CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

ATSDR’s Toxicological Profile for Dinitrophenols was released in 1995. In order to update the literature in this profile, ATSDR conducted a literature search focused on health effects information as described in Appendix B. Chapters 2, 3, and 7 were revised to reflect the most current health effects and regulations/guidelines data. In some cases, other sections of the profile were updated as needed or for consistency with the updated health effects data. However, the focus of the update to this profile is on health effects information.

In the 1930s, 2,4-dinitrophenol (DNP) was prescribed by physicians as a weight-reducing agent, but its use was discontinued due to health risks. In recent years, however, 2,4-DNP in tablet and powder form has been marketed for weight loss and body building by unregulated internet sources, leading to a number of human fatalities. These unregulated sources often provide information to potential users regarding dosing and how to combine with other stimulants, steroids, and growth hormone for body building purposes, without informing users of the risk of death. As a result of the growth in availability of 2,4-DNP to the general public, there is increased potential for exposure and health effects among police officers involved in seizure of material or arrest of users, mail and shipping company employees who handle shipments, health care providers who treat or decontaminate users, and family members who live with persons who purchase and/or use 2,4-DNP. In addition to the toxicity hazards associated with 2,4-DNP, this compound is explosive when dry and when heated or subjected to flame, shock, or friction (WHO 2015).

DNPs are also used in the manufacture of dyes, wood preservatives, photographic developers, explosives, and insecticides, and as a pH indicator. 2,4-DNP and other DNPs are released to the environment primarily during their manufacture and use, and from waste disposal sites. The most likely routes of exposure near hazardous waste sites would be breathing contaminated air, drinking contaminated water, eating contaminated food, or skin contact with contaminated soil. The toxicity of 2,4-DNP is greater at high ambient temperatures; therefore, susceptibility to the toxic effects may increase for workers at high workroom temperatures or in the general population at high environmental temperatures.
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1.2 SUMMARY OF HEALTH EFFECTS

The health effect literature on DNPs is largely limited to information on 2,4-DNP; information on the remaining isomers is restricted to a single animal study using intraperitoneal administration (Harvey 1959), an oral study in chickens (Robbins 1944), and in vitro genotoxicity or mechanistic data. Much of the scientific literature on effects of 2,4-DNP consists of case reports of human poisonings, clinical studies of its use as a weight-loss agent in the 1930s, and animal studies from the early 1900s. Recent years have seen additional case reports of human poisonings or fatalities, because 2,4-DNP continues to be marketed for weight loss by unregulated internet sources. A handful of animal studies examining focused endpoints have been conducted in the past 2 decades. Abundant data in humans document 2,4-DNP-induced dangerous increases in body temperature (hyperpyrexia) and basal metabolic rate (generally measured as oxygen consumption) that elicit secondary effects (Anderson et al. 1933; Bayer and Gray 1935; Bortz 1934; Castor and Beierwaltes 1956; Cutting and Tainter 1933; Cutting et al. 1934; Dameshek and Gargill 1934; Hsiao et al. 2005; Davidson and Shapiro 1934; Dintenfass 1934; Dunlop 1934; Eichert 1936; Epstein and Rosenbloom 1935; Geiger 1933; Goldman and Haber 1936; Holborow et al. 2016; Hunt 1934; Imerman and Imerman 1936; Le et al. 2015; Lee et al. 2014; Looney and Hoskins 1934; MacBryde and Taussig 1935; Masserman and Goldsmith 1934; McFee et al. 2004; Miranda et al. 2006; Poole and Haining 1934; Pugsley 1935; Rank and Waldeck 1936; Siegmueller and Narasimhaiah 2010; Simkins 1937a, 1937b; Suozzi et al. 2005; Stockton and Cutting 1934; Tainter and Wood 1934; Tainter et al. 1935b; Tewari et al. 2009; van Veenendaal et al. 2011). Some of these secondary effects include:

- decreased body weight or body weight gain;
- confusion, agitation, and delirium;
- increased respiratory rates and dyspnea;
- nausea, vomiting, and diarrhea;
- increased pulse or heart rate, palpitations, and altered blood pressure;
- muscle pain or weakness, elevated serum creatine kinase, and in some cases rhabdomyolysis;
- acute renal failure; and
- death, typically from cardiac arrest.

In case reports of fatal exposures, autopsy findings consist of edema, hyperemia, congestion, and/or hemorrhage in the lungs, liver, stomach and small intestine; these effects are consistent with those seen in fatal hyperthermia. Studies in animals (Bakke and Lawrence 1965; Caldeira da Silva et al. 2008; Dominguez et al. 1993; Gibson 1973; Haasio et al. 2002a, 2002b; Kaiser 1964; Pugsley 1935;
Schlagowski et al. 2014; Tainter and Cutting 1933a, 1933b) confirm the dose-related effects of 2,4-DNP on body temperature and basal metabolic rate. Figure 1-1 shows health effects found in humans and animals following oral exposure to 2,4-DNP.

**Figure 1-1. Health Effects Found in Humans and Animals Following Oral Exposure to 2,4-Dinitrophenol**

<table>
<thead>
<tr>
<th>Dose (mg/kg/day)</th>
<th>Effects in Humans</th>
<th>Effects in Animals</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-130</td>
<td>Acute: Death</td>
<td>Acute: Death; increased metabolic rate and body temperature; decreased body weight</td>
</tr>
<tr>
<td>11-16</td>
<td>Acute: Death, peripheral neuritis</td>
<td>Intermediate: Death, increased metabolic rate and body temperature; decreased body weight; cataracts; hypocalcemia; hematological changes; mitochondrial injury in muscle and liver; histopathological changes in liver</td>
</tr>
<tr>
<td>6 - 10</td>
<td>Acute: Death; increased basal metabolic rate and body temperature; agranulocytosis; peripheral neuritis</td>
<td>Chronic: Decreased survival, decreased body weight</td>
</tr>
<tr>
<td>1-5</td>
<td>Acute: Death; increased basal metabolic rate and body temperature; decreased body weight; dermal lesions; cataracts, peripheral neuritis</td>
<td>Intermediate: Death; increased basal metabolic rate and body temperature; decreased body weight; dermal lesions; cataracts, agranulocytosis</td>
</tr>
<tr>
<td>0.07</td>
<td>Provisional Intermediate and Chronic MRL (based on animal data)</td>
<td>Intermediate: Reduced body weight, reduced serum glucose, triglycerides, and insulin</td>
</tr>
<tr>
<td>0.00007 mg/kg/day</td>
<td></td>
<td>Chronic: Reduced body weight; Increased basal metabolic rate</td>
</tr>
</tbody>
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***DRAFT FOR PUBLIC COMMENT***
Mechanistic data indicate that DNP effects are related to the uncoupling of mitochondrial electron transport from oxidative phosphorylation, which results in the release of energy as heat, rather than storage in the chemical potential of adenosine triphosphate (ATP) (see Section 2.18.1). The uncoupling of oxidative phosphorylation has the potential to affect all tissues and organs. Exposure of humans to 2,4-DNP results in increased basal metabolic rate, increased perspiration, weight loss, and, at higher doses, increased heart and respiratory rates and hyperthermia. These effects occur rapidly (over several hours), and may present a significant risk of death. Stopping exposure to 2,4-DNP often leads to a complete recovery. Very limited data on the other DNP isomers indicate that 2,6-, 3,4-, and 3,5-DNP may have equivalent potential for increasing basal metabolic rate as 2,4-DNP, while 2,3- and 2,5-DNP appear to have lower potential.

Health endpoints that may not be related to increases in body temperature and basal metabolic rate are discussed below.

**Hepatic Effects.** Limited available data from humans do not suggest hepatic effects of 2,4-DNP apart from those related to its pyrexic effects; these data consist of case reports of poisonings, which lack information on pre-existing conditions, as well as clinical studies from the 1930s. Early human studies attributed yellow discoloration of the conjunctiva, sclera, and skin in exposed persons to jaundice, but these effects appear to result from direct discoloration by the compound itself. There are insufficient data to assess the hepatic effects of acute- or chronic-duration exposure to 2,4-DNP in animals, but well-conducted intermediate-duration studies in rats have shown increased serum enzymes indicative of liver toxicity and increased liver weights, along with microscopic changes (centrilobular hypertrophy, necrotic foci, and mitochondrial changes).

**Dermal Effects.** Human case reports of poisoning with 2,4-DNP after acute and intermediate oral exposures document yellow discoloration of skin, erythema, and pruritis, as well as maculopapular eruptions of the skin, sometimes covering the entire body.

**Ocular Effects.** Use of 2,4-DNP as a weight-loss agent in the 1930s was discontinued primarily because a small percentage of patients developed cataracts. Cataracts have also been observed in the yellow adipose strain of mouse, in vitamin C-deficient guinea pigs, and in ducks and chickens exposed orally, as well as in rabbits exposed intraperitoneally to 2,4-DNP. Rats and other mouse strains appear to be resistant. Although the mechanism for cataract formation is uncertain, uncoupling of oxidative phosphorylation may play an important role in this effect as well.
**Developmental Effects.** No information was located on developmental effects of 2,4-DNP in humans. Exposure to 2,4-DNP has resulted in developmental effects after gestational exposure of rats exposed orally and rats and mice exposed parenterally. Increases in the numbers of stillborn pups and neonatal pup deaths, as well as decreases in pup body weight in the early postnatal period were reported in rats exposed orally to 2,4-DNP in an Organisation for Economic Co-operation and Development (OECD) guideline reproduction/developmental toxicity screening study (Takahashi et al. 2009) and similar effects were reported in an earlier study (Wulff et al. 1935). Decreased fetal weight and length and increased resorptions were also reported in rats and mice exposed to 2,4-DNP via parenteral routes (Gibson 1973; Goldman and Yakovac 1964).

**Cancer Effects.** There are no epidemiological studies of cancer in humans exposed to any DNPs. 2,4-DNP has not been adequately tested for carcinogenicity in animals, and no studies were located regarding carcinogenicity in animals exposed to the other DNP isomers. The U.S. Environmental Protection Agency (EPA) (IRIS 2003), the Department of Health and Human Services (NTP 2016), and the International Agency for Research on Cancer (IARC 2017) have not evaluated the potential carcinogenicity of any of the DNPs. Metabolites of 2,4- and 2,5-DNP administered orally have increased tumor incidences in male rats, but not in female rats or in mice. 2-Amino-4-nitrophenol and 2-amino-5-nitrophenol have been designated as “not classifiable as to their carcinogenicity to humans” (IARC 1993a, 1993b).

No data show unequivocally that 2,4-DNP is genotoxic. The positive results of some of the DNA tests may reflect its cytotoxicity (decreased cellular metabolic rate).

### 1.3 MINIMAL RISK LEVELS (MRLs)

No studies were located regarding health effects in humans or animals (other than chickens) after inhalation or oral exposure to any isomer of DNP other than 2,4-DNP. Accordingly, the following discussion will focus on 2,4-DNP. The available information is considered insufficient to derive inhalation MRLs for 2,4-DNP. Although health effects have occurred in humans exposed to 2,4-DNP occupationally (Gisclard and Woodward 1946; Jiang et al. 2011; Perkins 1919), exposure appeared to involve both the inhalation and dermal routes, and exposure concentrations were not known or inadequately characterized. No studies were located regarding health effects in animals after inhalation exposure to 2,4-DNP. As shown in Figure 1-2, available oral data from humans identify death, body...
weight, effects on energy metabolism, and dermal, ocular, hematological, and neurological endpoints as the most sensitive effects of 2,4-DNP toxicity; laboratory animal data support the body weight and energy metabolism findings in humans. The provisional MRL value for intermediate-duration oral exposure to DNP is summarized in Table 1-1 and discussed in greater detail in Appendix A.

**Figure 1-2. Summary of Sensitive Targets of 2,4-Dinitrophenol – Oral**

Body weight and energy metabolism are the most sensitive targets of 2,4-dinitrophenol oral exposure.
Numbers in triangles and circles are the lowest LOAELs among health effects in humans and animals, respectively.

- **Acute (mg/kg/day):**
  - Dermal: 0.81
  - Body weight: 1
  - Energy metabolism: 1
  - Ocular: 2
  - Neuro: 2

- **Intermediate (mg/kg/day):**
  - Body weight: 0.07
  - Endocrine: 0.07
  - Death: 1
  - Energy metabolism: 1
  - Hematological: 1
  - Dermal: 2
  - Renal: 2
  - Hepatic: 2

- **Chronic (mg/kg/day):**
  - Body weight: 2
  - Ocular: 2
### Table 1-1. Minimal Risk Levels (MRLs) for Dinitrophenols

<table>
<thead>
<tr>
<th>Exposure duration</th>
<th>MRL</th>
<th>Critical effect</th>
<th>Point of departure</th>
<th>Uncertainty factor</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inhalation exposure (ppm)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>Insufficient data for MRL derivation</td>
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<td></td>
<td></td>
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<tr>
<td>Intermediate</td>
<td>Insufficient data for MRL derivation</td>
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<tr>
<td>Chronic</td>
<td>Insufficient data for MRL derivation</td>
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<tr>
<td><strong>Oral exposure (mg/kg/day)</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>Insufficient data for MRL derivation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>0.00007 (provisional) Decreased body weight 0.07 (LOAEL)</td>
<td>1,000</td>
<td>Caldeira da Silva et al. 2008</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic</td>
<td>Insufficient data for MRL derivation; however, the intermediate MRL is believed to be protective for chronic exposures</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*aSee Appendix A for additional information.

bProvisional MRL derived for 2,4-dinitrophenol.

LOAEL = lowest-observed-adverse-effect level