CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

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

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

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

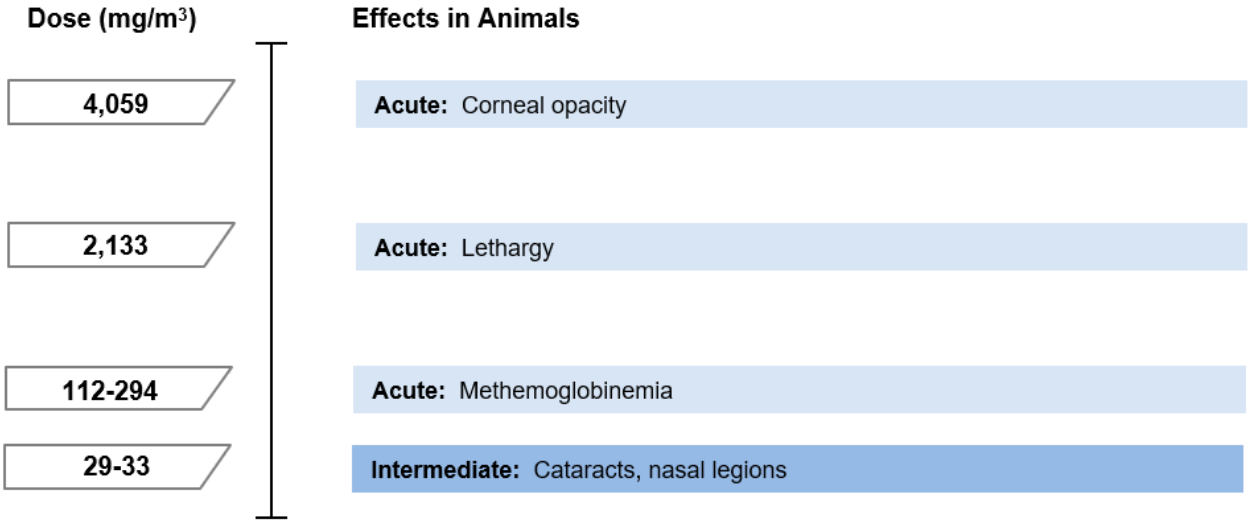
1.2 SUMMARY OF HEALTH EFFECTS

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

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

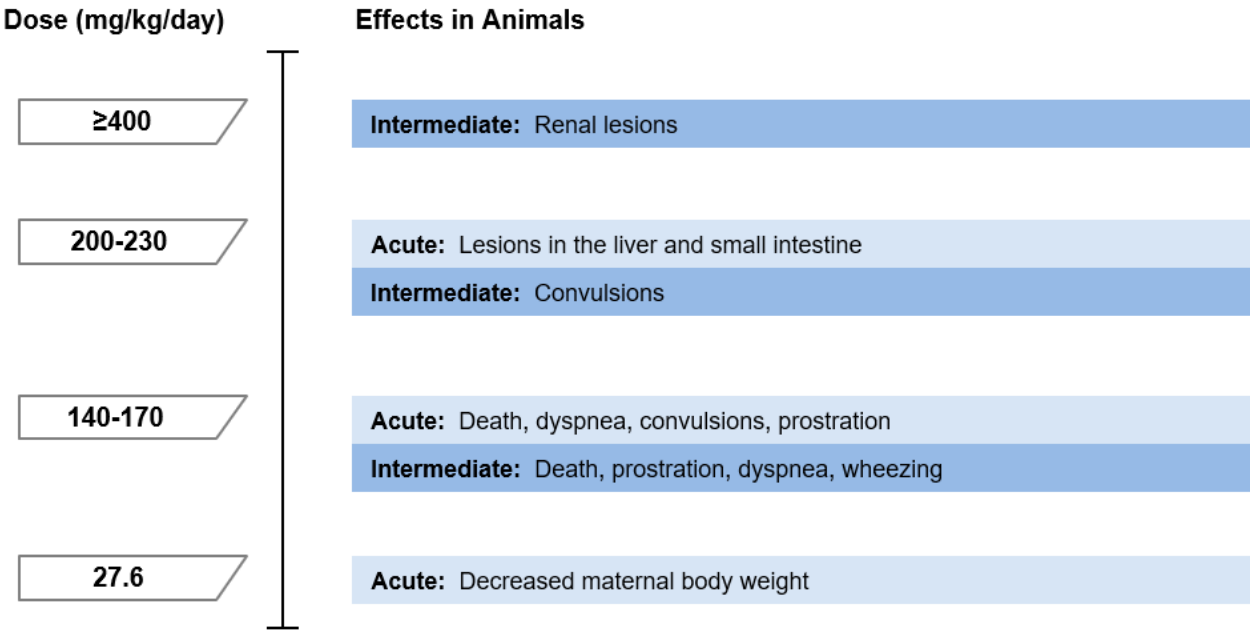
- Ocular effects are a suspected health effect of 4-nitrophenol.
- Body weight effects are not classifiable as a health effect of 4-nitrophenol following oral exposure.
- Hematological effects are not classifiable as a health effect of 4-nitrophenol following inhalation exposure.

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



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

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



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

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

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

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

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

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

1.3 MINIMAL RISK LEVELS (MRLs)

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

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

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

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

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

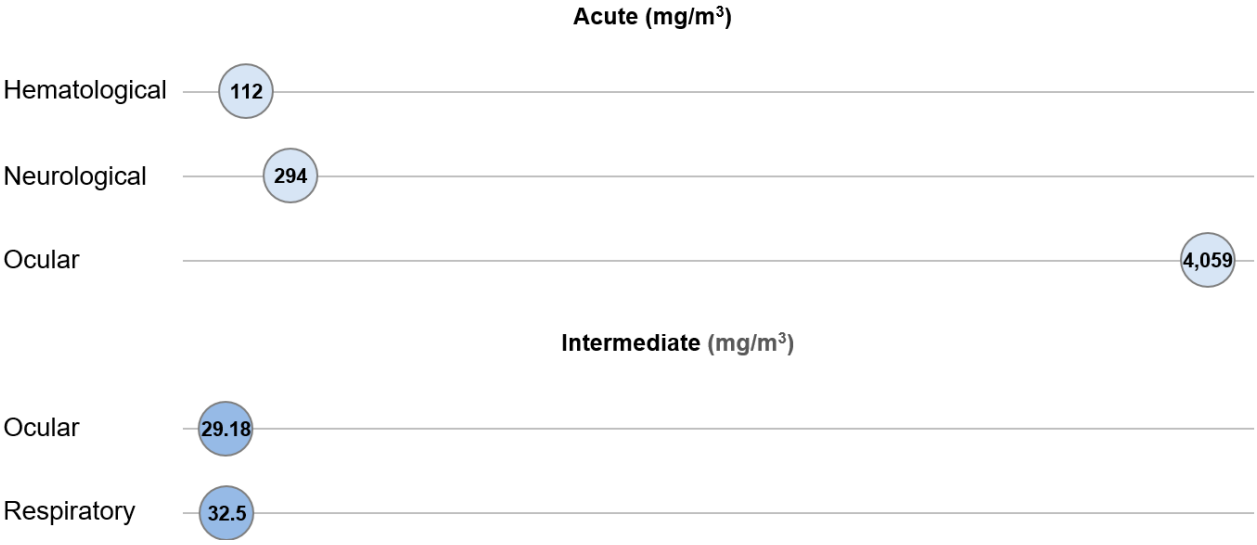


Figure 1-4. Summary of Sensitive Targets of Nitrophenols – Oral

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

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

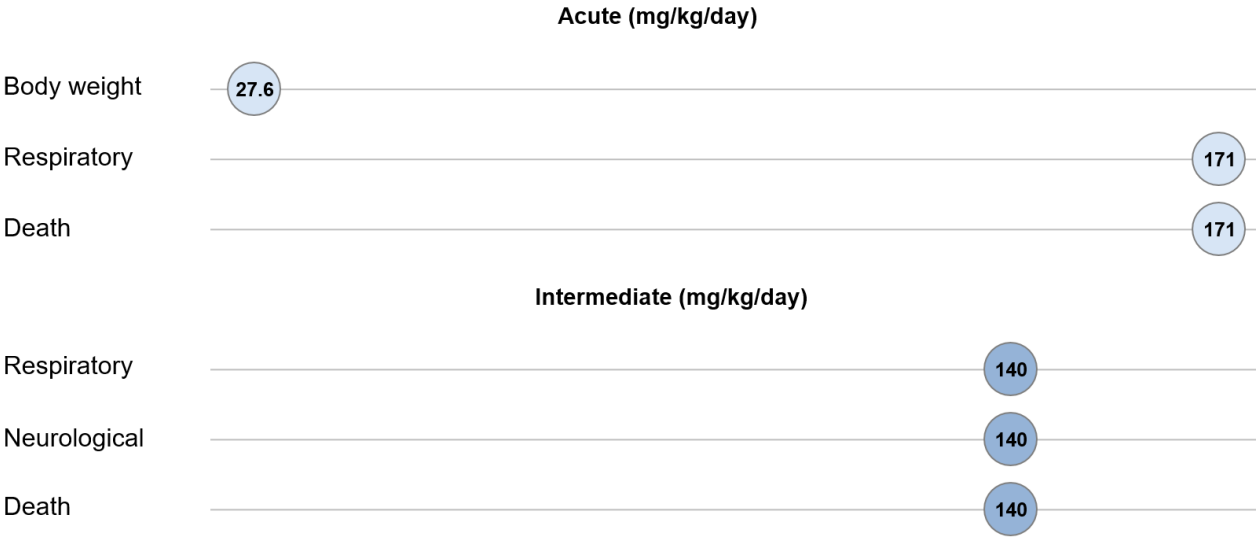


Table 1-1. Minimal Risk Levels (MRLs) for Nitrophenols[a]

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

[a]See Appendix A for additional information.