CHAPTER 2. HEALTH EFFECTS

OVERVIEW

2.1 INTRODUCTION

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

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

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

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

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

Levels of significant exposure (LSEs) for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a
considerable amount of judgment may be required in establishing whether an endpoint should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these endpoints. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose, frequency, and/or duration, and place into perspective the possible significance of these effects to human health.

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

The health effects of nitrophenols have been evaluated in experimental animal studies only. As illustrated in Figure 2-1, most of the health effects data come from oral and inhalation studies. Animal data are available for each exposure route and exposure duration category, however there are limited studies available for each. The majority of the studies evaluating the toxicity of nitrophenols focus on 4-nitrophenol, while only one study focused on the toxicity of 2-nitrophenol. No studies were identified in the literature that evaluated the toxicity of 3-nitrophenol. Many of the studies evaluating the toxicity of nitrophenols have evaluated a suite of endpoints. Body weight effects are the most examined effect in the literature, followed by hepatic, and neurological effects. The genotoxicity of 2- and 4-nitrophenol have also been examined, but no genotoxicity studies of 3-nitrophenol were identified in the literature.

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

- **Respiratory Endpoints.** Studies of respiratory effects of 4-nitrophenol exposure in animals have shown wheezing and dyspnea after oral exposure, and increased lung weight after inhalation exposure, however these effects were not consistently observed. Animal inhalation exposure to 2-nitrophenol has led to a significant increase in squamous metaplasia of the nasal epithelium.

- **Hematological Endpoints.** Studies of hematological effects in animals have been mixed, though an increase in methemoglobin, erythrocytes, hemoglobin, hematocrit, and creatinine have been observed after inhalation exposure to 4-nitrophenol. Results of a study investigating hematological effects in animals after 2-nitrophenol inhalation exposure were inconclusive.
• **Ocular Endpoints.** Animal studies on ocular effects of 4-nitrophenol have observed cataracts, corneal opacity, and ocular irritation after inhalation exposure, though no ocular effects were observed after oral exposure. Dermal exposure to 4-nitrophenol showed mixed results, with direct ocular application leading to severe conjunctival irritation, corneal opacity, and visible destruction of the iris, however these results were observed in a study that did not contain a control group. No ocular effects were observed after animal inhalation exposure to 2-nitrophenol.
Figure 2-1. Overview of the Number of Studies Examining Nitrophenols Health Effects

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

- Death: 8
- Body weight: 12
- Respiratory: 6
- Cardiovascular: 5
- Gastrointestinal: 7
- Hematological: 5
- Musculoskeletal: 4
- Hepatic: 9
- Renal: 8
- Dermal: 3
- Ocular: 6
- Endocrine: 6
- Immunological: 6
- Neurological: 9
- Reproductive: 8
- Developmental: 4
- Other Noncancer: 1
- Cancer: 0

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

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

<table>
<thead>
<tr>
<th>Figure keya</th>
<th>Species (strain)</th>
<th>Exposure parameters</th>
<th>Doses (mg/m³)</th>
<th>Parameters monitored</th>
<th>Endpoint</th>
<th>NOAEL (mg/m³)</th>
<th>Less serious LOAEL (mg/m³)</th>
<th>Serious LOAEL (mg/m³)</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith et al. 1988</td>
<td>RAT (Albino) 10M</td>
<td>2 weeks 5 days/week 6 hours/day</td>
<td>0, 294, 2,133</td>
<td>BC BW GN HE HP OW UR</td>
<td>Bd wt</td>
<td>2,133</td>
<td>Methemoglobin increase of 665%. Recovery day 14 erythrocytes, hemoglobin, and methemoglobin remained elevated by 7%, 7.5% and 250% respectively.</td>
<td>Corneal opacity and irritation</td>
<td>Decreased mean absolute and mean relative spleen weight (not otherwise described)</td>
</tr>
</tbody>
</table>

| Smith et al. 1988 | RAT (Albino) 10M | 2 weeks 5 days/week 6 hours/day | 0, 26, 112 | BC BW CS GN HE HP OW UR | Bd wt | 112 | Methemoglobin increase 200% | Corneal opacity and irritation |

INTERMEDIATE EXPOSURE

***DRAFT FOR PUBLIC COMMENT***
## Table 2-1. Levels of Significant Exposure to Nitrophenols – Inhalation

<table>
<thead>
<tr>
<th>Figure keya</th>
<th>Species (strain)</th>
<th>No./group</th>
<th>Exposure parameters</th>
<th>Doses (mg/m³)</th>
<th>Parameters monitored</th>
<th>Endpoint</th>
<th>NOAEL (mg/m³)</th>
<th>Serious LOAEL (mg/m³)</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hazleton 1983</td>
<td>RAT (Sprague- Dawley)</td>
<td>15M,15F</td>
<td>4 weeks 5 days/week 6 hours/day</td>
<td>0, 1, 5, 30</td>
<td>BC BI BW CS GN HP OW</td>
<td>Bd wt</td>
<td>30</td>
<td>30</td>
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</tr>
<tr>
<td>Hazleton 1984</td>
<td>RAT (Sprague- Dawley)</td>
<td>15M, 15F</td>
<td>4 weeks 5 days/week 6 hours/day</td>
<td>0, 5, 32.5, 61.5</td>
<td>BC BI BW CS GN HE HP LE OW OF</td>
<td>Bd wt</td>
<td>61.5</td>
<td>61.5</td>
<td>61.5</td>
</tr>
</tbody>
</table>

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* ***DRAFT FOR PUBLIC COMMENT***
### Table 2-1. Levels of Significant Exposure to Nitrophenols – Inhalation

<table>
<thead>
<tr>
<th>Figure key(^a)</th>
<th>Species (strain)</th>
<th>No./group</th>
<th>Exposure parameters</th>
<th>Doses (mg/m(^3))</th>
<th>Parameters monitored</th>
<th>Endpoint</th>
<th>NOAEL (mg/m(^3))</th>
<th>Less serious LOAEL (mg/m(^3))</th>
<th>Serious LOAEL (mg/m(^3))</th>
<th>Effects</th>
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</thead>
<tbody>
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<td>Hemato</td>
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<td>61.5</td>
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<td>Musc/skel</td>
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<td>61.5</td>
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<tr>
<td></td>
<td>Hepatic</td>
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<td>Renal</td>
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<td>Immuno</td>
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<td></td>
<td>61.5</td>
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</tr>
</tbody>
</table>

\(^a\) The number corresponds to entries in Figure 2-2.

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

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***DRAFT FOR PUBLIC COMMENT***
Figure 2-2. Levels of Significant Exposure to Nitrophenols – Inhalation
Acute (≤14 days)

- **Body Weight**
- **Respiratory**
- **Hematological**
- **Hepatic**

**DIGITAL SCALES**

- mg/m³

**R-Rat**

- ○ Animal - NOAEL
- ‡ Animal - LOAEL
- ● Animal - SLOAEL

***DRAFT FOR PUBLIC COMMENT***
Figure 2-2. Levels of Significant Exposure to Nitrophenols – Inhalation
Acute (≤14 days)

Renal  Ocular  Immunological  Neurological

mg/m³

1R 1R 1R 1R

10,000 1,000 100 10

R-Rat

○ Animal - NOAEL
● Animal - LOAEL
● Animal - SLOAEL

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

- Renal
- Ocular
- Endocrine
- Immunological
- Neurological
- Reproductive

mg/m³

R-Rat

○ Animal - NOAEL
● Animal - LOAEL
● Animal - SLOAEL

***DRAFT FOR PUBLIC COMMENT***
### Table 2-2. Levels of Significant Exposure to Nitrophenols – Oral

<table>
<thead>
<tr>
<th>Figure key</th>
<th>Species (strain)</th>
<th>Exposure parameters</th>
<th>Doses (mg/kg/day)</th>
<th>Parameters monitored</th>
<th>NOAEL (mg/kg/day)</th>
<th>Less serious LOAEL (mg/kg/day)</th>
<th>Serious LOAEL (mg/kg/day)</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>RAT (Sprague-Dawley) 21F</td>
<td>Once (GW)</td>
<td>0, 100</td>
<td>BI BW HE OW UR</td>
<td>Bd wt</td>
<td>100</td>
<td>100</td>
<td>Neuro</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td>4-nitrophenol</td>
<td>Hemato 100</td>
<td>Repro 100</td>
</tr>
<tr>
<td>2</td>
<td>RAT (Sprague-Dawley) 20F</td>
<td>10 days GD6-GD16 (GW)</td>
<td>0, 1.4, 13.8, 27.6</td>
<td>BW DX GN</td>
<td>Bd wt</td>
<td>13.8</td>
<td>27.6</td>
<td>Maternal body weight gain decreased by 12%</td>
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<tr>
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<td></td>
<td></td>
<td>4-nitrophenol</td>
<td>Develop 27.6</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>RAT (Sprague-Dawley) 12F</td>
<td>Once on GD11 (GW)</td>
<td>0, 333, 667, 1,000</td>
<td>BW DX RX</td>
<td>Death</td>
<td>667</td>
<td>3/13 rats died</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td>4-nitrophenol</td>
<td>Bd wt 1,000</td>
<td>Repro 1,000</td>
</tr>
<tr>
<td>4</td>
<td>RAT (Wistar) 9M</td>
<td>Once (G)</td>
<td>0, 200</td>
<td>BW HP OF OW</td>
<td>Bd wt</td>
<td>200</td>
<td></td>
<td>Hepatic 200</td>
</tr>
</tbody>
</table>

***DRAFT FOR PUBLIC COMMENT***
## 2. HEALTH EFFECTS

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

<table>
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<th>Figure key&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Species (strain)</th>
<th>Exposure parameters</th>
<th>Doses (mg/kg/day)</th>
<th>Parameters monitored</th>
<th>Endpoint (mg/kg/day)</th>
<th>Less serious LOAEL (mg/kg/day)</th>
<th>Serious LOAEL (mg/kg/day)</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Li et al. 2017</strong></td>
<td><strong>4-nitrophenol</strong></td>
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</tr>
<tr>
<td>5</td>
<td>RAT (Wistar) 12M</td>
<td>3 days</td>
<td>0, 200</td>
<td>BW HP OF OW</td>
<td>Bd wt</td>
<td>200</td>
<td></td>
<td>25% decrease</td>
</tr>
<tr>
<td></td>
<td><strong>Hepatic</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Hepatic sinuoid was wider compared to the control group, and the hepatocytes were disordered</td>
</tr>
<tr>
<td><strong>Monsanto 1990</strong></td>
<td><strong>2-nitrophenol</strong></td>
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<tr>
<td>6</td>
<td>Rat (Sprague-Dawley) 5F</td>
<td>9 days, daily</td>
<td>0, 50, 125, 250, 500, 1,000</td>
<td>BW, DX, RX, UR</td>
<td>Bd wt</td>
<td>1,000</td>
<td></td>
<td>92% increase in resorptions; 68% increase in post-implantation losses</td>
</tr>
<tr>
<td></td>
<td><strong>Renal</strong></td>
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<td></td>
<td><strong>Repro</strong></td>
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<td></td>
<td>500</td>
<td>1,000</td>
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</tr>
<tr>
<td><strong>Tang et al. 2016</strong></td>
<td><strong>4-nitrophenol</strong></td>
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<tr>
<td>7</td>
<td>RAT (Wistar) 4-6M</td>
<td>Once</td>
<td>0, 200</td>
<td>BW HP OW RX</td>
<td>Bd wt</td>
<td>200</td>
<td></td>
<td>Damage to the intestinal mucosal goblet cells and necrosis of intestinal epithelial cells</td>
</tr>
<tr>
<td></td>
<td><strong>Gastro</strong></td>
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<td><strong>200</strong></td>
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<tr>
<td><strong>Tang et al. 2016</strong></td>
<td><strong>4-nitrophenol</strong></td>
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</tr>
<tr>
<td>8</td>
<td>RAT (Wistar) 6M</td>
<td>3 days</td>
<td>0, 200</td>
<td>BW HP OW RX</td>
<td>Bd wt</td>
<td>200</td>
<td></td>
<td>40% decrease body weight gain</td>
</tr>
</tbody>
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<sup>a</sup> DRAFT FOR PUBLIC COMMENT
## Table 2-2. Levels of Significant Exposure to Nitrophenols – Oral

<table>
<thead>
<tr>
<th>Figure key</th>
<th>Species (strain)</th>
<th>Exposure parameters</th>
<th>Doses (mg/kg/day)</th>
<th>Parameters monitored</th>
<th>NOAEL (mg/kg/day)</th>
<th>Less serious LOAEL (mg/kg/day)</th>
<th>Serious LOAEL (mg/kg/day)</th>
<th>Effects</th>
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</thead>
<tbody>
<tr>
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<td></td>
<td></td>
<td></td>
<td>Gastro 200</td>
<td>Hepatic 200</td>
<td>Renal 200</td>
<td>Window</td>
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<td></td>
<td>12% decrease in relative liver weight</td>
<td>14% increase in relative kidney weight</td>
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<td>41% increase in relative adrenal gland weight</td>
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</tr>
<tr>
<td>Plasterer et al. 1985</td>
<td>MOUSE (CD1) 10F</td>
<td>8 days (GO)</td>
<td>0, 400</td>
<td>BW CS RX DX</td>
<td>Death 400</td>
<td>400</td>
<td>Decreased maternal survival by 19%</td>
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<td></td>
<td></td>
<td></td>
<td>Bd wt 400</td>
<td>Re pro 400</td>
<td>Develop 400</td>
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</tr>
<tr>
<td>Plasterer et al. 1985</td>
<td>MOUSE (CD1) 10F</td>
<td>8 days (GO)</td>
<td>0, 62.5, 125, 250, 500, 1,000</td>
<td>CS</td>
<td>Death 625.7</td>
<td>625.7</td>
<td>LD₅₀</td>
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<td></td>
<td>Bd wt 1,000</td>
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### INTERMEDIATE EXPOSURE

***DRAFT FOR PUBLIC COMMENT***
### Table 2-2. Levels of Significant Exposure to Nitrophenols – Oral

<table>
<thead>
<tr>
<th>Figure key</th>
<th>Species (strain) No./group</th>
<th>Exposure parameters</th>
<th>Doses (mg/kg/day)</th>
<th>Parameters monitored</th>
<th>NOAEL (mg/kg/day)</th>
<th>Less serious LOAEL (mg/kg/day)</th>
<th>Serious LOAEL (mg/kg/day)</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hazleton 1989</td>
<td>RAT (Sprague-Dawley) 20M, 20F</td>
<td>13 weeks 7 days/week (GW)</td>
<td>0, 25, 70, 140</td>
<td>BW, OW, Fi, GN, HP, BC, CS, BI</td>
<td>Death</td>
<td>25 F</td>
<td>1/20 died</td>
<td>70 M</td>
</tr>
<tr>
<td>Koizumi et al. 2001</td>
<td>RAT (Sprague-Dawley) 12M, 12F</td>
<td>18 days (G)</td>
<td>0, 80, 110, 160</td>
<td>BI BW CS HE HP LE OF OW UR</td>
<td>Bd wt</td>
<td>160</td>
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<td>Resp</td>
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<td>Repro</td>
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### Table 2-2. Levels of Significant Exposure to Nitrophenols – Oral

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<th>Figure key&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Species (strain)</th>
<th>No./group</th>
<th>Exposure parameters</th>
<th>Doses (mg/kg/day)</th>
<th>Parameters monitored</th>
<th>Endpoint</th>
<th>NOAEL (mg/kg/day)</th>
<th>Less serious LOAEL (mg/kg/day)</th>
<th>Serious LOAEL (mg/kg/day)</th>
<th>Effects</th>
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<tbody>
<tr>
<td>Koizumi et al. 2001</td>
<td>4-nitrophenol</td>
<td>13</td>
<td>RAT (Sprague-Dawley) 6M, 6F</td>
<td>18 days (G)</td>
<td>0, 110, 160, 230, 320</td>
<td>BI BW CS HE HP LE OF OW UR</td>
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<td>320 F</td>
<td>6/6 died</td>
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<td></td>
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<td>3/6 died</td>
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<td>Koizumi et al. 2001</td>
<td>4-nitrophenol</td>
<td>14</td>
<td>RAT (Sprague-Dawley) 12M, 12F</td>
<td>28 days (G)</td>
<td>0, 60, 160, 400, 1,000</td>
<td>BI BW FI GN HE HP OW UR</td>
<td>Death</td>
<td>1,000</td>
<td>10/12 M and 10/12 F died</td>
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***DRAFT FOR PUBLIC COMMENT***
### Table 2-2. Levels of Significant Exposure to Nitrophenols – Oral

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<th>Figure key&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Species (strain)</th>
<th>Exposure parameters</th>
<th>Doses (mg/kg/day)</th>
<th>Parameters monitored</th>
<th>NOAEL (mg/kg/day)</th>
<th>Less serious LOAEL (mg/kg/day)</th>
<th>Serious LOAEL (mg/kg/day)</th>
<th>Effects</th>
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<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td>Neuro 400</td>
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<td>Repro</td>
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<td></td>
<td>1,000</td>
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<td></td>
<td></td>
<td>Decrease in locomotor activity in 12/12 M and 12/12 F; prone/lateral position in 10/12 M and 10/12 F; tonic convulsions in 3/12 M and 4/12 F</td>
</tr>
</tbody>
</table>

<sup>a</sup>The number corresponds to entries in Figure 2-3.

BC = blood chemistry; Bl = biochemical indices; BW or Bd wt = body weight; CS = clinical signs; DX = developmental toxicity; F = female(s); Fl = food intake; G = gavage, neat or not specified vehicle; GN = gross necropsy; GO = gavage with oil vehicle; GW = gavage with aqueous vehicle; HE = hematological; HP = histopathology; Immuno = immunological; LE = lethality; LOAEL = lowest-observed-adverse-effect-level; M = male(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect-level; NS = not specified; OF = organ function; OW = organ weight; Resp = respiratory; RX = reproductive toxicity; UR = urinalysis.
Figure 2-3. Levels of Significant Exposure to Nitrophenols – Oral
Acute (≤14 days)

***DRAFT FOR PUBLIC COMMENT***
Figure 2-3. Levels of Significant Exposure to Nitrophenols – Oral
Acute (≤14 days)
Figure 2-3. Levels of Significant Exposure to Nitrophenols – Oral*
Intermediate (15-364 days)

*Differences in levels of health effects and cancer effects between males and females are not indicated in Figure 2-3. Where such differences exist, only the levels of effect for the most sensitive sex are presented.

***DRAFT FOR PUBLIC COMMENT***
**Figure 2-3. Levels of Significant Exposure to Nitrophenols – Oral**
Intermediate (15-364 days)

* Differences in levels of health effects and cancer effects between males and females are not indicated in Figure 2-3. Where such differences exist, only the levels of effect for the most sensitive sex are presented.

***DRAFT FOR PUBLIC COMMENT***
### Table 2-3. Levels of Significant Exposure to Nitrophenols – Dermal

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<th>Exposure parameters</th>
<th>Doses</th>
<th>Parameters monitored</th>
<th>Endpoint</th>
<th>NOAEL</th>
<th>Less serious LOAEL</th>
<th>Serious LOAEL</th>
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<tbody>
<tr>
<td>Angerhofer 1985</td>
<td>RAT (Sprague-Dawley)</td>
<td>12M, 24F</td>
<td>20 weeks 5 days/week (140 days prior to mating, through gestation and lactation)</td>
<td>0, 50, 100, 250 mg/kg/day</td>
<td>BW DX HP OW RX</td>
<td>Bd wt</td>
<td>250</td>
<td>50</td>
<td>Erythema, scaling, scabbing and cracking</td>
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</tbody>
</table>

- Resp: 250
- Cardio: 250
- Gastro: 250
- Musc/skel: 250
- Hepatic: 250
- Renal: 250
- Dermal: 50
- Ocular: 250
- Endocr: 250
- Immuno: 250
- Neuro: 250
- Repro: 250

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***DRAFT FOR PUBLIC COMMENT***
### Table 2-3. Levels of Significant Exposure to Nitrophenols – Dermal

<table>
<thead>
<tr>
<th>Figure key&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Species (strain)</th>
<th>Exposure parameters</th>
<th>Doses</th>
<th>Parameters monitored</th>
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<th>LOAEL</th>
<th>Serious LOAEL</th>
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<td>RAT (Sprague-Dawley)</td>
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<td>0, 50, 100, 250 mg/kg/day</td>
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<td>Bd wt 250</td>
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<td>Erythema, scaling, scabbing, and cracking</td>
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<td>NEURO</td>
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<td>10% decrease in relative brain weight</td>
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<sup>a</sup> DRAFT FOR PUBLIC COMMENT
## Table 2-3. Levels of Significant Exposure to Nitrophenols – Dermal

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<tr>
<th>Figure key&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Species (strain)</th>
<th>Exposure parameters</th>
<th>Doses</th>
<th>Parameters monitored</th>
<th>Endpoint</th>
<th>NOAEL</th>
<th>Less serious LOAEL</th>
<th>Serious LOAEL</th>
<th>Effects</th>
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<td>RAT (Sprague-Dawley) 10M, 10F</td>
<td>24 weeks 5 days/week F2 generation, dosing was done to F1 generation</td>
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<td>BW DX HP OW RX</td>
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<td>NTP 1993</td>
<td>MOUSE (Swiss-Webster) 60M, 60F</td>
<td>78 weeks 3 days/week</td>
<td>0, 40, 80, 160 mg/kg/day</td>
<td>CS GN HP LE OF</td>
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***DRAFT FOR PUBLIC COMMENT***
Table 2-3. Levels of Significant Exposure to Nitrophenols – Dermal

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<th>Species (strain)</th>
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<th>Doses</th>
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</table>

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

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2.2 DEATH

Inhalation

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

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

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

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

Oral

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

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

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

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

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

Dermal

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2. HEALTH EFFECTS

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

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

2.3 BODY WEIGHT

Inhalation

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

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

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2. HEALTH EFFECTS

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

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

**Oral**

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

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

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

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

**Dermal**

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

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

**Other**

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

2.4 RESPIRATORY

**Inhalation**

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

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

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

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

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

**Oral**

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

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

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

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

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

Dermal

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

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

Other

Intraperitoneal injection of nitrophenols in rats has shown a potential to increase respiration rates (Cameron 1958; Grant 1959). 2-, 3-, and 4-Nitrophenol were administered at doses of 120 mg, 45 mg, and 14 mg, respectively. Average increases in respiration rates of: 31% for 2-nitrophenol, 24% for 3-nitrophenol, and 2% for 4-nitrophenol (compared with a prior control period) were reported (Grant 1959). However, a control group that received an intraperitoneal injection of normal saline also experienced a 2% increase in respiration rate compared to the prior control period, which suggests the small increase in...
respiration rate observed in rats injected with 4-nitrophenol is not significant (Grant 1959). The toxicological significance of these findings is unclear.

2.5 CARDIOVASCULAR

*Inhalation*

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

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

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

*Oral*

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

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

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

Dermal

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

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

2.6 GASTROINTESTINAL

Inhalation

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

Limited information from two animal studies suggests that inhalation exposure to 2- or 4-nitrophenol was not associated with gastrointestinal effects. No histopathological changes to the gastrointestinal system were observed after intermediate inhalation exposure to 2-nitrophenol in rats at concentrations up to 61.5 mg/m³ (Hazleton 1984). No histopathological changes to the gastrointestinal system were observed after intermediate inhalation exposure to 4-nitrophenol in rats at concentrations up to 30 mg/m³ (Hazleton 1983).

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

Oral

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

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

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

Dermal

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

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

2.7 HEMATOLOGICAL

Inhalation

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

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

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

Hematological effects were also noted in studies investigating inhalation exposure to 4-nitrophenol. After exposing albino rats to 4-nitrophenol concentrations of 0, 26, or 112 mg/m$^3$ for 6 hours/day for 10 days, Smith et al. (1988) found that methemoglobin increased by 200% in males in the 112 mg/m$^3$ concentration group (1.5% methemoglobin in the 112 mg/m$^3$ group versus 0.5% methemoglobin in the control group). However, the levels returned to normal after a 14-day recovery period (0.2% methemoglobin); the NOAEL for these effects was 26 mg/m$^3$. Another study within this same publication that exposed albino rats to 4-nitrophenol concentrations of 0, 294, and 2,133 mg/m$^3$ for 10 days also found that methemoglobin levels increased by 665% (1.53% methemoglobin in the 2,133 mg/m$^3$ group versus 0.20% methemoglobin in the control group); the NOAEL for these effects was 294 mg/m$^3$. After 14 days of recovery, methemoglobin levels remained elevated by 250% (0.70% methemoglobin). In general, increases in total methemoglobin result in lower oxygen carrying and delivery capacity, which can cause hypoxia. High levels of methemoglobin may be associated with cyanosis and fatigue, weakness, dyspnea, headache, and dizziness. One rat in the Smith et al. (1988) study became cyanotic after the first exposure to this 4-nitrophenol concentration of 2,133 mg/m$^3$. It is estimated that rats have 2-5 times as much methemoglobin reductase activity, or the enzyme responsible for controlling the amount of methemoglobin in blood, than humans (Bloom and Brandt 2019). Thus, humans could potentially be more sensitive to 4-nitrophenol toxicity than rats. Other hematological effects observed included elevated erythrocytes, hemoglobin, hematocrit, and creatinine at 2,133 mg/m$^3$ 4-nitrophenol (Smith et al. 1988).
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Hazleton (1983) performed an intermediate-duration inhalation study of 4-nitrophenol toxicity in rats, exposing the animals intermittently to concentrations of 0, 1, 5, and 30 mg/m\(^3\) for 5 weeks. There were no hematological effects noted in the 1 mg/m\(^3\) concentration group; at 5 mg/m\(^3\) there was a statistically significant increase in methemoglobin compared to controls, but there was no similar increase in methemoglobin in the 30 mg/m\(^3\) concentration group (Hazleton 1983). As these results did not show a clear dose-response relationship between 4-nitrophenol exposure and increases in methemoglobin, the mechanistic link and the toxicological significance of the finding are unclear.

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

**Oral**

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

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

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

**Dermal**

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

**2.8 MUSCULOSKELETAL**

**Inhalation**

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

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

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

**Oral**

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

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

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

**Dermal**

No studies were identified regarding musculoskeletal effects in humans after dermal exposure of any duration to 2-, 3-, or 4-nitrophenol. No studies were identified regarding musculoskeletal effects in animals after dermal exposure of any duration to 2- or 3-nitrophenol. No studies were identified regarding musculoskeletal effects in animals after acute dermal exposure to 4-nitrophenol.
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No musculoskeletal effects were observed in a three-generation rat study with dermal doses of 4-nitrophenol as high as 250 mg/kg/day (Angerhofer 1985). Similarly, no musculoskeletal effects were observed in a 78-week chronic duration study of mice exposed to 4-nitrophenol at doses as high as 160 mg/kg (NTP 1993).

2.9 HEPATIC

*Inhalation*

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

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

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

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

*Oral*

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

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

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

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

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

Dermal

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

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

Other

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

2.10 RENAL

Inhalation

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

Hazleton (1984) reported no renal effects of intermittent inhalation exposure to 2-nitrophenol in rats at concentrations up to 61.5 mg/m³ for 4 weeks.

Smith et al. (1988) observed darker urine and proteinuria, as well as a 13% decrease in urine volume after intermittent exposure to 294 mg/m³ 4-nitrophenol for 2 weeks, but found no significant renal effects. Hazleton (1983) found no renal effects of intermediate intermittent inhalation exposure to 4-nitrophenol at concentrations up to 30 mg/m³ for 4 weeks.

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

Oral

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

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

***DRAFT FOR PUBLIC COMMENT***
2. HEALTH EFFECTS

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

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

Dermal

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

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

2.11 DERMAL

Inhalation

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

Oral

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

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

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

**Dermal**

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

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

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

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

**2.12 OCULAR**

*Inhalation*

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

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

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

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

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

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

Oral

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

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

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

Dermal
2. HEALTH EFFECTS

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

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

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

2.13 ENDOCRINE

Inhalation

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

Hazleton (1983) found no endocrine effects of intermittent inhalation exposure to 4-nitrophenol for 4 weeks in rats at concentrations up to 30 mg/m³, as judged by organ weight and histopathology of adrenals, thyroid, pituitary gland, thymus, pancreas, testes, and ovaries.

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

Oral

No studies were identified regarding endocrine effects in humans after oral exposure of any duration to 2-, 3-, or 4-nitrophenol. No studies were identified regarding endocrine effects in animals after oral exposure of any duration to 2- or 3-nitrophenol. No studies were identified regarding endocrine effects in animals after chronic oral exposure to 4-nitrophenol.
Tang et al. (2016) observed a 41% increase in adrenal gland weight after three days of daily gavage oil administration of 200 mg/kg/day 4-nitrophenol. However, no endocrine effects of intermediate duration, oral exposure to 4-nitrophenol in rats were found at doses up to 1,000 mg/kg/day after histopathological examination and organ weight evaluation of the pituitary gland, thymus, thyroid, adrenals, testes, ovaries, and pancreas (Hazleton 1989; Koizumi et al. 2001).

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

Dermal

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

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

Other

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

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

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

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

2.14 IMMUNOLOGICAL

*Inhalation*

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

Hazleton (1984) found no immunological effects of intermittent inhalation exposure to 2-nitrophenol for 4 weeks in rats at concentrations up to 61.5 mg/m³.

Decreased spleen weight was observed in rats after a 10-day exposure to 2,133 mg/m³ 4-nitrophenol; the NOAEL reported in this study for this effect was 294 mg/m³ (Smith et al. 1988). Hazleton (1983) found no immunological effects in rats after intermittent inhalation exposure to 4-nitrophenol for 4 weeks at concentrations up to 30 mg/m³.

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

*Oral*

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2. HEALTH EFFECTS

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

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

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

Dermal

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

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

2.15 NEUROLOGICAL

Inhalation

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

Hazleton (1984) found no neurological effects of intermediate-duration inhalation exposure for 4 weeks to 2-nitrophenol in rats at concentrations up to 61.5 mg/m³.

Lethargy was observed in rats after acute intermittent inhalation exposure for 2 weeks at a concentration of 2,133 mg/m³ 4-nitrophenol; the NOAEL reported in this study for this effect was 294 mg/m³ (Smith et
al. 1988). Hazleton (1983) found no neurological effects in rats after intermittent 4 week exposure to 4-nitrophenol at concentrations up to 30 mg/m³.

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

*Oral*

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

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

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

*Dermal*

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

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

2.16 REPRODUCTIVE

Inhalation

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

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

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

Oral

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

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

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

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

**Dermal**

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

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

**Other**

Although there is no evidence of reproductive toxicity after exposure to 4-nitrophenol through oral, inhalation, or dermal routes, 4-nitrophenol has been shown to alter reproductive function after parenteral exposure in both male and female rodents. Li et al. (2006) showed that male rats exposed to 0.1
mg/kg/day 4-nitrophenol for 7 days via subcutaneous injections exhibited a decrease in weight of seminal vesicles, ventral prostate, and glans penis; there were no effects noted in the male rats following exposure to 0.01 mg/kg/day. Li et al. (2006) also demonstrated that this exposure increased uterine weight at 10 mg/kg/day, but not at 1 mg/kg/day, in female rats. Luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels in the plasma were not altered in females, but these hormones increased significantly in males at 0.1 mg/kg/day; this indicates that 4-nitrophenol has estrogentic and anti-androgenic activities in vivo (Li et al. 2006). Li et al. (2009) also showed that acute exposure to 4-nitrophenol by subcutaneous injections at 0.01 mg/kg/day altered the plasma concentrations of luteinizing hormone (LH), follicle stimulating hormone (FSH) and testosterone in male rats (Li et al. 2009).

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

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

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

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

***DRAFT FOR PUBLIC COMMENT***
2. HEALTH EFFECTS

2.17 DEVELOPMENTAL

Inhalation

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

Oral

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

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

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

Dermal

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

No developmental effects were observed in a three-generation intermediate duration rat study with dermal doses of 4-nitrophenol as high as 250 mg/kg/day (Angerhofer 1985). Survivability from birth to weaning was effectively 100% for rat pups in all dosage groups in both the F1 and F2 generations, and all F2 pups that had not been directly dosed with 4-nitrophenol were normal in appearance, behavior, and growth (Angerhofer 1985).

2.18 CANCER

*Inhalation*

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

*Oral*

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

*Dermal*

There is only one study of carcinogenicity of 4-nitrophenol, which was the NTP (1993) study. This study was a chronic duration cancer assessment study in mice that administered dermal doses of 4-nitrophenol up to 160 mg/kg 3 days/week for 78 weeks. All organs and tissues were examined for gross lesions at the end of the study. No dose-related increases in malignant neoplasms were observed for any of the organs/tissues, despite the overall incidence of benign and malignant neoplasms being elevated in male mice in the low- and mid-dose groups. The authors concluded there was no evidence of carcinogenic activity in male or female Swiss-Webster mice exposed dermally to 4-nitrophenol doses up to 160 mg/kg.

The National Toxicology Program of the U.S. Department of Health and Human Services (NTP) has not classified the nitrophenols with regard to their human carcinogenicity. The Environmental Protection Agency (EPA) has classified 4-nitrophenol as Group D for carcinogenicity, indicating that there is inadequate information to determine its cancer potential. EPA has not evaluated 2- or 3-nitrophenol for carcinogenicity. The International Agency for Research on Cancer (IARC) has not classified the nitrophenols with regard to their human carcinogenicity.
2.19 GENOTOXICITY

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

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

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

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

<table>
<thead>
<tr>
<th>Species (test system)</th>
<th>End Point</th>
<th>Results Activation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prokaryotic organisms</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salmonella typhimurium (plate incorporation)</td>
<td>Gene mutation</td>
<td>No data</td>
<td>-</td>
</tr>
<tr>
<td>S. typhimurium (plate incorporation)</td>
<td>Gene mutation</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>S. typhimurium (plate incorporation)</td>
<td>Gene mutation</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>S. typhimurium (plate incorporation)</td>
<td>Gene mutation</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Escherichia coli sd-4-73 (spot test)</td>
<td>Gene mutation</td>
<td>No data</td>
<td>-</td>
</tr>
<tr>
<td>Bacillus subtilis (plate incorporation)</td>
<td>DNA damage</td>
<td>No data</td>
<td>-</td>
</tr>
<tr>
<td>S. typhimurium (plate incorporation)</td>
<td>DNA damage</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>S. typhimurium (plate incorporation)</td>
<td>DNA damage</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

* - Negative result

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

<table>
<thead>
<tr>
<th>Species (test system)</th>
<th>End Point</th>
<th>Results Activation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prokaryotic organisms</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salmonella typhimurium (plate incorporation)</td>
<td>Gene mutation</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>S. typhimurium (plate incorporation)</td>
<td>Gene mutation</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>S. typhimurium (plate incorporation)</td>
<td>Gene mutation</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>S. typhimurium (plate incorporation)</td>
<td>Gene mutation</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>S. typhimurium (plate incorporation)</td>
<td>Gene mutation</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Escherichia coli (plate incorporation)</td>
<td>Gene mutation</td>
<td>No data</td>
<td>-</td>
</tr>
<tr>
<td>Escherichia coli (spot test)</td>
<td>Gene mutation</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>E. coli (plate incorporation)</td>
<td>Prophage induction</td>
<td>No data</td>
<td>(+)</td>
</tr>
<tr>
<td>Proteus mirabilis</td>
<td>DNA damage</td>
<td>No data</td>
<td>(+)</td>
</tr>
<tr>
<td>E. coli</td>
<td>DNA repair</td>
<td>No data</td>
<td>-</td>
</tr>
<tr>
<td>S. typhimurium (disc assay)</td>
<td>DNA repair</td>
<td>No data</td>
<td>-</td>
</tr>
<tr>
<td>Bacillus subtilis (plate incorporation)</td>
<td>DNA damage</td>
<td>No data</td>
<td>+</td>
</tr>
<tr>
<td>S. typhimurium (plate incorporation)</td>
<td>DNA damage</td>
<td>No data</td>
<td>(+)</td>
</tr>
<tr>
<td>S. typhimurium (plate incorporation)</td>
<td>Gene mutation</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

***DRAFT FOR PUBLIC COMMENT***
## 2. HEALTH EFFECTS

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

<table>
<thead>
<tr>
<th>Species (test system)</th>
<th>End Point</th>
<th>Results Activation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drosophila melanogaster</td>
<td>Gene mutation</td>
<td>-</td>
<td>NTP 1993</td>
</tr>
<tr>
<td>Mammalian organisms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rat hepatocytes (culture)</td>
<td>DNA repair</td>
<td>No data</td>
<td>Probst et al. 1981</td>
</tr>
<tr>
<td>Mouse lymphoma cells</td>
<td>Forward mutation</td>
<td>-</td>
<td>Oberly et al. 1984</td>
</tr>
<tr>
<td>Mouse lymphoma cells</td>
<td>Forward mutation</td>
<td>-</td>
<td>Amacher and Turner 1982</td>
</tr>
<tr>
<td>Chinese hamster ovary cells (culture)</td>
<td>Inhibition of DNA synthesis</td>
<td>No data (+)</td>
<td>Garrett and Lewtas 1983</td>
</tr>
<tr>
<td>Chinese hamster ovary cells (culture)</td>
<td>Chromosomal aberrations</td>
<td>-</td>
<td>Andrews 1990a</td>
</tr>
<tr>
<td>Mouse L5178Y lymphoma TK +/- cells</td>
<td>Gene mutation</td>
<td>-</td>
<td>Richard and Clark 1990</td>
</tr>
<tr>
<td>Chinese hamster ovary cells (culture)</td>
<td>Chromosomal aberrations</td>
<td>+</td>
<td>NTP 1993</td>
</tr>
<tr>
<td>Chinese hamster ovary cells (culture)</td>
<td>DNA damage</td>
<td>-</td>
<td>Hartmann and Speit 1997</td>
</tr>
</tbody>
</table>

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