interference with oxidative phosphorylation.

2.13 ENDOCRINE

Information regarding DNOC-induced endocrine effects is limited. Although DNOC has been described to induce a syndrome similar to hyperthyroidism in humans (Dodds and Robertson 1933), blood triiodothyronine (T3) and thyroxin (T4) levels were decreased at all levels in rats given 2.5–20 mg/kg/day DNOC for 90 days (Den Tonkelaar et al. 1983). Histological examination revealed inactive thyroids. Absolute thyroid weights were decreased at 20 mg/kg/day, while relative thyroid weights were increased

at the same dose. Absolute weights were decreased for the pituitary gland at 10 and 20 mg/kg/day and the adrenal gland at 20 mg/kg/day, while the relative weights for both glands were increased at the same dose. Histological examination revealed fewer acidophilic cells in the pituitary gland and vacuolization of acini, no clear zona fasciculata, and swollen medullary cells in the adrenals. Atrophy of the Isle of Langerhans cells in the pancreas was also observed. Many of these effects were attributed to the ability of DNOC to uncouple oxidative phosphorylation, leading to a deficit in ATP. Changes in pituitary, thyroid, and adrenal weight and histology were not observed in rats given daily doses of DNOC in the range of 1.25–20 mg/kg/day for 3 weeks (Vos et al. 1983).

2.14 IMMUNOLOGICAL

Urticaria (hives) were reported in one female following ingestion of a TWA DNOC dose of 2.27 mg/kg/day for 11 days for treatment of obesity (Gordon and Wallfield 1935). Maculopapular urticarial eruptions, slightly reddish in color, involving both deltoids, the upper anterior chest, and both upper axillae were also observed in a female patient who received a TWA dose of 0.75 mg/kg/day DNOC for 11 weeks for weight reduction (Plotz 1936). DNOC did not cause allergic reactions ≤48 and 72 hours after concentrations of 0.5 or 1.0% were diluted in water and applied to the upper back of agricultural workers, former agricultural workers, and other human subjects (Lisi et al. 1987). However, a petechial rash was observed on the right shoulder of an individual engaged in cleaning the jets of spray booms of aircraft spraying a 10% solution of DNOC in oil (Stott 1956).

Data regarding immunological effects in animals are conflicting. Decreased absolute thymus weight was observed at 10 and 20 mg/kg/day and decreased relative thymus weight was noted at 20 mg/kg/day in rats given DNOC for 90 days (Den Tonkelaar et al. 1983). The relative weight of the spleen was slightly increased at 20 mg/kg/day, while the absolute weight was decreased at 20 mg/kg/day. Upon histological examination, the lymph nodes were underdeveloped, the thymus was atrophied, and the spleen had small follicles at 20 mg/kg/day. Changes in thymus, spleen, and mesenteric and popliteal lymph node weight and histology were not observed in rats given daily doses in the range of 1.25–20 mg/kg/day DNOC for 3 weeks (Vos et al. 1983). When IgM and IgG were further analyzed and quantified, DNOC had no effect on these immunoglobulins.

2.15 NEUROLOGICAL

Although data are limited, depression and lethargy appear to be common neurological signs observed in both humans and animals exposed to DNOC. These effects are most probably related to uncoupling of oxidative phosphorylation.

A spray operator who had inhaled a dense DNOC mist for an acute duration developed seizures and went into a coma prior to death (van Noort et al. 1960). An employee who was involved with mixing DNOC, refilling sprayer tanks with DNOC, and occasionally spraying DNOC for 5 weeks complained of headache and lassitude prior to hospital admission (Pollard and Filbee 1951). No tremors or exophthalmos were observed in a male factory worker who had been employed for 17 days pouring DNOC powder (Hunter 1950). Neurological effects such as mental depression and headaches were observed in two volunteers given 3 mg/kg/day DNOC orally for 4 days (Dodds and Robertson 1933) and in two of five volunteers given 0.92 and 1.27 mg/kg/day orally for 7 and 5 days, respectively (Harvey et al. 1951). Hemorrhage of the pia mater was observed in a DNOC spray operator who had accidentally ingested an unknown amount of DNOC and subsequently died (Bidstrup and Payne 1951). Prior to death, no neurological signs were reported for this worker. An overweight man who initially received two doses of 0.75 mg/kg/day DNOC for purposes of weight reduction complained of feeling dizzy (Plotz 1936). Following a drug withdrawal period of 2 weeks and a subsequent dose of 0.35 mg/kg/day DNOC, the patient complained of fatigue on the 7th day. Drowsiness, headaches, and ringing of the ears were experienced by a girl who ingested a TWA dose of 2.27 mg/kg/day DNOC for 11 days (Gordon and Wallfield 1935). Lethargy and mental depression were also common complaints of 15 patients who ingested an average of 1.05 mg/kg/day DNOC for 14–63 days (Ibrahim et al. 1934). A slight headache and lassitude were reported by a female patient who received 0.75 mg/kg/day DNOC for 8 weeks (Plotz 1936).

Lethargy was observed in rats 30 minutes after exposure to 0.1 or 100 mg/m^3 DNOC (King and Harvey 1953a). They remained lethargic for the 4-hour duration of exposure, and drinking and eating activities were reduced. Twitching, tremors, ataxia, or sluggishness were observed in cats that were exposed to aerosols of DNOC, either as a mist or as DNOC dust, for 4 hours at concentrations ≤36 mg/m^3 (Burkatskaya 1965a). Clinical signs of depression were observed in rats given single doses 227 mg/kg DNOC as the sodium salt (Ambrose 1942). In another acute rat study, a single oral dose of 19.8 mg/kg DNOC caused a 90–120% increase in brain blood flow within 4 hours posttreatment (Verschoyle et al. 1987). Brain blood flow returned to normal within 24 hours, while no histopathological changes were

observed in the brains of these rats. The authors concluded that the observed increase in brain blood flow was consistent with the expected increased metabolic rate produced by DNOC. Severe agitation and muscle twitches were observed within 60–80 minutes in mice that received a single oral dose of DNOC in the range of l0–35 mg/kg (Arustamyan 1972). The mice also became prostrate for 3–7 hours, approximately 2–3 hours posttreatment. Cats that received a single oral dose of 25 mg/kg DNOC developed ataxia and became sluggish during the first hour, while muscle twitches and weakness developed on the second day after exposure; the study was limited by reporting deficiencies regarding experimental details and data (Burkatskaya 1965b). Decreased absolute brain weight was observed at 20 mg/kg/day, and increased relative brain weight was observed at 10 and 20 mg/kg/day in rats given DNOC orally for 90 days; however, no histopathological lesions were observed in the brain (Den Tonkelaar et al. 1983).

2.16 REPRODUCTIVE

Limited information was located regarding potential for DNOC-induced reproductive effects in humans. Among 47 agricultural workers who became ill after dermal exposure to DNOC for about 8 hours, 3 were pregnant (Varnai and Kote 1969). One of these women gave birth to a full-term healthy child 3 days after exposure to DNOC. The women subsequently bore full-term healthy children.

DNOC did not affect either sperm counts, percent abnormal sperm, or testicular weights in mice given single oral doses in the range of 3–12 mg/kg/day for 5 days (Quinto et al. 1989). However, significantly decreased sperm motility and decreased percentage normal sperm were observed in rats at 7 or 14 days following cessation of DNOC oral dosing at 15 mg/kg/day for 5 days (Takahashi et al. 2004, 2006). Intermediate-duration studies provided conflicting data regarding reproductive effects in animals after oral exposure to DNOC. No histopathological lesions were observed in testes from rats fed diets that provided daily doses of 1–25 mg/kg/day for 77–182 days (Spencer et al. 1948) or 1.25–20 mg/kg/day for 3 weeks (Vos et al. 1983). However, absolute and relative weights of the testes/prostate were decreased, and reduced spermatogenesis or aspermatogenesis was observed in rats given 20 mg/kg/day DNOC for 90 days (Den Tonkelaar et al. 1983). The reason for the conflicting data for testicular effects in intermediate-duration studies is not clear. Absolute weight of ovaries was decreased at ≥5 mg/kg/day DNOC, and relative weight of uterus/ovary was decreased at 20 mg/kg/day DNOC (Den Tonkelaar et al. 1983). No corpora lutea were observed in the ovaries, and the uteri appeared juvenile at 20 mg/kg/day DNOC. Damaged ovaries and disrupted estrus cycles were observed in rats given oral doses of 5 mg/kg/day DNOC for 6 months (Vashakidze 1967). The investigators demonstrated that DNOC caused

an increase in gonadotrophic hormones in the hypophysis. This change in hormone balance may be the reason for the disruption of the functioning of the reproductive glands. A higher dose of 10 mg/kg/day DNOC also disrupted the reactivity of the vaginal mucosa to estrogenous influences. Further experiments also demonstrated that DNOC caused atrophy of the uterine horns. Because of the poor experimental design and because the data were not clearly presented, it is difficult to substantiate the conclusions made by the author. However, some of the findings from this study support those reported by Den Tonkelaar et al. (1983).

2.17 DEVELOPMENTAL

Limited information was located regarding potential DNOC-induced developmental effects in humans or animals. Among 47 agricultural workers who became ill after being exposed to DNOC for about 8 hours, 3 of the workers were pregnant (Varnai and Kote 1969). The women gave birth to healthy children, suggesting that DNOC was not fetotoxic in these cases. None of these workers were exposed to DNOC during the period of organogenesis and, thus, no conclusions can be drawn from these cases regarding the embryotoxicity of DNOC.

No developmental effects were observed when DBA strains of mice given 8 mg/kg/day DNOC from day 11 to 14 of gestation (Nehez et al. 1981). On the 18th day of gestation, the numbers of corpora lutea, implantations, live embryos, and resorbed embryos, pre-implantation loss, post-implantation loss, weight of embryos, and number of malformations did not differ significantly from the data obtained from the negative control group.

2.18 OTHER NONCANCER

Metabolic effects observed in humans include elevated body temperature, profuse sweating, and increased basal metabolic rate. These clinical signs are related to the uncoupling of oxidative phosphorylation by DNOC. Uncoupling of oxidative phosphorylation results in heat production that exceeds the organism's capacity to dissipate heat; consequently, fatal hyperthermia may occur. Elevated body temperature, profuse sweating, and/or increased metabolic rate were observed among workers involved in production of DNOC (Hunter 1950) or mixing and/or spraying DNOC (Bidstrup and Payne 1951; Buzzo and Guatelli 1949; Pollard and Filbee 1951; Steer 1950; van Noort et al. 1960). Increased basal metabolic rates, elevated body temperature, and/or excessive perspiration were also observed among individuals administered DNOC orally, typically for the intended purpose of body weight reduction (Dodds and Robertson 1933; Ibrahim et al. 1934; Plotz 1936).

Elevated body temperature was observed in rats exposed to DNOC aerosol at 100 mg/m^3 for 4 hours (King and Harvey 1953a). The body temperature was still elevated 20 hours following cessation of exposure. Increased blood glucose was observed in cats exposed to DNOC dust at 36 mg/m^3 or to an aerosol of DNOC in solution (mist) at 40 mg/m^3 for 4 hours (Burkatskaya 1965a). Body temperatures were increased by 0.6–1.4°C. Elevated body temperature and increased blood glucose were also observed in cats exposed to 2.0 mg/m^3 of DNOC mist for 1 month or 0.2 mg/m^3 of DNOC dust for 2–3 months (Burkatskaya 1965a). These effects were first noted during the first l–2 weeks of exposure. Urinary ketones, an indicator of endogenous fat catabolism, were increased in rats orally dosed at 2.5, 5, and 10 mg/kg/day DNOC for 90 days (Den Tonkelaar et al. 1983). Blood glucose was increased at 10 and 20 mg/kg/day DNOC, while blood protein was decreased only at 20 mg/kg/day DNOC. Blood pyruvate was also decreased at all doses. The increased blood glucose and decreased blood pyruvate were indicative of an inhibitory action of DNOC on glycolysis.

2.19 CANCER

No studies were located regarding cancer in humans or animals exposed to DNOC via inhalation, oral, or dermal routes.

2.20 GENOTOXICITY

DNOC has been tested for genotoxicity in a variety of *in vivo* and *in vitro* test systems (see Tables 2-4 and 2-5). Mostly positive results have been obtained in *in vivo* tests. As shown in Table 2-5, DNOC tested positive for sex-linked recessive lethal mutations in *Drosophila melanogaster* (Mueller and Haberzettl 1980), DNA damage in rat hepatocytes (Grilli et al. 1991), chromosomal aberrations in bone marrow cells of rats (Hrelia et al. 1990, 1994), chromosomal aberrations in mouse germ cells (Nehéz et al. 1978b) and bone marrow cells (Nehéz et al. 1978a, 1984), and dominant lethal mutations in mice (Nehéz et al. 1978a). When pregnant mice were administered DNOC by gavage during the second trimester of pregnancy, an increased frequency of chromosomal aberrations was found in the embryos (Nehéz et al. 1981). Two studies found negative results for chromosomal aberrations in male germ cells (Nehéz et al. 1982) and bone marrow cells (Kurinnyi et al. 1982) after mice were treated with DNOC.

Table 2-4. Genotoxicity of Dinitrocresols *In Vivo*

Species (exposure route)	Endpoint	Results	Reference
Drosophila melanogaster (feed)	Sex-linked recessive lethal	+	Mueller and Haberzettl 1980
Rat (7.5, 15, or 30 mg/kg single gavage dose)	Chromosomal aberrations	+	Hrelia et al. 1994
Rat (intraperitoneal)	DNA damage (unwinding rate) in hepatocytes	+	Grilli et al. 1991
Rat (intraperitoneal)	Chromosomal aberrations in bone marrow cells	+	Hrelia et al. 1990
Mouse (intraperitoneal)	Chromosomal aberrations in male germ cells	+	Nehéz et al. 1982
Mouse (intraperitoneal)	Chromosomal aberrations in male germ cells	+	Nehéz et al. 1978b
Male mouse (intraperitoneal)	Dominant lethality	+	Nehéz et al. 1978a
Mouse (intraperitoneal)	Chromosomal aberrations in bone marrow cells	+	Nehéz et al. 1978a
Mouse (intraperitoneal)	Chromosomal aberrations in bone marrow cells	+	Nehéz et al. 1984
Mouse (subcutaneous)	Chromosomal aberrations in bone marrow cells	+	Nehéz et al. 1984
Male mouse (intraperitoneal)	Chromosomal aberrations in F1, F2, and F4 generations	+	Nehéz et al. 1984
Male mouse (intraperitoneal)	Chromosomal aberrations in F1 generation	+	Nehéz et al. 1978a
Female mouse (oral during first trimester of pregnancy)	Chromosomal aberrations in embryos	–	Nehéz et al. 1981
Female mouse (oral during second trimester of pregnancy)	Chromosomal aberrations in embryos	+	Nehéz et al. 1981
Mouse (route not specified)	Chromosomal aberrations in bone marrow cells	–	Kurinnyi et al. 1982

– = negative result; + = positive result; DNA = deoxyribonucleic acid

Table 2-5. Genotoxicity of Dinitrocresols *In Vitro*

		Results		
		Activation		
Species (test system)	Endpoint	With	Without	Reference
Salmonella typhimurium (eight histidine-requiring mutants)	Gene mutation	No data	–	Andersen et al. 1972
S. typhimurium (TA98)	Gene mutation	+	–	Nishimura et al. 1982
S. typhimurium (TA100)	Gene mutation	–	–	Nishimura et al. 1982
S. typhimurium (TA98, TA1537, TA2637)	Gene mutation	+[a]	+	Remondelli et al. 1986

Table 2-5. Genotoxicity of Dinitrocresols *In Vitro*

Species (test system)	Endpoint	Results: Activation With	Results: Activation Without	Reference
S. typhimurium (TA92, TA100, TA1535)	Gene mutation	–	–	Remondelli et al. 1986
S. typhimurium (TA98, TA1537)	Gene mutation	No data	–	Somani et al. 1981
S. typhimurium (TA100)	Gene mutation	No data	+	Somani et al. 1981
S. typhimurium (TA97, TA98, TA100, TA102)	Gene mutation	–	–	Hrelia et al. 1990, 1994
S. typhimurium (TA1535, TA1538)	Gene mutation	No data	+	Sundvall et al. 1984
S. typhimurium (TA98, TA100)	Gene mutation	+[a]	+	Sundvall et al. 1984
S. typhimurium (TA98NR)	Gene mutation	No data	(+)	Sundvall et al. 1984
S. typhimurium (TA100NR)	Gene mutation	No data	–	Sundvall et al. 1984
S. typhimurium (TA98)	Gene mutation	–[b]	–[b]	Sundvall et al. 1984
S. typhimurium (TA100)	Gene mutation	+[a,b]	+[b]	Sundvall et al. 1984
S. typhimurium (TA100, TA1535, TA1538)	Gene mutation	–[c]	–[c]	Spanggord et al. 1982b
S. typhimurium (TA98)	Gene mutation	–[c]	+[c]	Spanggord et al. 1982b
S. typhimurium (TA1537)	Gene mutation	+[c]	+[c]	Spanggord et al. 1982b
S. typhimurium (TA98)	Gene mutation	No data	+	Remondelli et al. 1986
Escherichia coli WP29 (hcr^+), WP29 (hcr^-)	Gene mutation	No data	–	Nagy et al. 1975
E. coli T_4 bacteriophage rII mutants	Gene mutation	No data	–	Andersen et al. 1972
E. coli T_4 bacteriophage wildtype	Gene mutation	No data	–	Andersen et al. 1972
Proteus mirabilis PG273 (wildtype), PG713 (rec^- hcr^-)	DNA repair	No data	+	Adler et al. 1976
Saccharomyces cerevisiae D7 strain	Mitotic crossing over	No data	+	Hrelia et al. 1990
Human peripheral blood lymphocytes	Sister chromatid exchange	–	–	Hrelia et al. 1990, 1994
Human blood leukocytes	Chromosomal aberrations	No data	+	Nehéz et al. 1978a
Human blood peripheral lymphocytes	Unscheduled DNA synthesis	–	–	Hrelia et al. 1994

Table 2-5. Genotoxicity of Dinitrocresols *In Vitro*

Species (test system)	Endpoint	Results: Activation: With	Results: Activation: Without	Reference

[a]Mutagenicity was decreased by the addition of S9.
[b]Test substance was 2,6-dinitro-*p*-cresol.
[c]Test substance was 4,6-dinitro-*m*-cresol.

+ = positive results; (+) = weakly positive results; – = negative results; DNA = deoxyribonucleic acid

Mixed results have been obtained from *in vitro* assays of DNOC. In tests for reverse mutations in *Salmonella typhimurium*, some investigators found consistently negative results with and/or without metabolic activation in several strains (Andersen et al. 1972; Hrelia et al. 1990, 1994; Nishimura et al. 1982); others found some positive results without metabolic activation in *S. typhimurium* strains TA98, TA1537, TA2637 (Remondelli et al. 1986), TA100 (Somani et al. 1981; Sundvall et al. 1984), TA1538, TA98NR, and TA1535 (Sundvall et al. 1984). When a metabolic activation system was used, the frequency of reverse mutations caused by DNOC was generally decreased (Remondelli et al. 1986; Sundvall et al. 1984). However, some investigators found negative results in the same strains for which other investigators found positive results (see Table 2-5). The reason for these inconsistent results is not clear. A positive result without activation was also found for forward mutations in *S. typhimurium* strain TA98 (Remondelli et al. 1986). DNOC was consistently negative for reverse mutation in *Escherichia coli* (Nagy et al. 1975) and *E. coli* T4 bacteriophage rII mutants and for forward mutation in *E. coli* T4 bacteriophage wildtype (Andersen et al. 1972). DNOC was positive in a DNA repair assay in *Proteus mirabilis* (Adler et al. 1976). In eukaryotic systems, positive results were found for mitotic crossing over in *Saccharomyces cerevisiae* (Hrelia et al. 1990) and for chromosomal aberrations in cultured human blood leukocytes (Nehéz et al. 1978a). However, negative results were obtained for unscheduled DNA synthesis and sister chromatid exchange in human peripheral lymphocytes (Hrelia et al. 1990, 1994).

2.21 MECHANISMS OF ACTION

DNOC has a relatively low pK_a and K_{ow} (see Chapter 4), but no information was located to indicate whether absorption of DNOC following inhalation, oral, or dermal exposure occurs by passive diffusion or by active transport.

Evidence from one study suggests that DNOC (rather than a metabolite) is the putative toxic agent (Smith et al. 1953). Results of genotoxicity studies indicate that DNOC is more genotoxic in the absence (rather than the presence) of exogenous metabolic activation systems. Acute toxic effects are related to DNOC acting directly on cell metabolism and interfering with oxidative phosphorylation. DNOC is believed to cause an acceleration of metabolic processes that are part of the tricarboxylic acid (TCA) cycle (Parker et al. 1951). During the TCA cycle, the energy produced from the catabolism of glucose is stored in the form of ATP. DNOC produces its accelerative effect by interrupting the phosphate transfer to adenosine diphosphate (ADP) to form ATP. Uncoupling allows electron transport to proceed unchecked even when ATP synthesis is inhibited. As a consequence, more ADP and inorganic phosphate are available to drive the TCA cycle, and most of the energy produced from catabolism of glucose is not stored in high-energy phosphate bonds as ATP, but is given off as heat (Parker et al. 1951). If heat production exceeds the capacity for heat loss, fatal hyperthermia may result (Murphy 1986). Signs of DNOC toxicity such as hyperthermia, tachycardia, increased respiration and basal metabolic rates, perspiration, cataractogenesis, and death in humans and animals are related to the uncoupling of oxidative phosphorylation. Several case reports have described the occurrence of elevated body temperatures and complaints of excessive perspiration from employees and patients exposed to DNOC (Bidstrup et al. 1952; Plotz 1936; Pollard and Filbee 1951; Stott 1956).

Several *in vitro* studies have further demonstrated the ability of DNOC to uncouple oxidative phosphorylation (Castilho et al. 1997; Ilivicky and Casida 1969; Muscatello et al. 1975; Verschoyle et al. 1987; Williamson and Metcalf 1967). In one study, the uncoupling action of DNOC and other dinitrophenol derivatives, as well as the relationship between their uncoupling potency and toxicity, were investigated (Ilivicky and Casida 1969). Mitochondria from mouse liver and brain were equally sensitive to the uncoupling action of DNOC. Isolated brain and liver mitochondria from mice treated with dinitrophenols derivatives other than DNOC were completely uncoupled or inhibited only when the dose resulted in severe symptoms of poisoning (Ilivicky and Casida 1969). DNOC was not tested in this experiment, but the data from these studies suggest that a relationship between the severity of DNOC toxicity and the extent of uncoupling by DNOC may exist.

In another *in vitro* study, the effect of uncoupling by DNOC on the structure of rat liver mitochondria was investigated using electron microscopy (Muscatello et al. 1975). When the mitochondria were placed in the uncoupled state, the rate of oxygen uptake was increased and the mitochondria appeared condensed with deep invaginations of the inner membrane, compared to its expanded configuration when DNOC

was not present. The authors also determined that the ultrastructural modification was as rapid as the functional one.

Active transport is required for the absorption and movement of biologically important molecules across a membrane against a concentration gradient. This process, which requires ATP, can be inhibited if DNOC is present. Results from an *in vitro* study of neonatal pig intestinal epithelium indicated DNOC inhibition of active transport by via uptake of gamma-globulin (Lecce 1966).

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

3.1 TOXICOKINETICS

- DNOC is rapidly absorbed following inhalation, oral, or dermal exposure.
- Limited human and animal data indicate that absorbed DNOC is distributed to most tissues, but does not accumulate in any particular tissue.
- Available animal data indicate that DNOC is biotransformed to less toxic metabolites; conjugation represents only a minor pathway to elimination.
- DNOC appears to be metabolized to less toxic metabolites readily eliminated via the urine. Although small quantities of DNOC may be conjugated, most of the dose appears to be reduced to mono amino derivatives and then subsequently conjugated prior to excretion. These relatively harmless metabolites have been found in the urine and kidney of humans and animals exposed to DNOC.

3.1.1 Absorption

DNOC is rapidly absorbed by the respiratory tract in humans and animals. A serum DNOC concentration of 1,000 µg/mL was detected in a spray operator 24–36 hours after inhaling a dense DNOC mist for an acute duration (van Noort et al. 1960). A blood DNOC concentration of 60 µg/g was detected in a spray operator who had been exposed to DNOC during mixing and/or spraying operations over a 5-week period (Pollard and Filbee 1951). In an occupational exposure study involving DNOC manufacturers, winter-washer sprayers, and cereal-crop sprayers, a correlation between blood DNOC levels and the symptoms and signs of poisoning was observed (Bidstrup et al. 1952). These data indicate that DNOC was absorbed from the respiratory tract; however, dermal absorption may have been involved as well. Limited studies in rats also show that DNOC is absorbed after inhalation exposure (King and Harvey 1953a, 1954).

DNOC is readily absorbed by the gastrointestinal tract in humans and animals. The detection of DNOC in liver, stomach, kidney, heart, and brain of two humans who committed suicide by ingesting DNOC provides evidence of gastrointestinal absorption (Sovljanski et al. 1971). DNOC was readily absorbed when 75 mg DNOC/day was given to five volunteers for 5 days (Harvey et al. 1951; King and Harvey 1953b). Further analysis of the data for these volunteers revealed that they excreted approximately 7% of the total DNOC dose in the urine over 13 days from the first dosing days (King and Harvey 1953b). In

the first 24 hours after a single dose of 75 mg, an average of 39.2% of the dose could be accounted for by blood levels and 1.3% by urinary levels.

Studies in animals reveal differences among species. Maximum blood DNOC concentrations of 72.2 µg/g at 6 hours after the last dose of 20 mg/kg/day for 9 days and 105 µg/g at 3.5 hours after a single dose of 30 mg/kg DNOC were found in rats (King and Harvey 1953b). The gastrointestinal absorption of DNOC was approximately 20, 10, and 5% of the dose at 1, 2, and 7 hours after dosing, respectively. When rabbits were similarly treated, peak values were 54.7 µg/g at 4.5 hours after multiple doses of 25 mg/kg/day DNOC and 49.5 µg/g at 6 hours after a single dose of 30 mg/kg. Blood DNOC levels of 25, 34, and 50 µg/g were detected in rabbits given single oral doses of 10, 15, or 18 mg/kg DNOC, respectively (Truhaut and De Lavaur 1967).

In two rats given oral doses of 0.4 mg/kg ^{14}C-DNOC, 60% of the radioactive dose was accounted for in blood, urine, and tissues from one rat that was killed 1 day later and the other rat that was killed 3 days later (Leegwater et al. 1982). In the rat killed 1 day later, 15% of the radioactive dose was detected in the blood, while 28.7% was accounted for in the urine and approximately 41% was distributed to other body tissues. In the rat killed 3 days after dosing, 5.5% of the radioactive dose was detected in the blood, while 41% was accounted for in the urine and approximately 20% was distributed to other body organs.

As part of a study to determine the influence of dietary fats on the absorption of DNOC, mean blood levels of 50.7, 71.0, 81.0, 76.3, 61.4, 42.6, 28.3, and 19.1 µg/mL DNOC were detected at 15 minutes, 1, 3, 6, 12, 24, 30, and 48 hours, respectively, after rats were given a single dose of 15 mg/kg DNOC in saline (Starek and Lepiarz 1974). Gavage administration of olive oil, rape seed oil, or castor oil immediately after DNOC resulted in some alteration of these blood levels, indicating that the influence of fats on the amount of DNOC absorbed from the gastrointestinal tract depends on the type and dose of the fat. In general, readily digested olive oil was associated with little change in DNOC blood levels, the more slowly digested rape seed oil slightly inhibited DNOC absorption, and castor oil decreased the absorption considerably. This latter result probably reflects castor oil's cathartic effect.

DNOC is rapidly absorbed by the skin in small quantities by humans (Batchelor et al. 1956; Harvey et al. 1951; Steer 1951) and rabbits (King and Harvey 1953a). Blood DNOC levels were increased by l–3 µg/g within <6 hours in three male volunteers who had an aqueous solution of DNOC dermally applied to the forearms (Harvey et al. 1951). In an experimental study, two volunteers initially placed one foot and subsequently both feet in a pail containing a 1% solution of DNOC (van Noort et al. 1960). Serum

DNOC levels were 2–4, 3–4, 7.5–8, and 27 µg/mL (roughly equivalent to µg/g) at 1, 2, 5.5, and 6.5 hours, respectively, after exposure. These data suggest that DNOC accumulated during the exposure period and probably very little was eliminated within this time. DNOC has also been detected in the blood of spray operators following occupational exposure of 63.2 mg/hour for 548 hours over 5 days (Batchelor et al. 1956). DNOC serum levels did not exceed 4.3 µg/g in six of these spray operators, and no correlation was apparent between total hours of exposure and serum levels. In a separate case study, 75 µg/g DNOC was recovered from the blood of a spray operator who died after dermal exposure to DNOC for an unspecified period (Steer 1951).

Blood DNOC levels peaked at 10–40 µg/g within l–2 hours in rabbits dermally exposed to 1 or 2 mg/cm^2 of DNOC (King and Harvey 1953a). A second dose of DNOC caused another increase in the blood DNOC values. Detection of blood DNOC 48 hours after exposure at levels higher with dermal exposure than for other routes suggests that skin acts as a reservoir for DNOC.

3.1.2 Distribution

Information regarding distribution of DNOC in humans and animals after inhalation exposure is limited. About 0.9 µg/g of DNOC was recovered from the cerebrospinal fluid of a worker exposed to unknown levels of DNOC during mixing and/or spraying operations over a 5-week period (Pollard and Filbee 1951).

Concentrations of 16, 20, 31, and 28 µg/g were recovered from the lungs of four rats exposed to 0.1 mg/m^3 DNOC for 4 hours (King and Harvey 1953a). The concentrations of DNOC in the alimentary tract and contents were 2.5, 3.1, 2.8, and 2.2 µg/g. The recovery of DNOC from the alimentary tract probably resulted from enterohepatic circulation and/or impaction of the aerosol along the trachea and bronchi and subsequent mucociliary action to bring it up to the epiglottis to be swallowed.

DNOC was detected in several organs of two humans who had committed suicide after ingesting unknown quantities of DNOC (Sovljanski et al. 1971). The following levels in each respective individual were: 13 and 400 mg/100 g in the stomach, 0.75 and 10 mg/100 g in the intestines, 0.3 and 4.72 mg/100 g in the liver, 0.125 and 2.0 mg/100 g in the kidneys, 0.3 and 2.42 mg/100 g in the heart, and 0.125 and 1.2 mg/100 g in the brain.

In two rats given oral doses of 0.4 mg/kg ^{14}C-DNOC, approximately 20–41% of the radioactive dose was distributed to other body tissues (Leegwater et al. 1982). In the rat killed 1 day after the dose, 15% of the dose was detected in the blood, 5.0% in the liver, 0.94% in the kidney, 0.08% in the spleen, 6.67% in the gastrointestinal tract, and 28% in the residual carcass. In the rat killed 3 days after dosing, 5.5% was detected in blood, 2.3% in liver, 0.9% in kidneys, 0.04% in spleen, 4.0% in gastrointestinal tract, and 12.6% in residual carcass.

No information was located regarding distribution of DNOC *per se* in animals after oral exposure, but the metabolite, 6-amino-4-nitro-*o*-cresol was detected in the liver, kidney, and brain of rabbits given single doses of DNOC (Truhaut and De Lavaur 1967). The ratio of 6-amino-4-nitro-*o*-cresol to DNOC increased from 0.42 to 5.29 in the kidney when the dose increased from 10 to 20 mg/kg DNOC.

DNOC was detected in unspecified tissues of a spray operator who died after dermal exposure to an unknown amount of DNOC (Steer 1951). About 0.9 µg/g of DNOC was recovered from the cerebrospinal fluid of a spray operator thought to have been exposed dermally and by inhalation to an unknown amount of DNOC over a 5-week period (Pollard and Filbee 1951). The blood level was approximately 37 µg/g on the same day, indicating a relatively smaller distribution to the cerebrospinal fluid.

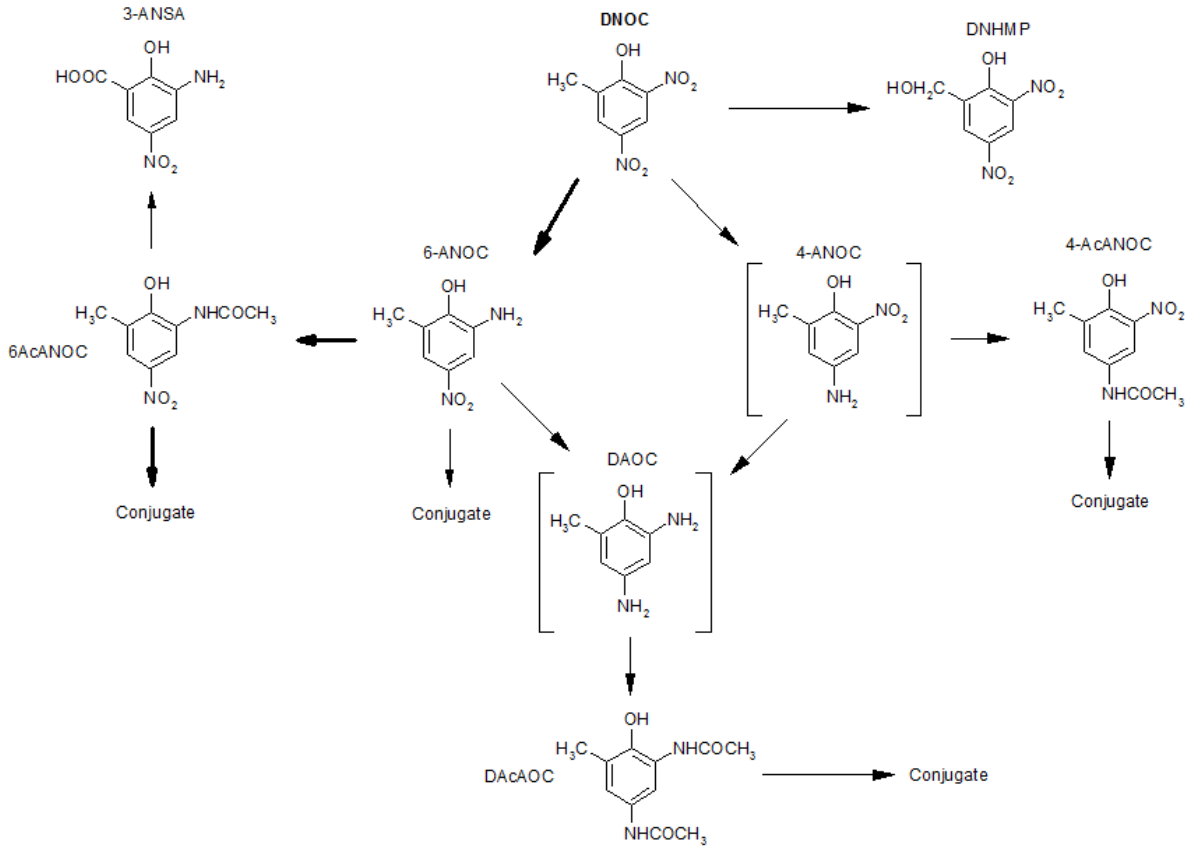
DNOC was measured in the serum, brain, spleen, kidney, liver, muscle, lung, and heart of rats at 30 minutes and 1, 2, 3, 4, 5, and 6 hours after a subcutaneous dose of 10 mg/kg (Parker et al. 1951). Except for liver and lung tissues, tissue DNOC increased from levels of 0.5–8.0 to 3.5–19 µg/g during the first 3 hours, but declined to levels of 1.5–10.5 µg/g during the next 3 hours. Liver levels fell from 14 µg/g at 30 minutes to 8 µg/g at 6 hours, while lung levels increased from 18 µg/g at 30 minutes to 20.5 µg/g at 2 hours and 30 µg/g at 6 hours. More DNOC was distributed to the lungs, heart, liver, and kidneys than to other tissues analyzed at the end of 6 hours. This can be attributed to increased blood supply to these organs and their relative affinity for DNOC. A single dose of 20 mg/kg DNOC resulted in DNOC tissue levels of 8, 7, and 45 µg/g in liver, kidney, and serum, respectively, 24 hours after the injection. A subcutaneous dose of 20 mg/kg/day for 40 days resulted in DNOC tissue levels of 7, 7, and 38 µg/g in liver, kidney, and serum, respectively, 24 hours after the last injection. The data suggest that there was no tendency for DNOC to accumulate in these body tissues. In addition, there was no difference in these tissue levels when the levels were compared 24 or 48 hours after the last injection (either single or multiple dose injections).

3.1.3 Metabolism

The metabolic fate of DNOC has been determined from a limited number of *in vivo* metabolic studies in experimental animals (Leegwater et al. 1982; Parker et al. 1951; Smith et al. 1953; Truhaut and De Lavaur 1967). In one study, no amino-nitrophenol, glucuronides, or ethereal sulfates were detected in urine from dogs or rabbits that received 10 mg/kg DNOC subcutaneously (Parker et al. 1951). Only DNOC was detected in the urine. The data from two other studies suggest that DNOC is biotransformed to less toxic metabolites in rats (Leegwater et al. 1982) and rabbits (Smith et al. 1953; Truhaut and De Lavaur 1967). Proposed metabolic pathways for 4,6-DNOC are presented in Figure 3-1. Unchanged DNOC and conjugated and unconjugated metabolites of DNOC were recovered from urine 2 days after rabbits received oral doses of 20–30 mg/kg DNOC (Smith et al. 1953). Less than 20% of the dose was excreted as metabolites; almost 5% of the dose was excreted as unchanged DNOC and 1% was excreted as conjugated DNOC. Therefore, the conjugation of DNOC represents a minor pathway. The metabolites were derivatives of 6-amino-4-nitro-*o*-cresol (6-ANOC; approximately11–12% of the dose). Approximately 1–1.5% of the dose was represented by 6-acetamido-4-nitro-*o*-cresol (6-AcANOC); approximately 10% of the dose was represented by O-conjugates of 6-AcANOC. Small amounts of 3-amino-5-nitrosalicylic acid (3-ANSA) and derivations of 4-amino-6-nitro-o-cresol (4-ANOC) were also excreted. The 6-nitro group appears to be more readily reduced than the 4-nitro group. According to the pathway, the acetylated metabolite (6-AcANOC) of 6-ANOC is further metabolized to traces of 3-ANSA and larger amounts of conjugates of 6-AcANOC. Metabolites 6-ANOC and 6-AcANOC were far less toxic than DNOC when oral doses were given to rabbits, suggesting that the major detoxification pathway in rabbits occurs via reduction at the 6-nitro group rather than via conjugation of the hydroxyl group of DNOC alone.

No amino derivatives of DNOC were detected in the blood, bone marrow, or adipose tissue, but 6-ANOC was detected in the liver, kidneys, and brain of rabbits that received an oral dose of 18 mg/kg DNOC (Truhaut and De Lavaur 1967). No 4-ANOC was detected in these tissues. Both DNOC and 6-ANOC were recovered from the urine as 25–38% of the dose. Smaller amounts of 4-ANOC were also detected in the urine. Further experiments demonstrated that as the dose of DNOC increased, the ratio of 6-ANOC to DNOC in urine increased. The data from this study support the findings of Smith et al. (1953) by demonstrating that the metabolic reduction of DNOC to 6-ANOC was the major detoxification pathway and that this pathway becomes more important at higher doses.

Figure 3-1. Proposed Metabolic Pathways for 4,6-Dinitro-*o*-Cresol (DNOC)



3-ANSA = 3-amino-5-nitrosalicylic acid; 4-AcANOC = 4-acetamido-6-nitro-*o*-cresol; 4-ANOC = 4-amino-6-nitro-*o*-cresol; 6-AcANOC = 6-acetamido-4-nitro-*o*-cresol; 6-ANOC = 6-amino-4-nitro-*o*-cresol; DAcAOC = 4,6-diacetamido-*o*-cresol; DAOC = 4,6-diamino-*o*-cresol; DNHMP = 4,6-dinitro-2-hydroxymethylphenol; DNOC = 4,6-dintro-*o*-cresol

Source: WHO 2000

The following urinary metabolites were identified and quantitated in a rat given 0.4 or 6.0 mg/kg ^{14}C-DNOC: 6-ANOC (l–2%); 6-AcANOC (2–3%); 4,6-dinitro-2-hydroxymethylphenol (DNHMP; 4–5%); 4,6-diacetamido-o-cresol (DAcAOC; 18%); and 4-acetamido-6-nitro-o-cresol (4-AcANOC; l–2%) (Leegwater et al. 1982). In addition, the urine contained several unknown metabolites and conjugates. In another experiment, the metabolites 6-ANOC, 6-AcANOC, and DAcAOC were also identified in a 24-hour urine sample from rabbits given 20 mg/kg. This study confirms findings of King and Harvey (1953a, 1953b), Smith et al. (1953), and Truhaut and De Lavaur (1967) showing slow elimination of

DNOC and reduction as the major metabolic pathway. The metabolites DNHMP and DAcAOC had not been previously found in rats.

Rat caecal contents were incubated with DNOC to determine whether the compound is metabolized in the large intestine (Ingebrigtsen and Froslie 1980). About 80% of DNOC was metabolized to 6-ANOC within 1 hour. Within the next 12 hours, 90% of this metabolite was further reduced to 4,6-diamino-*o*-cresol (DAOC). The authors determined that the caecal microorganisms in rats were responsible for the reduction of DNOC and its subsequent metabolites to diamino derivatives. Although not detected in humans or other monogastrics, these diamino derivatives are formed in sufficient quantities in ruminants to cause methemoglobinemia, which can be fatal in these species (Froslie 1973).

3.1.4 Excretion

Based on measured DNOC blood levels of a worker likely exposed to DNOC by a combination of inhalation and dermal routes (Pollard and Filbee 1951), an elimination rate constant of 0.002 $hour^{-1}$ and a half-life of 153.6 hours were determined (King and Harvey 1953b). A peak urinary quantity of 22 mg DNOC was found on the third day after the employee was admitted to the hospital and 5 weeks after his initial exposure (Pollard and Filbee 1951). About 89.9 mg of DNOC was eliminated via the urine over the 20 days after admission. The data suggest that humans have a relatively inefficient mechanism for eliminating DNOC and this may be due to slow detoxification and excretion or storage of DNOC in the body. In the only inhalation study located for animals, an elimination rate constant of 0.01 $hour^{-1}$ was determined for female hooded rats exposed to 2 mg/m^3 of DNOC aerosols for 5 hours (King and Harvey 1954). This was determined to correspond to an initial blood level of 60 µg/g that would result in essentially complete elimination of DNOC in 182 hours.

Urinary excretion data from five humans who each ingested 75 mg DNOC/day for 5 days suggested that at least 7% of the dose was slowly eliminated over a 13-day period (King and Harvey 1953b). The amount of DNOC excreted in the urine was independent of the concentration of DNOC in the blood of three humans. Species differences in urinary elimination have been found among animals administered DNOC orally. Elimination rate constants were 0.0105 and 0.0112 $hour^{-1}$ in rats given nine daily doses of 20 mg/kg/day DNOC and a single dose of 30 mg/kg DNOC, respectively (King and Harvey 1953b). The half-lives for DNOC were 26.8 and 28.5 hours for the multiple dose study and the single dose study, respectively. The authors calculated that an initial blood level of 60 µg/g DNOC will be eliminated almost completely from the blood within 182 hours. Higher elimination rate constants were obtained for

rabbits compared to rats; that is, 0.0448 $hours^{-1}$ for the multiple-dose study and 0.0454 $hours^{-1}$ for the single-dose study (King and Harvey 1953b). The half-lives were also shorter (6.6–6.7 hours) than those obtained for rats. Most of the excreted amount (average 6.4% of the dose) was eliminated through the urine in the first 5 hours. After comparing the data from humans, rats, and rabbits, the authors concluded that the rabbit is most efficient in detoxifying and eliminating DNOC. In another study, the elimination rate constants for DNOC in rats, rabbits, guinea pigs, mice, and monkeys given single unspecified oral doses of DNOC were 0.01, 0.045, 0.032, 0.036, and 0.01 $hours^{-1}$, respectively (Lawford et al. 1954).

In another oral rabbit study, DNOC and its metabolite, 6-ANOC, which were detected in the urine, made up 25–38% of a 10–15 mg/kg DNOC oral dose (Truhaut and De Lavaur 1967). Of this amount, 82–97% was eliminated within 1 day, and the rest was excreted within 2–3 days. As the dose of DNOC increased from 10 to 20 mg/kg, the ratio of 6-ANOC to DNOC in urine increased from 0.66 to 1.47 when measured at 2.5–3.75 hours postdosing.

Within 2 days after receiving a single oral dose of 20–30 mg/kg DNOC, Chinchilla rabbits excreted <20% of the dose as metabolites (Smith et al. 1953). Unchanged DNOC accounted for approximately 5% of the dose and conjugated DNOC accounted for approximately 1%. Derivatives of 6-ANOC comprised approximately 11–12% of the dose, including 6-AcANOC (1–1 .5% of the dose), O-conjugates of this metabolite (10% of the dose), and unspecified amounts of 3-ANSA and derivatives of 4-ANOC that were also excreted in the urine.

In two rats given oral doses of 0.4 mg/kg ^{14}C-DNOC, about 29–41% of the radioactive dose was excreted in urine and 10–23% was excreted in the feces (Leegwater et al. 1982). The half-life for elimination of radioactivity was 1–1.5 days. In the rat killed 1 day postdosing, 28.7% of the dose was excreted in the urine and 28% in feces. In the rat killed 3 days postdosing, excretion amounted to 23% of the dose in the first 24 hours, 16.4% in the next 24 hours, and 11.5% in the third 24 hours. Fecal excretion amounted to 7.1% in the first 24 hours, 9.3% in the second 24 hours, and 6.2% in the third 24-hour period. The following urinary metabolites were determined in a rat given 0.4 or 6.0 mg/kg ^{14}C-DNOC: DNOC (3–4%); 6-ANOC (l–2%); 6-AcANOC (2–3%); DNHMP (4–5%); DAcAOC (18%); and 4-AcANOC (l–2%). The urine contained several unknown metabolites and conjugates. The dose of DNOC had little effect on the distribution pattern of metabolites. In another experiment, the metabolites 6-ANOC, 6-AcANOC, and DAcAOC were identified in a 24-hour urine sample from rabbits given 20 mg/kg DNOC. This study confirms findings of King and Harvey (1953a, 1953b) and Smith et al. (1953), showing slow elimination of DNOC and reduction as the major metabolic pathway.

An average concentration of 0.8 µg/g DNOC with a range of 0.6–1.3 µg/g was detected in the urine from spray operators exposed dermally to 63.2 mg DNOC/hour (Batchelor et al. 1956). Of the 183 urine samples obtained from the spray workers, only 5 contained ≥0.5 µg/g DNOC as the sodium salt (limit of detection). Three of four spray operators, who were exposed to DNOC primarily by the dermal route for 14 days to 4 months, had initial serum DNOC levels of <5–100 µg/mL at the time of hospitalization (van Noort et al. 1960). In two of these patients, serum levels decreased from 60 to 40 µg/mL in 1 week and from 100 to 5 µg/mL in 3 weeks, respectively. Although the initial serum DNOC level was not determined in the fourth patient, 10 µg/mL DNOC was detected in the serum 1 month after exposure, suggesting that the initial serum level was extremely high. Thus, DNOC was eliminated slowly and at similar rates in these humans. A peak urinary DNOC excretion of 22 mg was observed on the third day after the employee was admitted to the hospital and 5 weeks after his initial combined dermal and inhalation exposure to DNOC (Pollard and Filbee 1951). A total of 89.9 mg of DNOC was eliminated via the urine over the 20 days after admission.

Urinary DNOC accounted for 10% of the total dose of 0.5–80 mg/animal over 3 days after the last, daily, subcutaneous injection of DNOC in rabbits and dogs (Parker et al. 1951). The determined elimination rate constants for DNOC were 0.02, 0.077, 0.021, 0.04, and 0.02 $hour^{-1}$ in rats, rabbits, guinea pigs, mice, and monkeys, respectively, following single intraperitoneal doses of DNOC (Lawford et al. 1954). Neither the sex of the test species nor the magnitude of the DNOC dose had a marked effect on the elimination of DNOC in rats given various intraperitoneal doses of DNOC (King and Harvey 1954). Elimination rate constants ranged from 0.013 to 0.019 $hours^{-1}$ for the 20 mg/kg dose and from 0.01 to 0.018 $hours^{-1}$ for the 5, 10, and 15 mg/kg dose groups. The determined mean elimination rate constant was 0.015 $hour^{-1}$ for this study.

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

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

mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic endpoints.

No PBPK models were located for dinitrocresols.

3.1.6 Animal-to-Human Extrapolations

Animal models may serve as indicators of potential DNOC-induced health effects relevant to humans. However, humans excrete DNOC and/or its metabolites much more slowly than do laboratory animals. An estimated elimination rate constant for internalized DNOC in humans was reported to be 0.002 $hour^{-1}$ (Pollard and Filbee 1951). Lawford et al. (1954) estimated elimination rate constants of 0.01, 0.045, 0.032, 0.036, and 0.01 $hours^{-1}$ for rats, rabbits, guinea pigs, mice, and monkeys given single oral doses of DNOC. King and Harvey (1953b) concluded that the rabbit is most efficient at detoxifying and eliminating DNOC. Evidence of slower elimination of DNOC from exposed humans and a lack of adequate comparative toxicokinetic data between humans and laboratory animals preclude meaningful interspecies extrapolations.

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 dinitrocresols are discussed in Section 5.7, Populations with Potentially High Exposures.

No data identifying subpopulations of humans inherently more susceptible to the toxic effects of DNOC were located. Animal studies did not indicate that there were sex or age differences in the susceptibility to DNOC toxicosis.

Several human studies suggest that people living in tropical or warm climates are more susceptible to DNOC toxicity than people in cooler climates (Bidstrup and Payne 1951; Pollard and Filbee 1951; Stott 1951). This phenomenon is supported by studies in rats and mice indicating that environmental temperature increases the toxicity of DNOC (Harvey 1959; King and Harvey 1953a). Some human subpopulations that are predisposed to a syndrome known as malignant hyperthermia may be more likely to develop fatal hyperthermia following DNOC exposure. Malignant hyperthermia is an inherited disease of skeletal muscle characterized by a drug-induced hyperpyrexia (Schroeder and McPhee 1990). Human populations with this inherited disease are predisposed to acute hyperthermic reactions triggered by stress or drugs, such as anesthetic agents, skeletal muscle relaxants, and amide local anesthetics (Britt 1979). Although no data were located linking DNOC with malignant hyperthermia, persons with the genetic predisposition may be more susceptible to the hyperthermic effects of DNOC.

DNOC is an uncoupler of oxidative phosphorylation and causes metabolic disturbances. People with compromised metabolic rates may be more susceptible to DNOC toxicity; however, no such population has been identified.

3.3 BIOMARKERS OF EXPOSURE AND EFFECT

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

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

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

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.2, Children and Other Populations that are Unusually Susceptible.

3.3.1 Biomarkers of Exposure

Detection of DNOC in body fluids or tissues can serve as a qualitative indication that exposure to DNOC occurred. DNOC and/or its metabolites have been measured in various body fluids and tissues such as blood, urine, liver, stomach, intestine, brain, and heart of humans (Harvey et al. 1951; King and Harvey 1953b; Sovljanski et al. 1971) and animals (King and Harvey 1953a; Leegwater et al. 1982; Truhaut and De Lavaur 1967). Detectable blood and urinary levels of DNOC have been found in humans exposed occupationally by the inhalation and dermal routes (Batchelor et al. 1956; Bidstrup et al. 1952; Pollard and Filbee 1951; Steer 1951) or experimentally by the oral and dermal routes (Harvey et al. 1951; King and Harvey 1953b). Although the exposure concentrations in occupational studies were not known, the experiments in volunteers provide information on doses and durations. Thus, the measurement of DNOC in blood is a useful indicator of exposure; however, since DNOC is still detectable in the blood as much as 40 days after exposure, it may not be a reliable indicator of exposure history.

Following oral dosing of volunteers with DNOC, only 7% of the administered dose was excreted in the urine during 13 days postadministration (King and Harvey 1953b). Therefore, urinary levels of DNOC and/or its metabolites may not be useful biomarkers to quantify exposure. Yellow staining of skin, sclera,

or conjunctiva may alert a physician to the possibility of DNOC exposure. This yellow staining is not a sign of icterus, but is due to the yellow color of DNOC.

3.3.2 Biomarkers of Effect

DNOC exposure results in a hypermetabolic state that resembles heat exhaustion and heat stroke. The basal metabolic rate was increased by 70–100% within 3 days in two humans given 3 mg/kg/day DNOC (Dodds and Robertson 1933). Headaches, hyperthermia, profuse sweating, increased pulse rate, and dyspnea are other common signs and symptoms associated with DNOC exposure. In severe cases, tachycardia, delirium, coma, and convulsions are usually observed in humans. An increased basal metabolic rate may, therefore, indicate profound metabolic disturbances.

3.4 INTERACTIONS WITH OTHER CHEMICALS

Very little information was located regarding interactions of DNOC with other chemicals, but the toxicity of DNOC is influenced by several physical and environmental factors.

Environmental temperatures influenced the mortality rate among rats after oral exposure to DNOC (King and Harvey 1953a). Six out of 12 rats died after being given 20 mg/kg at 37–40°C, while only 2 of 12 rats died after being given twice the dose (40 mg/kg) at almost half the temperature (20–22°C). It appears that increased environmental temperatures increased the toxicity of DNOC in rats. The authors further proposed that the increase in environmental temperature exacerbated the increased metabolic effect of DNOC, but did not appear to initiate or stimulate any reactions affecting the linkage of DNOC to any intracellular or extracellular substances. Environmental temperatures could also alter normal body functions so that the rate of absorption, diffusion, distribution, or metabolism of a compound would be changed. A similar observation was made in another study after rats given intraperitoneal doses of DNOC were exposed to 8, 26, or 36°C (Keplinger et al. 1959). The approximate lethal dose was 42 mg/kg at 8°C, 28 mg/kg at 26°C, and 18 mg/kg at 36°C. In mice given 22 mg/kg DNOC subcutaneously, the mean time of death (LT_{50}) values decreased as environmental temperature increased (Tesic et al. 1972). Hence, DNOC was most toxic at high temperatures and least toxic at cold temperatures.

An attempt was made to determine the best treatment regimen for rats and mice exposed to intraperitoneal doses of 2.5–30 mg/kg DNOC (Harvey 1959). Fifty percent mortality was observed at 2.5 mg/kg DNOC and 100% mortality was observed at ≥5.0 mg/kg when rats were exposed to 39–41°C. Sponging with

water within 1 hour of exposure to DNOC completely protected all rats given doses of 2.5–10 mg/kg. This protective effect was not observed at 20 or 30 mg/kg DNOC. Removal of the rats to a cold room completely protected the rats treated with 10 mg/kg, but had no effect on mortality at 20 mg/kg. The authors concluded that cooling of the skin may be beneficial in reducing the toxicity of DNOC in humans. Because rats eliminate DNOC more rapidly than humans, sponging and cooling treatment would have to be prolonged and efficient. In the same study, administration of 4-methyl-2-thiouracil, an inhibitor of the thyroid gland, 1 hour after injection of DNOC reduced mortality to 50% at 5.0 mg/kg, but had no effect on mortality at 10.0 mg/kg. No mechanism was proposed for this interaction between DNOC and 4-methyl-2-thiouracil. Similar results of sponging with water or treatment with 4-methyl-2-thiouracil were found with mice.

Mean time to death was prolonged in mice pretreated with vitamin E, vitamin A, and/or glucose 30 minutes before dosing with DNOC (Tesic et al. 1972). Thiamazole increased the mean time to death by a factor of 2.72, while chlorpromazine was more protective than thiamazole. The authors proposed that chlorpromazine may cause a significant reduction in oxidative processes and decrease in body temperature, while the protective effect of thiamazole may be associated with its ability to decrease basal metabolic rate.

Gavage administration of olive oil, rape oil, or castor oil to rats immediately after DNOC resulted in some alteration of blood DNOC levels, indicating that the influence of fats on the amount of DNOC absorbed from the gastrointestinal tract depends on the type and dose of the fat (Starek and Lepiarz 1974). In general, readily digested olive oil had little effect on blood levels, the more slowly digested rape oil slightly inhibited DNOC absorption, and castor oil decreased the absorption considerably. A nonpurgative dose of 0.2 mL of castor oil inhibited DNOC absorption from the alimentary tract, while a purgative dose of 1.0 mL inhibited absorption for the first 6 hours and then increased blood DNOC levels in the next few hours. In some instances, castor oil inhibited DNOC absorption by as much as 43–49% at 6 hours after the oil was given. Aspirin enhances uncoupling of oxidative phosphorylation and therefore increases DNOC toxicity (Ellenhorn and Barceloux 1988).

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

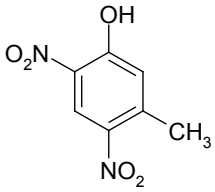
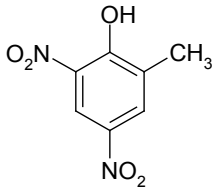
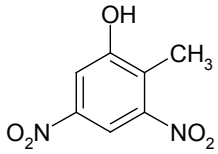
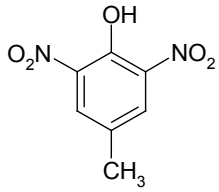
4.1 CHEMICAL IDENTITY

Table 4-1 lists common synonyms, trade names, and other pertinent identification information for selected dinitrocresols.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Table 4-2 lists important physical and chemical properties of dinitrocresols.

Table 4-1. Chemical Identity of Dinitrocresols

Chemical name	4,6-Dinitro-*m*-cresol	4,6-Dinitro-*o*-cresol[a]	3,5-Dinitro-*o*-cresol	2,6-Dinitro-*p*-cresol[a]
Synonym(s) and registered trade name(s)	2,4-Dinitro-5-methylphenol; 3-methyl-4,6-dinitrophenol	DNOC; DNC; 3,5-dinitro-2-hydroxytoluene; 2-methyl-4,6-dinitrophenol; Antinonnin; Detal; Dinitrol; Effusan; Selinon; others[b]	2-Methyl-3,5-dinitrophenol	DNPC; 3,5-dinitro-4-hydroxy toluene; Victoria Orange; Victoria Yellow
Chemical formula	$C_7H_6N_2O_5$	$C_7H_6N_2O_5$	$C_7H_6N_2O_5$	$C_7H_6N_2O_5$
Chemical structure				
CAS Registry Number	616-73-9	534-52-1	497-56-3	609-93-8

[a]All information obtained from ChemID 1993 and HSDB 1994 except where noted.
[b]Merck 1989.

CAS = Chemical Abstracts Service

Table 4-2. Physical and Chemical Properties of Dinitrocresols

Chemical name	4,6-Dinitro-*m*-cresol	4,6-Dinitro-*o*-cresol[a]	3,5-Dinitro-*o*-cresol[b]	2,6-Dinitro-*p*-cresol[c]
Molecular weight	198.13	198.13	198.13	198.13
Color	No data	Yellow	Yellow	Yellow
Physical state	No data	Solid	Solid	Solid
Melting point	No data	87.5°C; 86.5°C[d]	85.8°C	80–81°C; 85°C[d]
Boiling point	No data	312°C[e]	No data	No data
Density	No data	No data	1.49 g/cm^3 [f]	No data
Odor	No data	Odorless[g]	No data	No data
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
pK_a	No data	4.46[h]; 4.38[i]; 4.35[j]	No data	No data
Solubility:				
Water	No data	130 mg/L at 15°C[k]	No data	290 mg/L
Organic solvents	No data	Soluble in ethanol (4.3 g/100 g), acetone (100 g/100 g), and benzene (37 g/100 g)[g]	Soluble in ether, ethanol, and acetone[d]	Soluble in ether, ethanol, and acetone[d]
Partition coefficients:				
Log K_{ow}	No data	2.12[l], 2.56[m], 2.16[i], 2.85[n]	No data	No data
Log K_{oc}	No data	2.35–2.77[a,o]	No data	No data
Vapor pressure	No data	1.05x10^{-4} mmHg at 25°C[p] 3.6x10^{-4} mmHg at 35°C[r,s]	5.2x10^{-5} mmHg at 20°C[q]	No data
Henry's law constant	No data	1.4x10^{-6} atm-m^3/mol at 25°C[t,u]	No data	No data
Autoignition temperature	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data
Flammability limits	No data	No data	No data	No data

Table 4-2. Physical and Chemical Properties of Dinitrocresols

Conversion factors	1 mg/m^3 = 0.12 ppm	1 mg/m^3 = 0.12 ppm	1 mg/m^3 = 0.12 ppm	1 mg/m^3 = 0.12 ppm
Explosive limits	No data	No data	No data	No data

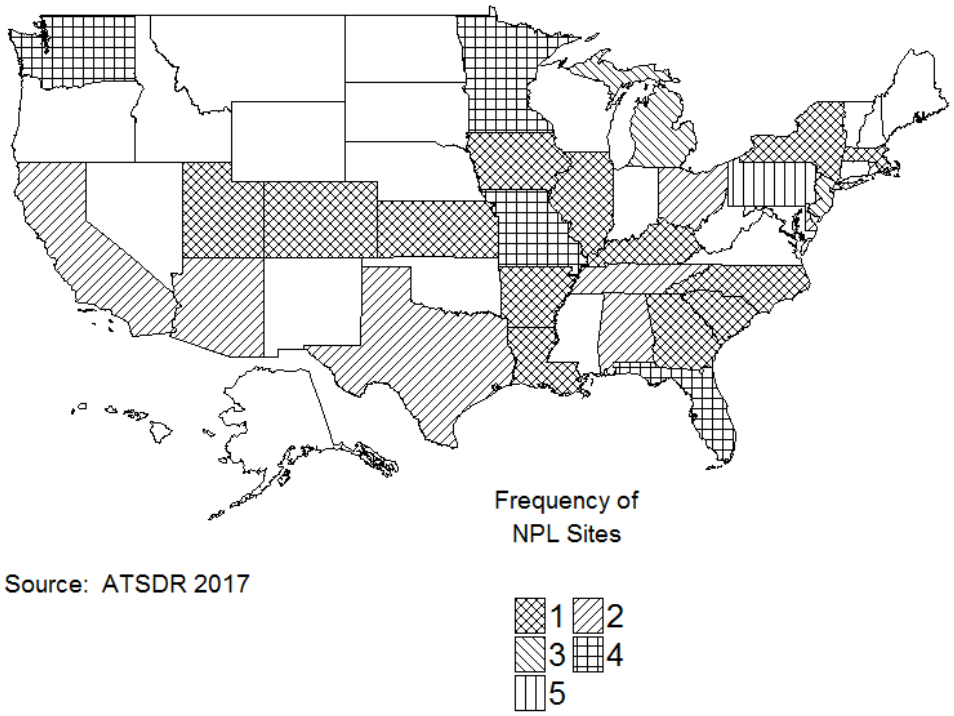
[a]All information obtained from Merck 1989 unless otherwise noted.
[b]All information obtained from Lide 1993 unless otherwise noted.
[c]All information obtained from EPA 1988a unless otherwise noted.
[d]Lide 1993.
[e]ACGIH 1986.
[f]Bailey and White 1965 (no temperature value given).
[g]Metcalf 1978.
[h]Cessna and Grover 1978.
[i]Jafvert et al. 1990.
[j]Weber 1972.
[k]Meister 1991.
[l]Schwarzenbach et al. 1988.
[m]GEMS 1986.
[n]Loehr and Krishnamoorthy 1988.
[o]Kenaga 1980.
[p]Suntio et al. 1988.
[q]EPA 1979.
[r]Plimmer 1976.
[s]Hamaker and Kerlinger 1969.
[t]Shen 1982a.
[u]Shen 1982b.

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

4,6-Dinitro-o-cresol has been identified in at least 56 of the 1,854 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2017). However, the number of sites in which 4,6-dinitro-o-cresol has been evaluated is not known. The number of sites in each state is shown in Figure 5-1. Of these sites, 56 are located within the United States.

Figure 5-1. Number of NPL Sites with 4,6-Dinitro-o-cresol Contamination



Source: ATSDR 2017

- The most likely route of exposure to DNOC for the general population is via ingestion of DNOC in drinking water.
- A daily intake of DNOC from drinking water has not been estimated, based on a lack of pertinent data.
- DNOC is primarily used as an intermediate in pesticide manufacturing.
- DNOC is not likely to volatilize appreciably from water or soil. Available data indicate that biodegradation of DNOC does not occur rapidly.

5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.2.1 Production

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

Table 5-1. Facilities that Produce, Process, or Use 4,6-Dinitro-*o*-Cresol (DNOC)

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
IN	1	100	999	12

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

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

Source: TRI16 2017 (Data are from 2016)

DNOC is prepared by sulfonating o-cresol with excess sulfuric acid at 80–100 °C and subsequently nitrating 4,6-disulfonic-*o*-cresol (produced by the sulfuric acid) with nitric acid or nitrous fumes (Harvey 1953). 2,6-Dinitro-*p*-cresol is prepared by nitrating *p*-cresol with nitric acid in acetic acid or a nitric acid-sulfuric acid mixture (Harvey 1953). Neither 4,6-dinitro-*m*-cresol nor 3,5-dinitro-*o*-cresol can be produced on a commercial level by the simple nitration of *o*- or *m*-cresol (Harvey 1953). The current production volume of this compound is not known, but the production volume was between 0.1 and 1.0 million pounds in 1977 (EPA 1988a).

5.2.2 Import/Export

Comprehensive current data on the import/export of the dinitrocresols were not located in the literature. However, three U.S. companies imported small amounts (<100,000 pounds or 45,300 kg) of DNOC in 1977 (EPA 1988a). Two tariff categories are defined covering a variety of meta- and ortho- forms of dinitrocresols. During 1992, tariffs were collected from imports totaling 10,719 kg of dinitrocresols;

during 1993, tariffs were collected from imports totaling 800 kg of dinitrocresols (NTDB 1994). The available information suggests a decrease in the import volumes since the late 1970s.

5.2.3 Use

DNOC is a nonsystemic stomach poison and contact insecticide. In the United States, the EPA canceled its registration as a pesticide agent starting in 1991 (EPA 1993b; Farm Chemicals Handbook 1993; HSDB 1994). It is strongly phytotoxic for broad-leaved plants, and its use as an insecticide in the United States has been limited to dormant sprays, especially for such fruit trees as apples or peaches. As a contact herbicide, it was used to control broad-leaved weeds in cereals and to desiccate potato and leguminous seed crops before harvesting (Worthing 1987). 2,4-Dinitro-6-sec-butylphenol, which is less expensive and a more effective herbicide, had begun to replace DNOC by the late 1980s (EPA 1988a). DNOC has been used as a free radical polymerization inhibitor (EPA 1988a). 2,6-Dinitro-p-cresol is used as an intermediate for synthesis of fungicides and biologically active compounds, dyes, and pharmaceuticals, and as a polymerization inhibitor for vinyl aromatic compounds (EPA 1988a; Hawley 1981).

5.2.4 Disposal

Rotary kiln incineration at a temperature range of 820–1,000°C and residence times of seconds for liquid and gaseous wastes and hours for solids can totally destroy dinitrocresols. Fluidized bed incineration at a temperature range of 450–980°C and residence times of seconds for liquid and gaseous wastes and longer for solid wastes can also destroy dinitrocresols. Mixing dinitrocresols with a more flammable solvent may facilitate incineration. Containers used for dinitrocresols that are not to be reused can be disposed by burial in a designated landfill (HSDB 1994).

5.3 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2005). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ ≥10 full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953

(limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes ≥25,000 pounds of any TRI chemical or otherwise uses >10,000 pounds of a TRI chemical in a calendar year (EPA 2005).

5.3.1 Air

Estimated releases of 1 pound (<0.001 metric tons) of DNOC to the atmosphere from one domestic manufacturing and processing facility in 2016, accounted for about 100% of the estimated total environmental releases from facilities required to report to the TRI (TRI16 2017). These releases are summarized in Table 5-2.

Table 5-2. Releases to the Environment from Facilities that Produce, Process, or Use 4,6-Dinitro-*o*-Cresol (DNOC)[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
IN	1	1	0	0	0	No data	1	No data	1
Total	1	1	0	0	0	0	1	0	1

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

RF = reporting facilities; UI = underground injection

Source: TRI16 2017 (Data are from 2016)

5.3.2 Water

There were no estimated releases of DNOC to surface water from one domestic manufacturing and processing facility in 2016 required to report to the TRI (TRI16 2017). There were no data on releases to publicly owned treatment works (POTWs) (TRI16 2017; see Table 5-2).

5.3.3 Soil

There were no estimated releases of DNOC to soils from one domestic manufacturing and processing facility in 2016 required to report to the TRI (TRI16 2017). There were no releases via underground injection (TRI16 2017; see Table 5-2).

5.4 ENVIRONMENTAL FATE

5.4.1 Transport and Partitioning

In laboratory experiments, photolysis of *o*-cresol in the presence of nitrogen oxides produced dinitrocresols in the aerosol phase (Grosjean 1984, 1985). It was, therefore, presumed that dinitrocresols would be present in the ambient atmosphere in aerosol form (Grosjean 1984, 1985). The distance of atmospheric transport for DNOC depends on the half-life and the physical state of the compound in air. Residence times during atmospheric transport can be sufficiently long so that such physical removal processes as wet or dry deposition may be important. The efficiency of both wet and dry precipitation is higher for particulate matter than for compounds that exist in the gas phase in the air (Schroeder et al. 1987). Therefore, atmospheric dinitrocresols, which exist predominantly in the particulate phase, may be removed by rain and snow, and these compounds may not be transported long distances from their source of emission. The detection of DNOC in rain and snow, and the observation that the ratio of concentrations of DNOC in rainwater to concentrations in air during a rain event was 5.6×10^4, confirm the importance of these removal processes (Alber et al. 1989; Leuenberger et al. 1988; Tremp et al. 1986). Precipitation of atmospheric dinitrocresols transports the compound from air to land and water.

The pK_a value of 4.4 (see Table 4-2) for DNOC suggests that in natural waters with a pH 5–9, >50% of the compound exists in the ionic state at pH 5 and the percent of ionic forms increases as the pH increases. In addition to this dissociation effect, DNOC may form H-bonds in water (EPA 1979), reducing its vapor pressure and chances of volatility from water. Using a Henry's law constant value of 1.4×10^{-6} atm-m^3/mole (Shen et al. 1982a, 1982b) and an estimation method (Thomas 1990), the estimated

volatilization half-life of DNOC from a typical river 1 m deep, with a current speed of 1 m/second, and an overhead wind speed of 3 m/second, is 36 days. Therefore, direct volatilization from water will not be significant for DNOC.

The partitioning of DNOC from water to solids present in water transports the compound from the water phase to suspended solids and sediment. The adsorption of DNOC from water by suspended solids and sediment is pH dependent, and the adsorption increases as the pH of the solution decreases (Frissel and Bolt 1962; Jafvert 1990). The adsorption of DNOC also depends on the clay and organic carbon content of the suspended solids and sediment; an increase in either value increases adsorption (EPA 1979; Frissel and Bolt 1962; Jafvert 1990). This adsorption will decrease the concentration of DNOC in water. DNOC's adsorption coefficient (a Freudlich sorption parameter, Kp) of 590 mg/g (Dobbs et al. 1987; Dobbs et al. 1989) indicates that the compound moderately sorbs to suspended solids and sediment in water. However, in Rhine River water with a pH of 7.9 (Wanner et al. 1989), only an estimated 9.3% of DNOC accumulated in bottom sediment (Halfon and Bruggemann 1989). This low adsorption may be due to high water pH, lack of clay, or a low organic carbon content of the sediment, or a combination of these factors.

No experimental data regarding the bioconcentration potential of DNOC in aquatic organisms were located. Based on an estimated bioconcentration factor (BCF) of 40 (Kenaga 1980), the bioconcentration of DNOC in aquatic organisms may not be significant; however, based on an estimated log octanol/water partition coefficient (log K_{ow}) value of 2.85, DNOC may bioaccumulate in aquatic organisms (Loehr and Krishnamoorthy 1988). Given that DNOC exists predominantly in ionic forms in most natural waters (pH 5–9) and that the compound is markedly toxic to fish, bioconcentration is not expected to be important (EPA 1979).

Given the low values for vapor pressure (1.05×10^{-4} mm Hg) (see Table 4-2) and Henry's law constant (1.4×10^{-6} atm·m^3/mol) (see Table 4-2), and the consideration that the majority of the compound will be either in an ionic state or tied up through H-bonds, volatilization is not a significant transport process for DNOC from soil to the air. However, some loss of DNOC by volatilization via co-distillation with water may occur, as observed (Kaufman 1976) in the case of dinoseb, with its active ingredient 2,3-dinitro-6-sec-butyl-phenol. Volatilization is expected to occur more readily with an increase in soil acidity (which facilitates the formation of undissociated species DNOC), moisture content, and temperature (Kaufman 1976); however, a laboratory study of two types of soil found no loss of DNOC by volatilization in 65 days (Loehr 1989). The adsorption of DNOC to soil increases with a decrease in soil

pH and an increase in clay and organic carbon contents of soil. The estimated soil sorption (K_{oc}) values ranging from 2.35 to 2.77 indicate that this compound is moderately adsorbed in soil. Therefore, DNOC shows moderate mobility in soil, but because of its short persistence in soil (<1 month), the compound may not leach beyond 5 cm (Ammon 1985). Similar conclusions were reached by other investigators. In spite of moderate mobility, DNOC leaching was not observed from soil columns with at least 16 bed volumes of leachate (Pohland et al. 1987). On the other hand, the water soluble salts of DNOC (sodium, potassium, calcium, and ammonium) might be expected to leach into soil. Although no experimental data were located, it seems likely that DNOC will transfer to adjacent surface water or land via runoff water from treated fields or waste sites.

5.4.2 Transformation and Degradation

Air. The two processes likely to remove dinitrocresols from the atmosphere are reactions with hydroxyl and nitrate radicals (Atkinson et al. 1992). No experimental kinetic data are available for these two reactions (Grosjean 1991). The rate constant for the gas phase reaction of dinitrocresols with OH radicals is 3.0×10^{-14} cm^3/molecule-second (Grosjean 1991). Using the method of Atkinson (1988), the estimated rate constant for this reaction is 2.1×10^{-13} cm^3/molecule-second. Based on an average ambient atmospheric concentration of OH radicals in the northern hemisphere of 5×10^5 radicals/cm^3 (Atkinson 1988) and either of the rate constant values, the estimated half-life of the DNOC reaction with OH radicals is >77 days. Since dinitrocresols are expected to be present predominantly in the particulate phase in the atmosphere, the reaction rate will be even slower compared to the gas phase reaction rate (Grosjean 1991). The reactions of phenol and cresols with NO_3 radicals may be significant processes in the air (Atkinson et al. 1992). However, the products of these reactions with phenol or cresols are *o*- and possibly *p*- substituted nitrophenol and cresol compounds (Atkinson et al. 1992). Since both *o* and *p* positions are already occupied by nitro substituents, the reaction of DNOC with NO_3 radicals does not seem to be a significant atmospheric process.

Photolysis of dinitrocresols is another reaction that can be significant for the destruction of these compounds in the air. In water, the neutral DNOC species has a light absorption spectrum with a shoulder at 305 nm (Schwarzenbach et al. 1988). Therefore, it is possible that atmospheric DNOC will absorb sunlight and undergo a reaction such as nucleophilic displacement of the nitro group by a hydroxyl group. Experimental evidence of such transformation reactions is not available (Kaufman 1976). Photolysis of a structurally similar compound, dinoseb (which has a sec-butyl group in place of the

o-methyl group), produced side-chain hydroxylation or unsaturation (of the sec-butyl group), but no nucleophilic substitution of nitro groups (Kaufman 1976).

Water. Both neutral and anionic species of DNOC show absorption shoulders at wavelengths >300 nm (Schwarzenbach et al. 1988). However, photolysis of DNOC in water involving nucleophilic displacement of the nitro group by the hydroxyl group does not seem likely (EPA 1979). The photochemical reduction of the nitro group in DNOC is possible in water in the presence of a reducing agent (e.g., ascorbic acid or ferrous ions) and a sensitizer, such as chlorophyll (EPA 1979). However, there is no experimental evidence of the photochemical reduction of DNOC in water.

The estimated rate constants for the reaction of DNOC and 2,6-dinitro-*p*-cresol with singlet oxygen in water at pH ~7 are 1.25×10^5/molecule-second and 1.43×10^7/molecule-second, respectively (Tratnyek and Holgne 1991). Based on an average concentration of singlet oxygen in eutrophic freshwater of 4×10^{-14} M (Tratnyek and Holgne 1991) and the above reaction rate constants, this reaction may be insignificant for DNOC. The estimated half-life for 2,6-dinitro-*p*-cresol due to this reaction is 14 days, and it may be a significant process for the destruction of 2,6-dinitro-*p*-cresol in eutrophic freshwater.

Several pure cultures of microorganisms isolated from soil or sediment, such as *Corynebacterium simplex* (Gundersen and Jensen 1956; Jensen and Gundersen 1955), *Rhizobium leguminosarum* (Hamdi and Tewfik 1970), *Veillonella alkalescens* (McCormick et al. 1976), unadapted or phenol-adapted *Pseudomonas* sp. (Chambers and Kabler 1964; Tewfik and Evans 1966), and *Azotobacter* sp. (Wallnoefer et al. 1978), can biodegrade DNOC. Above a certain concentration, DNOC may be toxic to organisms. For example, at concentrations >500 mg/L, DNOC may be toxic to *C. simplex* (Bollen 1961). The degradation pathway will depend on the microorganism. It has been shown that *C. simplex* releases nitro groups of DNOC as nitrite ions (Gundersen and Jensen 1956). *Pseudomonas* sp. may biodegrade DNOC by ring cleavage. Successive replacement of nitro groups with hydroxyl groups can also occur, forming trihydroxytoluene (Golovleva et al. 1992; Tewfik and Evans 1966). The biodegradation may proceed by the successive reduction of nitro groups to amino groups by *V. alkalescens* and a *Pseudomonas* sp. (McCormick et al. 1976; Williams 1977). The metabolites that have been isolated as biodegradation products are 6-amino-4-nitro-*o*-cresol, 6-acetamido-4-nitro-*o*-cresol, 2-methyl-6-nitro-catechol, 2-methyl-6-amino-catechol, and 2,3,5-trihydroxytoluene (Tewfik and Evans 1966; Wallnoefer et al. 1978). Although these studies with pure cultures of microorganisms are important to establish degradative pathways, their relevance to environmental situations is uncertain.

The biodegradation of DNOC was also tested with a mixture of microorganisms in activated sludge (Thorn and Agg 1975; Zahn and Wellens 1980), garden soil, compost, river mud, sediment of a waste lagoon (Tabak et al. 1964), and settled domestic waste water (Tabak et al. 1981). These biodegradation studies with mixtures of microorganisms concluded that DNOC does not rapidly degrade under these conditions.

A patented waste treatment process that used activated sludge with added powdered activated carbon removed 99% of DNOC from influent that contained 11 μg/L of the compound (Patterson and Kodukala 1981). However, it is difficult to separate the contribution of the biological process from the adsorption effect of the activated carbon in removing DNOC from the influent. DNOC was resistant to anaerobic biodegradation under methanogenic conditions (O'Connor and Young 1989). Both laboratory die-away tests and experiments with natural marine plankton communities showed that DNOC was resistant to anaerobic biodegradation (Kuiper and Hanstveit 1988). Based on observations following a pesticide spill on the Rhine River involving DNOC, it was estimated that half of the initial DNOC had disappeared (due to a combination of biotic and abiotic processes) within 30 days (Capel et al. 1988).

Sediment and Soil. The transformation and degradation pathways of DNOC in soil and sediment have not been studied thoroughly. The photolysis of DNOC in soil below the surface layer and in sediment is not significant due to the lack of available sunlight. DNOC does not contain any functional groups amenable to hydrolysis (EPA 1988a). It has been speculated that adsorbed DNOC may undergo hydrolysis on clay surfaces under acidic conditions (EPA 1979), but there is no experimental evidence. Biodegradation may be the most significant process for the transformation and degradation of DNOC in soil.

Work reported in Bruinsma (1960) documents that above certain dosage levels, DNOC may be toxic to many types of soil microorganisms. These findings help explain a pattern in the available literature where the biodegradability of DNOC is widely taken for granted, but where the results of different empirical studies on the persistence of DNOC in soils may show widely differing results. The effects of DNOC toxicity to soil flora also make it difficult to interpret persistent (or disappearance) findings in terms of chemical kinetics and such concepts as half-lives.

In a soil column experiment, the estimated time for degradation of one-half the original amount of DNOC was 14 days (Kincannon and Lin 1985). These results are in line with findings from field plot analyses in Germany (Hurle and Rademacher 1970), where the disappearance of one-half the initial DNOC levels

took 15 days. Other investigators have estimated that the persistence of DNOC in soil ranges from 14 days to >l month (Ammon 1985; Goring et al. 1975; Jensen and Lautrup-Larsen 1967). However, in a study to determine the treatability potential of waste sludge from explosives production, no loss of DNOC was observed in two soil samples in 65 days (Loehr 1989). The soil in this experiment was not previously exposed to industrial chemicals, wastes, or any pretreatment to acclimate the microorganisms to the chemicals.

5.5 LEVELS IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to dinitrocresols depends, in part, on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of dinitrocresols 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 dinitrocresols 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 lowest limit of detections that are achieved by analytical analysis in environmental media.

Table 5-3. Lowest Limit of Detection Based on Standards[a]

Media	Detection limit	Reference
Air	0.07 mg/m^3	NIOSH 1984
Drinking water	0.009 µg/L	Di Corcia and Marchetti 1992
Surface water and groundwater	0.07 µg/L	Buchholz and Pawliszyn 1993
Soil	0.005 mg/kg	Roseboom et al. 1981
Sediment	160 µg/L	EPA 1986a
Whole blood	<0.5 mg/L	Parker 1949

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

Detections of dinitrocresols in air, water, and soil at NPL sites are summarized in Table 5-4.

Table 5-4. Dinitrocresols Levels in Water, Soil, and Air of National Priorities List (NPL) Sites

Medium	Median[a]	Geometric mean[a]	Geometric standard deviation[a]	Number of quantitative measurements	NPL sites
Water (ppb)	10	44.3	55,100	5	5
Soil (ppb)	270,000	77,100	9,040	7	6
Air (ppbv)	No data				

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

5.5.1 Air

Other than in workplace air (see Section 5.6), no data regarding the concentrations of DNOC in ambient air in the United States were located. From the concentration of DNOC in rainwater during a rain event in Dubendorf, Switzerland, the concentration of DNOC in air was estimated to be (from rainwater to air partition ratio) 0.05 µg/m^3 (0.06 ppb) (Leuenberger et al. 1988).

5.5.2 Water

DNOC was detected at a concentration range of 8–400 µg/L in waste water resulting from the production and purification of trinitrotoluene (Spanggord et al. 1982a). DNOC was also qualitatively detected in the waste waters of a plant in England that produced pest control chemicals (EPA 1988a) and in two effluents from unspecified chemical plants in the United States (EPA 1976b). In a project that monitored pollutant levels in urban runoff water of 1.5 cities in the United States, DNOC was not detected (detection limit unspecified) in any runoff water (Cole et al. 1984). The Great Lakes Water Quality Board has not viewed DNOC as a toxic substance of critical concern based on levels typically encountered in water from Lakes Erie and Michigan (Great Lakes Water Quality Board 1983). DNOC was detected at a concentration of <10 µg/L in water from the Potomac River near Quantico, Virginia (Hall et al. 1987). Following an accidental spill in 1986, the estimated concentration of DNOC in Rhine River water in Nauf, Switzerland, was 100–430 µg/L (Capel et al. 1988). In California, where DNOC had been used as a pesticide, DNOC was detected in five groundwater samples at a maximum concentration of 35 µg/L (Cohen 1986; Holden 1986). In 1985, DNOC was detected in rainwater from Dubendorf, Switzerland, at concentrations ranging from 0.95 to 2.9 µg/L (Leuenberger et al. 1988; Tremp et al. 1986).

5.5.3 Sediment and Soil

DNOC is expected to be found in soil near plants where the pesticide is produced and formulated, near disposal sites, and in agricultural and waste lands to which the pesticide was applied. No quantitative data regarding the levels of DNOC in soil were located. Similarly, DNOC is expected to be found in the sludge of waste treatment plants, such as pesticide manufacturing plants, trinitrotoluene production plants, and in the sediment of rivers where the pesticide has been discharged from manufacturing plants or carried by runoff water from treated lands or waste disposal sites. However, no quantitative data regarding the levels of DNOC in sludge were located. Studies on the lower Grand Calumet River around the Indian Harbor area (Hoke et al. 1993) has documented sediment concentration of DNOC ranging from 0.24 to 2.08 mg/kg (dry weight).

5.5.4 Other Media

DNOC was not found in fish collected between 1980 and 1981 from Great Lakes harbors and tributaries (Devault 1985). DNOC was detected below the tolerance level on Rumanian plums at harvest time and in potatoes from treated fields in what was formerly East Germany (HSDB 1994).

5.6 GENERAL POPULATION EXPOSURE

The general population could be exposed to DNOC from inhaling air or ingesting food and drinking water. To estimate the daily intake of DNOC by the general population from inhaling ambient air or ingesting drinking water and food, the levels of DNOC in these media must be known, and these values were not located in the literature. There was no indication in the literature that DNOC is used in any consumer products that could lead to dermal exposure.

Workers involved in manufacturing and formulating, incinerating, or spraying the pesticide on agricultural products and waste lands, and possibly workers involved in remediating Superfund sites containing this pesticide could have been or might be occupationally exposed to DNOC. Of all the possible exposure scenarios, the level of dermal exposure of workers during spraying of DNOC in the field has actually been measured. During spray-thinning of apples with liquid sprays, the estimated average dermal exposure may range from 22.5 to 63.2 mg/hour, and the corresponding average inhalation exposure may range from <0.05 to 0.4 mg/hour (Batchelor et al. 1956; Durham and Wolfe 1962; Wolfe 1976). The DNOC levels in the urine of sprayers before, during, and after the exposure period were also determined, and DNOC was detected in 5 of 183 spray operators. The DNOC concentrations in urine in

these 5 samples ranged from 0.6 to 1.3 mg/L, with an average of 0.8 mg/L (Batchelor et al. 1956). The concentration of DNOC in plasma of spray operators following a total exposure period of 5–48 hours ranged from <l to 4.3 mg/kg (Batchelor et al. 1956).

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

As discussed (see Section 5.6), spray operators are one group of people that could have experienced potentially high exposures (higher than background levels) to DNOC. Other occupational groups discussed in Section 5.6 have the potential to be exposed to DNOC at higher levels than the general population, but no experimental evidence of higher exposure among these occupational groups was located.

Within the general population, people who live near incinerators burning DNOC, DNOC disposal facilities, and DNOC manufacturing and formulating plants are potentially exposed to higher than background concentrations of DNOC. However, no study located in the literature provided evidence of higher than background exposure to DNOC among these groups of the population. Moreover, no study demonstrated the potential for higher than background exposure to DNOC from consuming excessive amounts of certain foods (e.g., sprayed apples or contaminated fish).

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 dinitrocresols 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 dinitrocresols.

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

6.1 Information on Health Effects

Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to dinitrocresols 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 dinitrocresols. The number of human and animal studies examining each endpoint is indicated regardless of whether an effect was found and the quality of the study or studies.

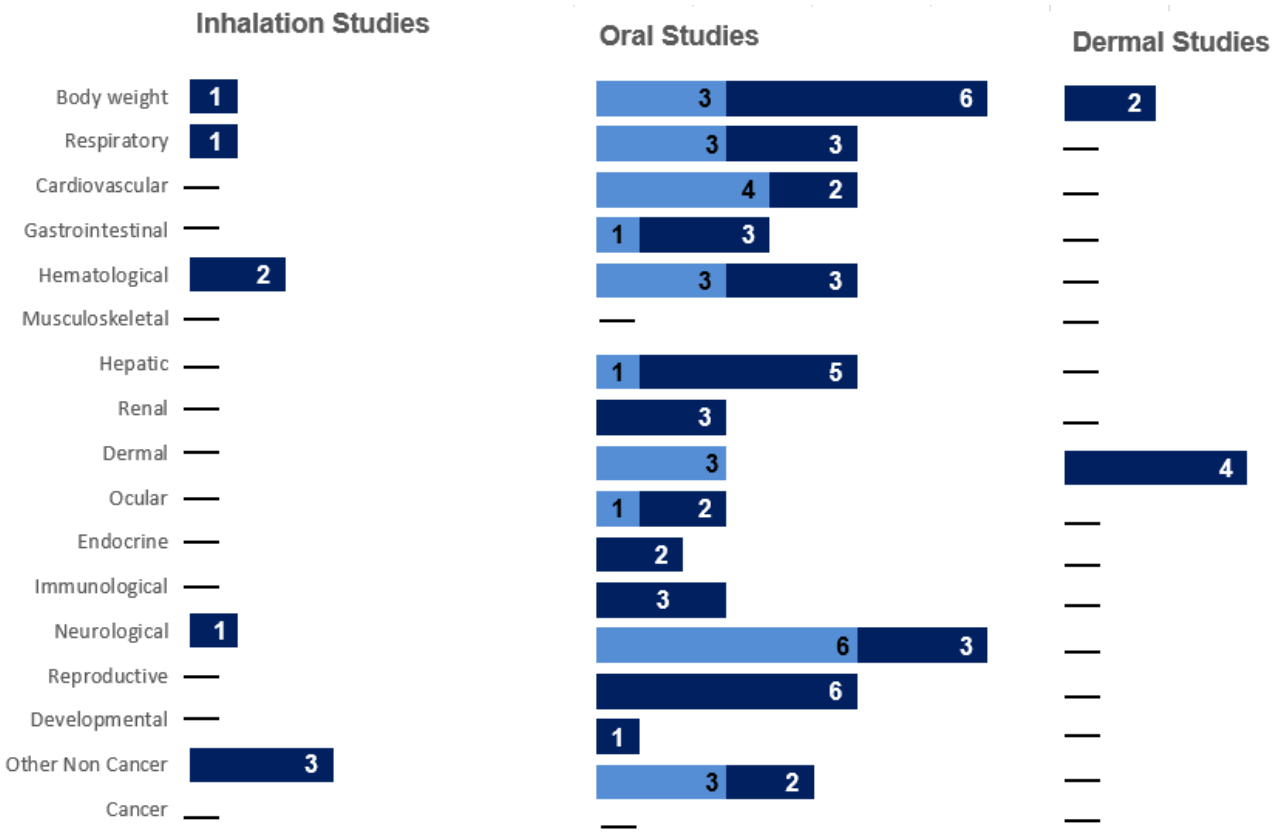
6.2 Identification of Data Needs

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

DNOC acts directly on cell metabolism and interferes with oxidative phosphorylation. The effect of DNOC on increasing the basal metabolic rate was the basis for its use in weight reduction. However, DNOC has not been legally used for weight reduction since the 1950s. DNOC was also formerly used as an herbicide, but EPA began cancelling uses of DNOC as a pesticide in 1987. Therefore, it is not likely

Figure 6-1. Summary of Existing Health Effects Studies on Dinitrocresols By Route and Endpoint

Potential body weight, hepatic, and cancer effects were the most studied endpoints
The majority of the studies examined oral exposure in **animals** (versus **humans**)



*Includes studies discussed in Chapter 2; the number of studies include those finding no effect.

that human subpopulations would be exposed to significant levels of DNOC. In light of these facts, the urgency of additional animal studies is questionable. If human subpopulations with significant potential for exposure to DNOC are identified, they should be monitored for exposure, toxicokinetics, and health endpoints.

Inhalation MRLs. No inhalation MRLs have been derived for DNOC because data for all durations are insufficient. Although health effects have occurred in humans occupationally exposed to DNOC, exposure probably involved both the inhalation and dermal routes, and exposure concentrations were not known. Only one study was located regarding health effects in animals after inhalation exposure to DNOC. In this study, rats exposed to 0.1 or 100 mg/m^3 DNOC for 4–5 hours were lethargic, and rats exposed to 100 mg/m^3 had increased respiratory rates and body temperatures (King and Harvey 1953a). No NOAEL was identified, and other endpoints were not evaluated. Additional animal studies could be designed to adequately assess the effects of acute-, intermediate-, and chronic-duration inhalation exposure to DNOC.

Oral MRLs. MRLs of 0.004 mg/kg/day were derived for acute- and intermediate-duration oral exposure to DNOC based on a LOAEL of 0.35 mg/kg/day based on excessive perspiration, fatigue, and dizziness in a human who took DNOC for weight reduction (Plotz 1936). Similar signs and symptoms were reported among other individuals taking DNOC orally at doses in the range of 0.58–3 mg/kg/day (Dodds and Robertson 1933; Harvey et al. 1951; Ibrahim et al. 1934; Plotz 1936). Animal studies used higher doses of DNOC, and toxicokinetic studies indicate that humans tend to accumulate DNOC to a greater extent and eliminate DNOC more slowly than animals (King and Harvey 1953b). Therefore, additional animal studies would not likely provide adequate information from which to derive MRLs for humans. No chronic-duration oral MRL was derived for DNOC due to the lack of chronic-duration oral studies of humans or animals. DNOC has not been used for weight reduction or pesticide applications for decades; therefore, it is unlikely that humans would be chronically exposed to DNOC. Animal studies do not appear necessary because toxicokinetic studies indicate that humans tend to accumulate DNOC to a greater extent and eliminate DNOC more slowly than animals (King and Harvey 1953b). A lack of adequate data regarding the toxicokinetics in humans precludes extrapolation from animals to humans.

Health Effects. Genotoxicity tests demonstrate DNOC-induced clastogenicity in human and animal systems. No information was located regarding potential carcinogenicity of DNOC in humans or animals. Well-designed chronic toxicity/carcinogenicity animal studies could be performed to assess the potential carcinogenicity of DNOC.

Based on findings of decreased sperm motility and decreased percentage normal sperm in mice treated orally with DNOC (Takahashi et al. 2004, 2006), a well-designed multigenerational study could be performed to assess the effects of DNOC on reproductive success in rats and/or mice.

Limited data are available regarding the potential for DNOC-induced developmental effects in animals (Nehéz et al. 1981). A well-designed developmental toxicity study of rats and/or mice could be performed to assess the potential effects of DNOC on development. Limited information was located regarding the potential immunotoxicity of DNOC in humans (Gordon and Wallfield 1935; Plotz 1936; Scott 1956).

A single animal study (Vos et al. 1983) found no evidence of immunotoxicity in rats following repeated oral exposure to DNOC. Additional animal studies could be designed to more rigorously evaluate the potential immunotoxicity of DNOC.

Epidemiology and Human Dosimetry Studies. No epidemiological studies of workers or other populations exposed to DNOC were located; however, a survey of workers (Bidstrup et al. 1952) and case reports involving occupational exposure (Bidstrup and Payne 1951; Hunter 1950; Pollard and Filbee 1951; Steer 1951) or oral use of DNOC as a weight-reducing drug (Gordon and Wallfield 1935; Ibrahim et al. 1934; Plotz 1936) are available. In addition, some experimental studies in humans were conducted (Dodds and Robertson 1933; Harvey et al. 1951). The main limitation of the studies involving workers is that exposure concentrations were not known; however, the individuals who took DNOC as a weight-reducing drug did so under medical supervision, so doses and durations are known. Similarly, the experimental studies in humans provide information on doses and durations. The available studies in humans have shown that DNOC increases basal metabolic rate, body temperature, pulse, heart rate, and respiratory rate and causes profuse perspiration, excessive thirst, lethargy, dizziness, and fatigue. These endpoints appear to be the most sensitive. Studies in animals have shown that the toxicity of DNOC is exacerbated in hot environments (King and Harvey 1953a). This suggests that people who live and work in tropical climates, particularly agricultural workers who use pesticides, may be more susceptible to the adverse effects of DNOC. Therefore, agricultural workers in the tropics or people who live or work near hazardous waste sites anywhere, but particularly in tropical climates, could be studied to establish cause-and-effect relationships.

Biomarkers of Exposure and Effect. DNOC and/or its metabolites have been measured in various body fluids and tissues. However, it is difficult to determine the extent and timing of exposure from urine or blood levels because DNOC persists in the human body for relatively long periods. DNOC-induced adverse effects are not specific to DNOC. If individuals with DNOC exposure are identified, research to develop more reliable biomarkers of exposure and effect would facilitate future medical surveillance.

Absorption, Distribution, Metabolism, and Excretion. Available data indicate that DNOC is more slowly metabolized and/or excreted in humans than laboratory animals. Additional animal studies would not likely be useful for predictions of toxicokinetics in humans. Studies in humans would be unethical. However, blood and/or urine from individuals who may have been exposed to DNOC could be examined for DNOC metabolites.

Comparative Toxicokinetics. The target organs of DNOC appear to be similar in animals and humans because the mechanism of toxicity (i.e., uncoupling of oxidative phosphorylation) occurs in each species. If additional toxicokinetic data become available for humans and laboratory animals, such data could be used to determine whether a particular animal model might be useful for extrapolating results to humans.

Children's Susceptibility. No information was located to indicate age-related differences in DNOC toxicity. It does not appear necessary to design animal studies that would evaluate potential age-related differences in DNOC toxicity at this time.

Physical and Chemical Properties. Some of the physical and chemical properties (e.g., K_{ow} Henry's law constant), often useful in estimating environmental fate and transport processes, are available for DNOC but not for other isomers of dinitrocresols (see Table 4-2). Although not as important as DNOC, it would still be useful to develop such data for other commercially available isomers of dinitrocresols.

Production, Import/Export, Use, Release, and Disposal. The production and import/export data in recent years for the different isomers of dinitrocresols including DNOC are not available. These data are important for assessing the trend in use for these chemicals. It is known that exposure to DNOC primarily occurs in the workplace (Batchelor et al. 1956; Durham and Wolfe 1962; Wolfe 1976). Since DNOC has been used as a pesticide on certain trees and to control broad-leaved weeds (Worthing 1987), it may have entered certain foods (e.g., apples, cereals). Since DNOC has been primarily used as a

pesticide for agricultural products and on land for locust control (Worthing 1987) and is inefficiently transported from soil to other media (Ammon 1985; Kaufman 1976; Loehr 1989), soil is the environmental medium in which DNOC is expected to be found most frequently. Although some data on the methods of DNOC disposal are available (HSDB 1994), more information on disposal methods and their efficiency in destroying DNOC would be helpful. EPA has regulations governing the disposal of DNOC wastes (HSDB 1994).

Environmental Fate. The partition of DNOC from water to soil and sediment depends on the pH and organic carbon and clay content of soil and sediment (Frissel and Bolt 1962; Jafvert 1990). When soil and sediment have a low pH and high organic carbon and clay content, DNOC partitions from water to soil and sediment. DNOC has been detected infrequently in groundwater (Holden 1986), indicating that only under certain conditions (e.g., when sandy soil is treated with DNOC), will it transport from soil to groundwater. The abiotic reactions that may degrade/transform DNOC in air, water, and soil are not known with certainty. Therefore, studies of the natural chemical processes (e.g., photolysis, oxidation/ reduction) that may degrade/transform DNOC would be helpful.

Bioavailability from Environmental Media. Available information regarding the absorption rate of DNOC after inhalation, oral, or dermal exposure is discussed in the Toxicokinetics Section (Section 3.1). No quantitative data regarding the bioavailability of DNOC from inhalation of, ingestion of, and dermal contact with contaminated water, or inhalation of and dermal contact with contaminated soil are available. It will be helpful to develop quantitative data for bioavailability of DNOC from environmental media. However, the bioavailability from these routes of exposure are expected to be <l00%, because the compound may be present partially in the sorbed state in air, water, and soil.

Food Chain Bioaccumulation. No experimental data for the bioaccumulation potential of DNOC from water to aquatic organisms were located. However, according to one group of investigators, DNOC may bioaccumulate in terrestrial and aquatic organisms (Loehr and Krishnamoorthy 1988). An experimental determination of the bioaccumulation potential for DNOC in terrestrial or aquatic organisms would be helpful. Biomagnification potential for DNOC is unknown.

Exposure Levels in Environmental Media. Other than in workplace air, no data regarding the ambient level of DNOC in air were located. Similarly, no data regarding the levels of DNOC in drinking water and total diet sample were available that would permit an estimation of the daily intake of DNOC from these routes of exposure. Data regarding the levels of DNOC in air, drinking water, and total diet

would be useful for estimating daily DNOC intake by the general population from the various environmental media.

Reliable monitoring data for the levels of dinitrocresols in contaminated media at hazardous waste sites are needed so that the information obtained on levels of dinitrocresols in the environment can be used in combination with the known body burden of dinitrocresols to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Exposure Levels in Humans. Other than in a few instances arising from occupational exposure (Batchelor et al. 1956; Durham and Wolfe 1962; Wolfe 1976), the levels of DNOC in body tissues and fluids of humans are not available. To assess the severity of occupational exposure, it may be useful to determine the background levels of DNOC in the different tissues and body fluids of the general population. This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. No studies are available to assess whether children are at a higher exposure risk than adults. Studies examining potential exposure sources for children would be useful.

Analytical Methods. The analytical methods presently available are capable of determining DNOC in fatty and nonfat foods at levels well below the tolerance limit (Hopper et al. 1992; Roseboom et al. 1981). Methods for DNOC in water are sufficiently sensitive to monitor concentrations well below the MRL for a 70-kg individual (Buchholz and Pawliszyn 1993; Di Corcia and Marchetti 1992). The method for DNOC in air is sensitive to concentrations below the Occupational Safety and Health Administration (OSHA) standard of 0.2 mg/m^3 (NIOSH 1984), but is inconvenient for personal monitoring because of the liquid contained in the bubbler. Methods are currently available for determining degradation products obtained as a result of DNOC biodegradation by pure cultures of microorganisms (Gundersen and Jensen 1956; McCormick et al. 1976; Tewfik and Evans 1966). The limits of detection have not been established for degradation products. If the degradation products are of interest, methods need to be refined and validated.

In humans, a significant portion of absorbed DNOC appears in the urine as the metabolite, 4-amino-2-methyl-6-nitrophenol (WHO 1975). The measurement of this metabolite may be an indicator for DNOC exposure (WHO 1975). Analytical methods for determining DNOC and its urinary metabolite are available (Smith et al. 1953; Truhaut and De Lavaur 1967), although the limits of detection for these

methods have not been documented. Harvey et al. (1951) and King and Harvey (1953b) used paper chromatography to study DNOC in blood after exposures of 0.9–1.3 mg/kg/day and the methods were adequate to detect DNOC for many days after exposure. It seems likely that the methods would be sensitive enough to detect DNOC in blood, at least shortly after the exposure, but this has not been shown. The metabolites 4,6-dinitro-2-hydroxymethylphenol and 4,6-diacetamido-*o*-cresol have also been determined in urine using thin-layer chromatography in conjunction with field desorption mass spectrometry (van der Greel and Leegwater 1983). The limits of detection were not reported for this method either. However, neither blood nor urinary levels of DNOC are reliable indicators for magnitude or the time of exposure to DNOC (Harvey et al. 1951; King and Harvey 1953b). The DNOC levels in any other tissue or body fluid of humans have not been correlated with the magnitude and duration of exposure to DNOC. The identification of a biomarker that can be correlated with the level of exposure to DNOC would be helpful and is needed. The analytical methods should be updated and validated.

6.3 Ongoing Studies

No ongoing studies were identified for DNOC.

CHAPTER 7. REGULATIONS AND GUIDELINES

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

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

Table 7-1. Regulations and Guidelines Applicable to Dinitrocresols

Agency	Description	Information	Reference
	Air		
EPA	RfC	No data	IRIS 2017
WHO	Air quality guidelines	No data	WHO 2010
	Water & Food		
EPA	Drinking water standards and health advisories	No data	EPA 2012
	National primary drinking water regulations	No data	EPA 2009
	RfD	No data	IRIS 2017
WHO	Drinking water quality guidelines	No data	WHO 2017
FDA	EAFUS	No data[a]	FDA 2013
	Cancer		
ACGIH	Carcinogenicity classification	No data	ACGIH 2016
HHS	Carcinogenicity classification	No data	NTP 2016
EPA	Carcinogenicity classification	No data	IRIS 2017
IARC	Carcinogenicity classification	No data	IARC 2017
	Occupational		
ACGIH	TLV		ACGIH 2016
	DNOC	0.2 mg/m^3 [b]	
OSHA	PEL (8-hour TWA) for general industry, shipyards and construction		OSHA 2016a, 2016b, 2016c
	DNOC	0.2 mg/m^3 [b]	
NIOSH	REL (up to 10-hour TWA)		NIOSH 1994, 2016
	DNOC	0.2 mg/m^3 [b]	
	IDLH		
	DNOC	5 mg/m^3 [c]	

Table 7-1. Regulations and Guidelines Applicable to Dinitrocresols

Agency	Description	Information	Reference
	Emergency Criteria		
EPA	AEGLs-air	No data	EPA 2016
AIHA	ERPGs	No data	AIHA 2015
DOE	PACs-air		DOE 2016a
	DNOC		
	PAC-1[d]	0.6 mg/m^3	
	PAC-2[d]	0.83 mg/m^3	
	PAC-3[d]	5 mg/m^3	

[a]The EAFUS list of substances contains ingredients added directly to food that FDA has either approved as food additives or listed or affirmed as GRAS.
[b]Skin notation: potential significant contribution to the overall exposure by the cutaneous route.
[c]Based on acute toxicity data in humans and animals.
[d]Definitions of PAC terminology are available from DOE (2016b).

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = acute exposure guideline levels; AIHA = American Industrial Hygiene Association; DNOC = 4,6-dinitro-*o*-cresol; DOE = Department of Energy; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; ERPG = emergency response planning guidelines; FDA = Food and Drug Administration; GRAS = generally recognized as safe; HHS = Department of Health and Human Services; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health concentrations; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = Protective Action Criteria; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TLV = threshold limit values; TWA = time-weighted average; WHO = World Health Organization

CHAPTER 8. REFERENCES

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APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

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

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

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

APPENDIX A

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Human Health Sciences, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published MRLs. For additional information regarding MRLs, please contact the Division of Toxicology and Human Health Sciences, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-57, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Dinitrocresols
CAS Numbers: 534-52-1; 616-73-9; 497-56-3; 609-93-8
Date: August 1995
March 2017—Updated literature search
Profile Status: Final
Route: Inhalation
Duration: Acute

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

Rationale for Not Deriving an MRL: Although health effects have occurred in humans occupationally exposed to DNOC, exposure probably involved both the inhalation and dermal routes, and exposure concentrations were not known. Only one study was located regarding health effects in animals after inhalation exposure to DNOC. In this study, rats exposed to 0.1 or 100 mg/m^3 DNOC for 4–5 hours were lethargic, and rats exposed to 100 mg/m^3 had increased respiratory rates and body temperatures (King and Harvey 1953a). No NOAEL was identified, and other endpoints were not evaluated. Therefore, data are insufficient to derive MRLs for inhalation exposure to DNOC.

Agency Contact (Chemical Manager): Jessilynn Taylor, M.S., CDR USPHS

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Dinitrocresols
CAS Numbers: 534-52-1; 616-73-9; 497-56-3; 609-93-8
Date: August 1995
March 2017—Updated literature search
Profile Status: Final
Route: Inhalation
Duration: Intermediate

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

Rationale for Not Deriving an MRL: Although health effects have occurred in humans occupationally exposed to DNOC, exposure probably involved both the inhalation and dermal routes, and exposure concentrations were not known. Only one study was located regarding health effects in animals after inhalation exposure to DNOC. In this study, rats exposed to 0.1 or 100 mg/m^3 DNOC for 4–5 hours were lethargic, and rats exposed to 100 mg/m^3 had increased respiratory rates and body temperatures (King and Harvey 1953a). No NOAEL was identified, and other endpoints were not evaluated. Therefore, data are insufficient to derive MRLs for inhalation exposure to DNOC.

Agency Contact (Chemical Manager): Jessilynn Taylor, M.S., CDR USPHS

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Dinitrocresols
CAS Numbers: 534-52-1; 616-73-9; 497-56-3; 609-93-8
Date: August 1995
March 2017—Updated literature search
Profile Status: Final
Route: Inhalation
Duration: Chronic

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

Rationale for Not Deriving an MRL: Although health effects have occurred in humans occupationally exposed to DNOC, exposure probably involved both the inhalation and dermal routes, and exposure concentrations were not known. Only one study was located regarding health effects in animals after inhalation exposure to DNOC. In this study, rats exposed to 0.1 or 100 mg/m^3 DNOC for 4–5 hours were lethargic, and rats exposed to 100 mg/m^3 had increased respiratory rates and body temperatures (King and Harvey 1953a). No NOAEL was identified, and other endpoints were not evaluated. Therefore, data are insufficient to derive MRLs for inhalation exposure to DNOC.

Agency Contact (Chemical Manager): Jessilynn Taylor, M.S., CDR USPHS

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:**	4,6-Dinitro-*o*-cresol (DNOC)
CAS Numbers:	534-52-1
Date:	August 1995 March 2017—Updated literature search
Profile Status:	Final
Route:	Oral
Duration:	Acute
MRL	0.004 mg/kg/day
Critical Effect:	Excessive perspiration, fatigue, and dizziness
Reference:	Plotz 1936
Point of Departure:	LOAEL of 0.35 mg/kg/day
Uncertainty Factor:	100
LSE Graph Key:	4
Species:	Human

MRL Summary: An acute-duration oral MRL of 0.004 mg/kg/day was derived for DNOC based on excessive perspiration, fatigue, and dizziness in a human who took DNOC for the purpose of weight reduction (Plotz 1936). The MRL is based on a LOAEL of 0.35 mg/kg/day and a total uncertainty factor of 100 (10 for use of a LOAEL and 10 for human variability).

Selection of the Critical Effect: Five healthy male volunteers weighing 59–81.4 kg who received 75 mg/day of DNOC (0.92–1.27 mg/kg/day) on 5 consecutive days experienced lassitude, headache, and malaise (Harvey et al. 1951). Two of an unspecified number of human subjects who received 3 mg/kg/day of DNOC had a 70–100% increase in metabolic rate within 3 days, and a slight increase in pulse rate, sweating, lethargy, headache, loss of appetite, and definite greenish-yellow pigmentation of the conjunctivae (Dodds and Robertson 1933).

In a case report of 15 patients who received 50 mg of DNOC/day (average dose consumed 1.05 mg/kg/day for 14–63 days), the average amount of weight loss was 0.45 kg/week (Ibrahim et al. 1934). DNOC caused an increase in basal metabolic rate, excessive perspiration, thirst, and fatigue. Yellow pigmentation of the conjunctivae occurred in all cases. Thus, it appears that some individuals were able to tolerate higher doses of DNOC for longer periods of time before developing symptoms. For this reason, the acute oral LOAEL of 0.35 mg/kg/day was considered to be an appropriate basis for the intermediate-duration MRL as well as for the acute-duration MRL. Animal studies all used higher doses of DNOC than human studies. Toxicokinetic studies indicate that humans tend to accumulate DNOC to a greater extent and eliminate DNOC more slowly than animals (King and Harvey 1953b). Furthermore, the use of DNOC as a weight-reducing drug in humans was carried out under medical supervision, and information on actual doses and durations were available. Therefore, the LOAEL of 0.35 mg/kg/day for excessive perspiration, fatigue, and dizziness was selected as the critical effect.

Selection of the Principal Study: The study of Plotz (1936) provided the lowest adverse effect level data for humans.

Summary of the Principal Study:

Plotz M. 1936. Dinitro-ortho-cresol. A metabolic stimulator and its toxic side-actions. N Y State J Med 41:266-268.

Three human subjects were administered DNOC for the purpose of weight reduction; the investigator took DNOC in a self-experiment as well. One subject received 0.75 mg/kg/day for 3 days, but experienced elevated body temperature, fatigue, and dizziness after 2 days. After a 2-week period without DNOC exposure, treatment was resumed at 0.35 mg/kg/day, and the subject complained of excessive perspiration, fatigue, and dizziness on the 7th day. The average doses taken by the other patients and the investigator were 0.58–1.0 mg/kg/day for periods of 4–11 weeks. Basal metabolic rate, pulse, blood pressure, body temperature, and body weight were monitored. Signs of toxicity included marked palpitations, elevated pulse rate, elevated body temperature, excessive perspiration, fatigue, lassitude, headache, a greenish tinge to the sclerae, and maculopapular, urticarial eruptions.

Selection of the Point of Departure for the MRL: The LOAEL of 0.35 mg/kg/day for excessive perspiration, fatigue, and dizziness was selected as the point of departure for deriving an MRL for acute-duration oral exposure to DNOC.

Calculations: None.

Uncertainty Factor: The LOAEL of 0.35 mg/kg/day was divided by a total uncertainty factor of 100:

- 10 for use of a LOAEL
- 10 for human variability

MRL = LOAEL ÷ uncertainty factors
0.35 mg/kg/day ÷ (10 x 10) = 0.004 mg/kg/day

Other Additional Studies or Pertinent Information that Lend Support to this MRL: See *Selection of the Critical Effect* above.

Agency Contact (Chemical Manager): Jessilynn Taylor, M.S., CDR USPHS

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:**	4,6-Dinitro-*o*-cresol (DNOC)
CAS Numbers:	534-52-1
Date:	August 1995 March 2017—Updated literature search
Profile Status:	Final
Route:	Oral
Duration:	Intermediate
MRL	0.004 mg/kg/day
Critical Effect:	Excessive perspiration, fatigue, and dizziness
Reference:	Plotz 1936
Point of Departure:	LOAEL of 0.35 mg/kg/day
Uncertainty Factor:	100
LSE Graph Key:	4
Species:	Human

MRL Summary: An intermediate-duration oral MRL of 0.004 mg/kg/day was derived for DNOC based on excessive perspiration, fatigue, and dizziness in a human who took DNOC for the purpose of weight reduction (Plotz 1936). The MRL is based on a LOAEL of 0.35 mg/kg/day and a total uncertainty factor of 100 (10 for use of a LOAEL and 10 for human variability).

Selection of the Critical Effect: : Five healthy male volunteers weighing 59–81.4 kg who received 75 mg/day of DNOC (0.92–1.27 mg/kg/day) on 5 consecutive days experienced lassitude, headache, and malaise (Harvey et al. 1951). Two of an unspecified number of human subjects who received 3 mg/kg/day of DNOC had a 70–100% increase in metabolic rate within 3 days, and a slight increase in pulse rate, sweating, lethargy, headache, loss of appetite, and definite greenish-yellow pigmentation of the conjunctivae (Dodds and Robertson 1933).

In a case report of 15 patients who received 50 mg of DNOC/day (average dose consumed 1.05 mg/kg/day for 14–63 days), the average amount of weight loss was 0.45 kg/week (Ibrahim et al. 1934). DNOC caused an increase in basal metabolic rate, excessive perspiration, thirst, and fatigue. Yellow pigmentation of the conjunctivae occurred in all cases. Thus, it appears that some individuals were able to tolerate higher doses of DNOC for longer periods of time before developing symptoms. For this reason, the acute oral LOAEL of 0.35 mg/kg/day was considered to be an appropriate basis for the intermediate-duration MRL as well as for the acute-duration MRL. Animal studies all used higher doses of DNOC than human studies. Toxicokinetic studies indicate that humans tend to accumulate DNOC to a greater extent and eliminate DNOC more slowly than animals (King and Harvey 1953b). Furthermore, the use of DNOC as a weight-reducing drug in humans was carried out under medical supervision, and information on actual doses and durations were available. Therefore, the LOAEL of 0.35 mg/kg/day for excessive perspiration, fatigue, and dizziness was selected as the critical effect.

Selection of the Principal Study: The study of Plotz (1936) provided the lowest adverse effect level data for humans.

Summary of the Principal Study:

Plotz M. 1936. Dinitro-ortho-cresol. A metabolic stimulator and its toxic side-actions. N Y State J Med 41:266-268.

Three human subjects were administered DNOC for the purpose of weight reduction; the investigator took DNOC in a self-experiment as well. One subject received 0.75 mg/kg/day for 3 days, but experienced elevated body temperature, fatigue, and dizziness after 2 days. After a 2-week period without DNOC exposure, treatment was resumed at 0.35 mg/kg/day, and the subject complained of excessive perspiration, fatigue, and dizziness on the 7th day. The average doses taken by the other patients and the investigator were 0.58–1.0 mg/kg/day for periods of 4–11 weeks. Basal metabolic rate, pulse, blood pressure, body temperature, and body weight were monitored. Signs of toxicity included marked palpitations, elevated pulse rate, elevated body temperature, excessive perspiration, fatigue, lassitude, headache, a greenish tinge to the sclerae, and maculopapular, urticarial eruptions.

Selection of the Point of Departure for the MRL: The LOAEL of 0.35 mg/kg/day for excessive perspiration, fatigue, and dizziness was selected as the point of departure for deriving an MRL for intermediate-duration oral exposure to DNOC.

Calculations: None.

Uncertainty Factor: The LOAEL of 0.35 mg/kg/day was divided by a total uncertainty factor of 100:

- 10 for use of a LOAEL
- 10 for human variability

MRL = $BMDL_{05}$ ÷ uncertainty factors
0.35 mg/kg/day ÷ (10 x 10) = 0.004 mg/kg/day

Other Additional Studies or Pertinent Information that Lend Support to this MRL: See *Selection of the Critical Effect* above.

Agency Contact (Chemical Manager): Jessilynn Taylor, M.S., CDR USPHS

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Dinitrocresols
CAS Numbers: 534-52-1; 616-73-9; 497-56-3; 609-93-8
Date: August 1995
March 2017—Updated literature search
Profile Status: Final
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data from which to derive a chronic-duration oral MRL for DNOC.

Rationale for Not Deriving an MRL: There are no chronic-duration oral data for humans or animals.

Agency Contact (Chemical Manager): Jessilynn Taylor, M.S., CDR USPHS

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR DINITROCRESOLS

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 dinitrocresols.

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, and chemical interactions data for dinitrocresols. 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 dinitrocresols 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 dinitrocresols are presented in Table B-1.

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

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

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

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

B.1.1 Literature Search

The current literature search was intended to update the health effects sections of the existing toxicological profile for dinitrocresols (ATSDR 1995), thus, the literature search was restricted to studies published between January 1993 to March 2017. The following main databases were searched in March 2017:

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

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

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

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

Table B-2. Database Query Strings

Database search date	Query string
PubMed	
03/2017	((("2,4-Dinitro-5-methylphenol"[tw] OR "3-Methyl-4,6-dinitrophenol"[tw] OR "4,6-Dinitro-m-cresol"[tw] OR "5-methyl-2,4-dinitro-Phenol"[tw]) AND (1993/01/01 : 3000[dp] OR

Table B-2. Database Query Strings

Database search date	Query string
	1993/01/01 : 3000[crdat] OR 1993/01/01 : 3000[edat])) OR ((534-52-1[rn] OR 1604ZJR09T[rn] OR "4,6-dinitro-o-cresol"[supplementary concept] OR "4,6-dinitro-o-cresol"[nm]) AND (1993/01/01 : 3000[dp] OR 1993/01/01 : 3000[mhda])) OR (("3,5-Dinitro-o-cresol"[tw] OR "2-methyl-3,5-dinitro-Phenol"[tw] OR "3,5-Dinitro-ortho-cresol"[tw]) AND (1993/01/01 : 3000[dp] OR 1993/01/01 : 3000[crdat] OR 1993/01/01 : 3000[edat])) OR ((609-93-8[rn] OR L572BVH6NF[rn] OR "2,6-dinitro-p-cresol"[supplementary concept] OR "2,6-dinitro-p-cresol"[nm]) AND (1993/01/01 : 3000[dp] OR 1993/01/01 : 3000[mhda])) OR ((("2,4-Dinitro-6-methylphenol"[tw] OR "2,4-Dinitro-o-cresol"[tw] OR "2-Methyl-4,6-dinitrophenol"[tw] OR "3,5-Dinitro-2-hydroxytoluene"[tw] OR "4,6-dinitro-2-cresol"[tw] OR "4,6-Dinitro-o-cresol"[tw] OR "4,6-dinitro-ortho-cresol"[tw] OR "4,6-Dinitro-o-cresolo"[tw] OR "4,6-Dinitro-o-kresol"[tw] OR "4,6-Dinitrokresol"[tw] OR "6-Methyl-2,4-dinitrophenol"[tw] OR "Antinonin"[tw] OR "Antinonnin"[tw] OR "Arborol"[tw] OR "Capsine"[tw] OR "Chemsect DNOC"[tw] OR "Degrassan"[tw] OR "Dekrysil"[tw] OR "Detal"[tw] OR "Dillex"[tw] OR "Dinitro"[tw] OR "Dinitro-o-cresol"[tw] OR "Dinitrocresol"[tw] OR "Dinitrodendtroxal"[tw] OR "Dinitrol"[tw] OR "Dinoc"[tw] OR "Dinurania"[tw] OR "Ditrosol"[tw] OR "Dn-dry mix no. 2"[tw] OR "DNOC"[tw] OR "DNOK"[tw] OR "Dwunitro-o-krezol"[tw] OR "Effusan"[tw] OR "Effusan 3436"[tw] OR "Elgetol"[tw] OR "Elgetol 30"[tw] OR "Elipol"[tw] OR "Extrar"[tw] OR "Flavin-Samdoz"[tw] OR "Hedolit"[tw] OR "Hedolite"[tw] OR "Kreozan"[tw] OR "Kresamone"[tw] OR "Kresonite-E"[tw] OR "Krezotol 50"[tw] OR "LE dinitrocresol-4,6"[tw] OR "Lipan"[tw] OR "Neudorff DN 50"[tw] OR "Nitrador"[tw] OR "Nitrofan"[tw] OR "Oranz viktoria"[tw] OR "Prokarbol"[tw] OR "Rafex"[tw] OR "Rafex 35"[tw] OR "Raphatox"[tw] OR "Sandolin"[tw] OR "Sandolin A"[tw] OR "Selinon"[tw] OR "Sinox"[tw] OR "3,5-dinitro-2-hydroxy-Toluene"[tw] OR "Trifocide"[tw] OR "Trifrina"[tw] OR "Winterwash"[tw] OR "Zahlreiche bezeichnungen"[tw]) NOT medline[sb]) AND (1993/01/01 : 3000[dp] OR 1993/01/01 : 3000[crdat] OR 1993/01/01 : 3000[edat])) OR (("2,6-Dinitro-4-methylphenol"[tw] OR "2,6-Dinitro-p-cresol"[tw] OR "4-Methyl-2,6-dinitrophenol"[tw] OR "Dinitro-p-cresol"[tw] OR "DNPC"[tw] OR "3,5-dinitro-4-hydroxy-Toluene"[tw] OR "Victoria Orange"[tw] OR "Victoria Yellow"[tw] OR "Dinitro-para-cresol"[tw]) AND (1993/01/01 : 3000[dp] OR 1993/01/01 : 3000[crdat] OR 1993/01/01 : 3000[edat]))) OR ((Dinitrocresols[MeSH] AND (1993/01/01 : 3000[dp] OR 1993/01/01 : 3000[mhda])) OR (("Dinitrocresols"[tw] NOT medline[sb]) AND (1993/01/01 : 3000[dp] OR 1993/01/01 : 3000[crdat] OR 1993/01/01 : 3000[edat])))
Toxline	
03/2017	(616-73-9 [rn] OR 534-52-1 [rn] OR 497-56-3 [rn] OR 609-93-8 [rn] OR "2 4 dinitro 5 methylphenol" OR "3 methyl 4 6 dinitrophenol" OR "4 6 dinitro m cresol" OR "5 methyl 2 4 dinitro phenol" OR "2 4 dinitro 6 methylphenol" OR "2 4 dinitro o cresol" OR "2 methyl 4 6 dinitrophenol" OR "3 5 dinitro 2 hydroxytoluene" OR "4 6 dinitro 2 cresol" OR "4 6 dinitro o cresol" OR "4 6 dinitro ortho cresol" OR "4 6 dinitro o cresolo" OR "4 6 dinitro o kresol" OR "4 6 dinitrokresol" OR "6 methyl 2 4 dinitrophenol" OR "antinonin" OR "antinonnin" OR "arborol" OR "capsine" OR "chemsect dnoc" OR "degrassan" OR "dekrysil" OR "detal" OR "dillex" OR "dinitro" OR "dinitro o cresol" OR "dinitrocresol" OR "dinitrodendtroxal" OR "dinitrol" OR "dinoc" OR "dinurania" OR "ditrosol" OR "dn dry mix no 2" OR "dnoc" OR "dnok" OR "dwunitro o krezol" OR "effusan" OR "effusan 3436" OR "elgetol" OR "elgetol 30" OR "elipol" OR "extrar" OR "flavin samdoz" OR "hedolit" OR "hedolite" OR "kreozan" OR "kresamone" OR "kresonite e" OR "krezotol 50" OR "le dinitrocresol 4 6" OR "lipan" OR "neudorff dn 50" OR "nitrador" OR "nitrofan" OR "oranz viktoria" OR "prokarbol" OR "rafex" OR "rafex 35" OR "raphatox" OR "sandolin" OR "sandolin a" OR "selinon" OR "sinox" OR "3 5 dinitro 2 hydroxy toluene" OR "trifocide" OR "trifrina" OR "winterwash" OR "zahlreiche bezeichnungen" OR "3 5 dinitro o cresol" OR "2 methyl 3 5 dinitro phenol" OR "3 5 dinitro ortho cresol" OR "2 6 dinitro 4 methylphenol" OR "2 6 dinitro p cresol" OR "4 methyl 2 6 dinitrophenol" OR "dinitro p cresol" OR "dnpc" OR "3 5 dinitro 4 hydroxy

Table B-2. Database Query Strings

Database search date	Query string
	toluene" OR "victoria orange" OR "victoria yellow" OR "dinitro para cresol") AND 1993:2017 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org]
Toxcenter	
03/2017	FILE 'TOXCENTER' ENTERED AT 09:29:55 ON 29 MAR 2017 L1 1948 SEA 616-73-9 OR 534-52-1 OR 497-56-3 OR 609-93-8 L2 14 SEA 12167-18-9 L3 1960 SEA L1 OR L2 L4 1937 SEA L3 NOT TSCATS/FS L5 1752 SEA L4 NOT PATENT/DT L6 694 SEA L5 AND PY>=1993 ACTIVATE TOXQUERY/Q --------- L7 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L8 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L9 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L10 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L11 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L12 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L13 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L14 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L15 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L16 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?) L17 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) L18 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?) L19 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?) L20 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?) L21 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?) L22 QUE (ENDOCRIN? AND DISRUPT?) L23 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?) L24 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)

Table B-2. Database Query Strings

Database search date	Query string
	L25 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L26 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)
	L27 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L28 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L29 QUE (NEPHROTOX? OR HEPATOTOX?)
	L30 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L31 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L32 QUE L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29 OR L30 OR L31
	L33 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?)
	L34 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
	L35 QUE L32 OR L33 OR L34
	L36 QUE (NONHUMAN MAMMALS)/ORGN
	L37 QUE L35 OR L36
	L38 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?)
	L39 QUE L37 OR L38

	L40 344 SEA L6 AND L39
	L41 24 SEA L40 AND MEDLINE/FS
	L42 17 SEA L40 AND BIOSIS/FS
	L43 297 SEA L40 AND CAPLUS/FS
	L44 6 SEA L40 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS)
	L45 321 DUP REM L41 L42 L44 L43 (23 DUPLICATES REMOVED)
	L*** DEL 24 S L40 AND MEDLINE/FS
	L*** DEL 24 S L40 AND MEDLINE/FS
	L46 24 SEA L45
	L*** DEL 17 S L40 AND BIOSIS/FS
	L*** DEL 17 S L40 AND BIOSIS/FS
	L47 14 SEA L45
	L*** DEL 297 S L40 AND CAPLUS/FS
	L*** DEL 297 S L40 AND CAPLUS/FS
	L48 278 SEA L45
	L*** DEL 6 S L40 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS)
	L*** DEL 6 S L40 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS)
	L49 5 SEA L45
	L50 297 SEA (L46 OR L47 OR L48 OR L49) NOT MEDLINE/FS
	L51 278 SEA L50 AND CAPLUS/FS

Table B-2. Database Query Strings

Database search date	Query string
	D SCAN L50

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS[a]	
03/2017	Compounds searched: 616-73-9, 534-52-1, 497-56-3, 609-93-8, 12167-18-9
NTP	
03/2017	616-73-9 534-52-1 497-56-3 609-93-8 12167-18-9 2,4-Dinitro-5-methylphenol 3-Methyl-4,6-dinitrophenol 4,6-Dinitro-m-cresol 5-methyl-2,4-dinitro-Phenol 2,4-Dinitro-6-methylphenol 2,4-Dinitro-o-cresol 2-Methyl-4,6-dinitrophenol 3,5-Dinitro-2-hydroxytoluene 4,6-dinitro-2-cresol 4,6-Dinitro-o-cresol 4,6-dinitro-ortho-cresol 6-Methyl-2,4-dinitrophenol DNOC 3,5-Dinitro-o-cresol 2-methyl-3,5-dinitro-Phenol 3,5-Dinitro-ortho-cresol 2,6-Dinitro-4-methylphenol 2,6-Dinitro-p-cresol 4-Methyl-2,6-dinitrophenol Dinitro-p-cresol Dinitro-para-cresol DNPC 3,5-dinitro-4-hydroxy-Toluene Dinitrocresols Dinitrocresol
NIH RePORTER	
06/2017	Text Search: "2,4-Dinitro-6-methylphenol" OR "2,4-Dinitro-o-cresol" OR "2-Methyl-4,6-dinitrophenol " OR "3,5-Dinitro-2-hydroxytoluene" OR "4,6-dinitro-2-cresol" OR "4,6-Dinitro-o-cresol" OR "4,6-dinitro-ortho-cresol" OR "4,6-Dinitro-o-cresolo" OR "4,6-Dinitro-o-kresol" OR "4,6-Dinitrokresol" OR "6-Methyl-2,4-dinitrophenol" OR "Antinonin" OR "Antinonnin" OR "Arborol" OR "Capsine" OR "Chemsect DNOC" OR "Degrassan" OR "Dekrysil" OR "Detal" OR "Dillex" OR "Dinitro" OR "Dinitro-o-cresol" OR "Dinitrocresol" OR "Dinitrodendtroxal" OR "Dinitrol" OR "Dinoc" OR "Dinurania" OR "Ditrosol" OR "Dn-dry mix no. 2" OR "DNOC" OR "DNOK" OR "Dwunitro-o-krezol" OR

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	"Effusan" OR "Effusan 3436" OR "Elgetol" OR "Elgetol 30" OR "Elipol" OR "Extrar" OR "Flavin-Samdoz" OR "Hedolit" OR "Hedolite" OR "Kreozan" OR "Kresamone" OR "Kresonite-E" OR "Krezotol 50" OR "LE dinitrocresol-4,6" OR "Lipan" OR "Neudorff DN 50" OR "Nitrador" OR "Nitrofan" OR "Oranz viktoria" OR "Prokarbol" OR "Rafex" OR "Rafex 35" OR "Raphatox" OR "Sandolin" OR "Sandolin A" OR "Selinon" OR "Sinox" OR "Trifocide" OR "Trifrina" OR "Winterwash" OR "Zahlreiche bezeichnungen" (Advanced), Search in: Projects AdminIC: All, Fiscal Year: Active Projects
Other	Identified throughout the assessment process

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

The 2017 results were:

- Number of records identified from PubMed, TOXLINE, and TOXCENTER (after duplicate removal): 1,003
- Number of records identified from other strategies: 35
- Total number of records to undergo literature screening: 1,038

B.1.2 Literature Screening

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

- Title and abstract screen
- Full text screen

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

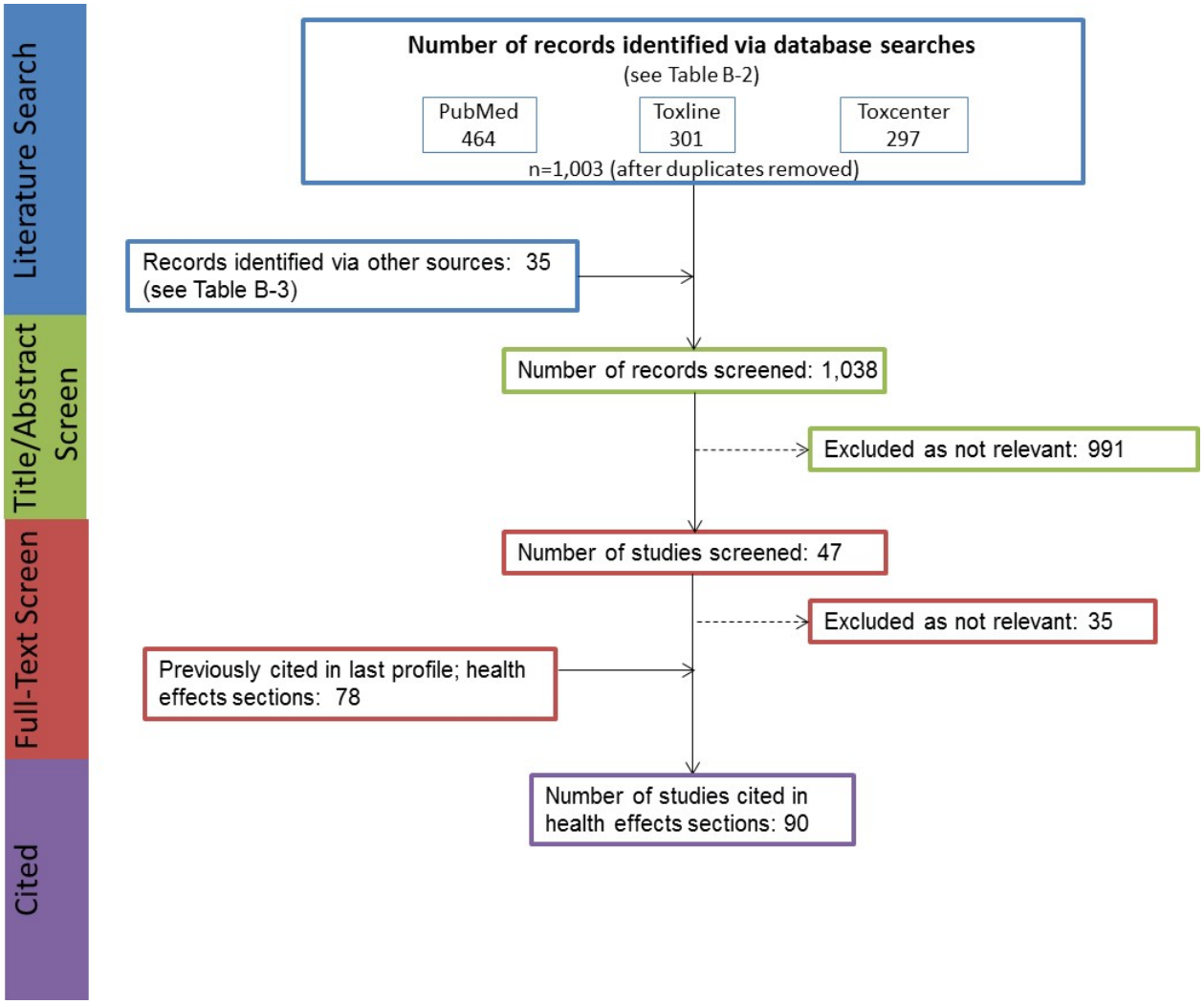
- Number of titles and abstracts screened: 1,038
- Number of studies considered relevant and moved to the next step: 47

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: 47
- Number of studies cited in the health effects sections of the existing toxicological profile (August, 1995): 78
- Total number of studies cited in the health effects sections of the updated profile: 90

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

Figure B-1. March 2017 Literature Search Results and Screen for Dinitrocresols



APPENDIX C. 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 C 5)

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

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

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

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

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

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

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

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

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

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

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

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

FIGURE LEGEND

See Sample LSE Figure (page C-6)

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

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

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

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

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

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

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

APPENDIX C

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

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

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

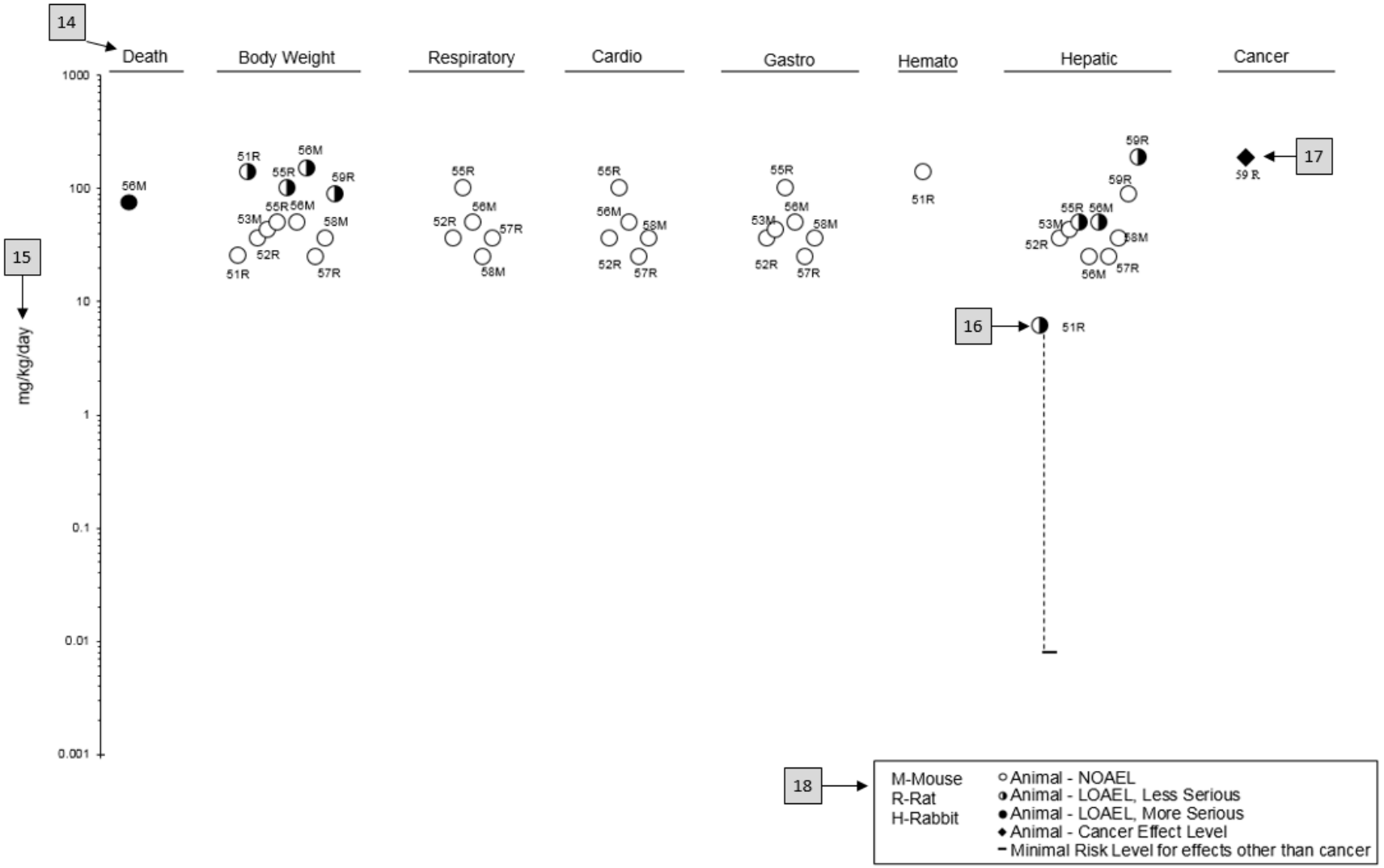
(11) [b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.1 mg/kg/day based on the $BMDL_{05}$ of 10 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

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

APPENDIX C

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

13 → Chronic (≥365 days)



APPENDIX D. 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 E. GLOSSARY

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

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

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

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

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

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

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

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

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

Carcinogen—A chemical capable of inducing cancer.

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

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

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

Ceiling Value—A concentration that must not be exceeded.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

APPENDIX F. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

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

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

NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NTP	National Toxicology Program
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PAC	Protective Action Criteria
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
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
TLV	threshold limit value
TLV-C	threshold limit value-ceiling value
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey

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

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