CHAPTER 6. ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of nitrophenols is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the adverse health effects (and techniques for developing methods to determine such health effects) of nitrophenols.

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

6.1 INFORMATION ON HEALTH EFFECTS

Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to nitrophenols that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of nitrophenols. The number of human and animal studies examining each endpoint is indicated regardless of whether an effect was found and the quality of the study or studies.

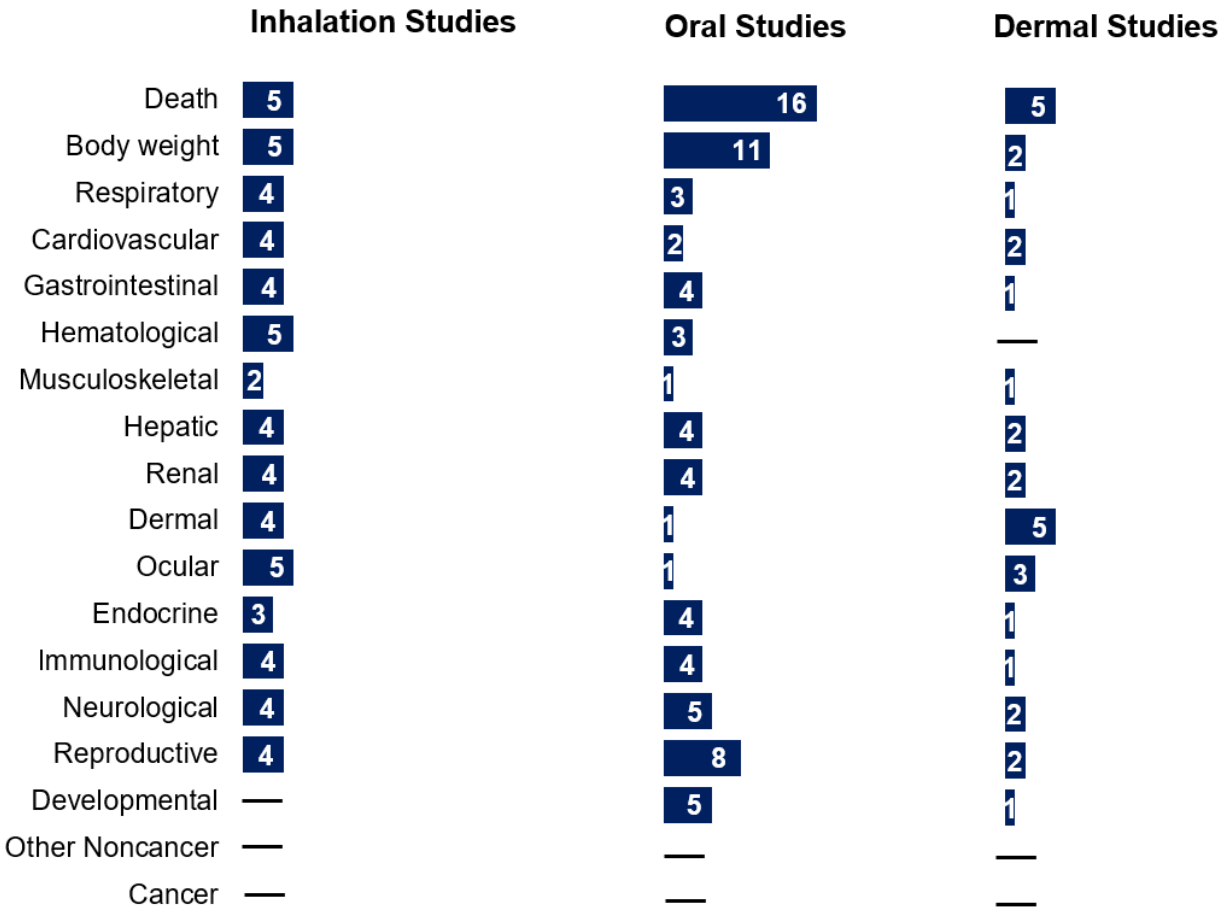
6.2 IDENTIFICATION OF DATA NEEDS

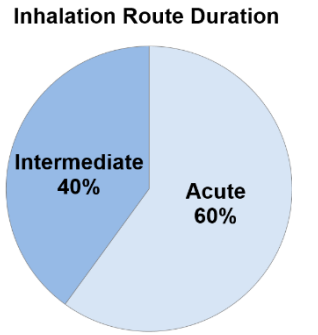
Missing information in Figure 6-1 should not be interpreted as a "data need." A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health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

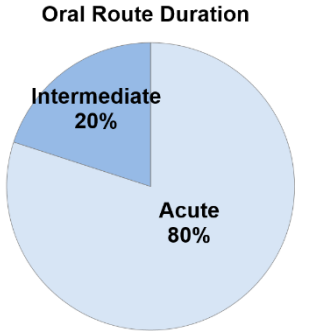
Figure 6-1. Summary of Existing Health Effects Studies on Exposure to Nitrophenols by Route and Endpoint *

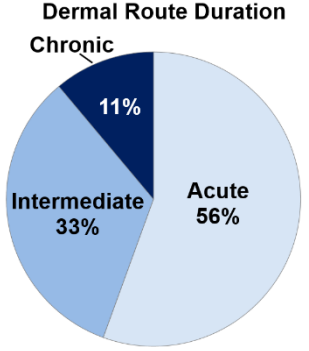
Potential reproductive, neurological, renal, hepatic, gastrointestinal, bodyweight, and cardiovascular effects were the most studied endpoints.

All available studies examined exposure in animals.









*Includes studies discussed in Chapter 2; the number of studies include those finding no effect. Figure 6-1 represents health effect studies only for 4-nitrophenol. Only one inhalation and one oral study were identified for 2-nitrophenol.

Acute-Duration MRLs. The available acute database was inadequate for deriving oral or inhalation MRLs for 2-, 3-, or 4-nitrophenol. No human data were available for any isomer via either route. No adequately conducted acute-duration animal inhalation studies were identified for 2- or 3-nitrophenol. Acute oral studies for 2-nitrophenol were limited to acute lethality studies and a gestational exposure study evaluating limited endpoints. Acute oral studies for 3-nitrophenol were limited to lethality studies. Available animal inhalation and oral data for 4-nitrophenol toxicity are considered inadequate for derivation of MRLs based on systematic review of the most sensitive endpoints, methemoglobinemia and body weight, respectively. Additional acute inhalation studies are needed to further investigate whether the hematological effects observed in rats can be corroborated and extrapolated across species. The additional data would add further confidence in this endpoint as a viable health effect for MRL development. Additional studies are needed to characterize health effects for lower-level oral doses of 4-nitrophenol. Studies are needed to characterize health effects following acute exposure to 2- and 3-nitrophenol.

Intermediate-Duration MRLs. The available intermediate-duration database was inadequate for deriving inhalation or oral MRLs for 2-, 3-, and 4-nitrophenol. No human data were available for any isomer via either route. No intermediate-duration inhalation data were available for 3-nitrophenol. For 2- and 4-nitrophenol, available studies were limited to a single 28-day study for each isomer. Additional intermediate inhalation studies on 2- and 4-nitrophenol are needed to corroborate the most sensitive endpoints of nasal lesions and cataracts, respectively. Additionally, mechanistic data underlying these effects would be useful, particularly studies designed to determine if cataracts are due to direct ocular contact with nitrophenol dust or systemic in origin. For oral exposure, no adequate intermediate-duration studies were identified for 2- or 3-nitrophenol. The intermediate oral database is also insufficient to derive an MRL for 4-nitrophenel, as the most sensitive effects (dyspnea, prostration) occurred at the lowest oral dose associated with lethality. As death is always considered a serious effect, an MRL is unable to be derived for health effects at this dose level (ATSDR 2018). Additional oral intermediate studies are needed to characterize health effects occurring at nonlethal doses. Studies are needed to characterize health effects following intermediate-duration oral exposure to 2- and 3-nitrophenol and intermediate-duration inhalation exposure to 3-nitrophenol.

Chronic-Duration MRLs. No adequately conducted chronic-duration human or animal studies were identified for 2-, 3-, or 4-nitrophenol; thus, the databases for each of these chemicals were inadequate for deriving chronic-duration MRLs.

Health Effects. There is a general lack of literature on the health effects of 2-, 3-, and 4-nitrophenol. The available literature suggests body weight, hematological, and ocular effects may be sensitive targets of toxicity after exposure to 4-nitrophenol, but no human studies have been published to date about either the toxicokinetics or the health effects of exposure to 2-, 3-, or 4-nitrophenol. This represents a very important data need, as epidemiologic evidence would strengthen the reliability of the available evidence from the existing animal study literature. Additional data are needed to investigate intermediate oral exposure in animals at low levels of 4-nitrophenol, as death was the most sensitive endpoint from the body of adequately conducted literature. There were many intraperitoneal studies that showed potential reproductive/endocrine effects in both male and female rats and mice; however, there were no studies using routes of exposure considered sufficient for MRL development, such as inhalation, oral, or dermal exposure. A data need exists for the study of reproductive/endocrine effects using these human-relevant routes of exposure at exposure levels relevant for human populations. A data need has also been identified to study the health effects of 3-nitrophenol in animals in all exposure routes and durations, as no current literature exists regarding the health effects of this chemical. Additional research on the relative potencies of 2-, 3-, and 4-nitrophenol would also add to the health effects literature.

Body weight. Based on systematic review, body weight effects following oral exposure are not classifiable as health effects following oral exposure to 4-nitrophenol due to no data in humans and low evidence from animal studies. Available oral studies of 4-nitrophenol have unexplained inconsistencies regarding decreased body weight following acute-duration exposure and no evidence of body weight effects following intermediate-duration exposure from a limited number of studies. Additional studies in multiple species evaluating 2-, 3-, and 4-nitrophenol would be useful to characterize whether body weight effects may be associated with nitrophenol exposure.

Hematological. Based on systematic review, hematological effects following inhalation exposure are not classifiable as health effects following oral exposure to 4-nitrophenol due to no data in humans and low evidence from animal studies. Two acute-duration inhalation experiments from a single report by Smith et al. (1988) suggest that methemoglobinemia may occur following exposure to 4-nitrophenol; however, these findings are not confirmed in intermediate-duration inhalation studies of 2- or 4-nitrophenol or oral exposure to 4-nitrophenol. Additional studies would help to identify the validity of the findings in the Smith et al. (1988) study. Mechanistic data supporting a mechanism by which nitrophenols could induce methemoglobinemia would also be useful.

Ocular. Based on systematic review, ocular effects are a suspected health effect of 4-nitrophenol due to no data in humans and a moderate level of evidence in animals. Ocular effects, including irritation, corneal opacity, and cataracts, have been observed following acute- and intermediate-duration inhalation exposure and direct eye contact with 4-nitrophenol. Mechanistic studies to determine whether ocular effects are due to direct ocular contact with nitrophenol dust or systemic in origin would be useful. Additional studies evaluating 2- and 3-nitrophenol would also be useful.

Epidemiology and Human Dosimetry Studies. No studies evaluating potential health effects in humans following exposure to nitrophenol were identified. Studies in humans that monitor exposure levels and health effects associated with nitrophenols would be useful.

Biomarkers of Exposure and Effect. Biomarkers of exposure specific to nitrophenols and its metabolites have not been determined. The metabolism of nitrophenols has been examined only in animal models. Additionally, urine has often been tested to identify exposure to nitrophenols. 2-Nitrophenol and 4-nitrophenol conjugates are completely and rapidly excreted in the urine. Therefore, unless a very high dose is given, urinary levels will fall to near zero in a short time (48 hours). It is not known if urinary excretion of 2- or 4-nitrophenol (or their conjugates) can be associated quantitatively with exposure to these chemicals due to other chemicals that are metabolized to form nitrophenols. A data need has been identified to determine biomarkers of exposure that are specific to nitrophenols.

Absorption, Distribution, Metabolism, and Excretion. A data need exists to further understand absorption, distribution, metabolism, and excretion of nitrophenols in humans exposed orally, dermally, and through inhalation. Pharmacokinetic studies in animals exposed to nitrophenols by inhalation, oral, and dermal routes provided limited information. Additional studies are needed to evaluate the toxicokinetics of nitrophenols following exposure in humans. A specific data need exists for further information regarding the possible distribution of 4-nitrophenol through the placental barrier, as fetal hemoglobin might be more sensitive to the effects of 4-nitrophenol.

Comparative Toxicokinetics. There are limited data available that allow for a comparison of the toxicokinetic properties across species. The lack of studies in humans along with the absence of unique biomarkers of exposure make inter-species comparisons of the effects difficult. A data need exists to further understand the toxicokinetics of 2-, 3-, and 4-nitrophenol in humans, as well as to identify unique biomarkers of exposure to these chemicals.

Children's Susceptibility. No human data are available regarding children's susceptibility. Available data from oral developmental studies do not indicate that developing animals are uniquely susceptible to toxicity following exposure to 4-nitrophenol. Developmental effects have not been evaluated in animals following inhalation exposure. Experimental studies in young animals and/or epidemiological data for children would be useful to address these data gaps.

Physical and Chemical Properties. The physical and chemical properties of 2- and 4-nitrophenol have been sufficiently characterized to permit estimation of its environmental fate. There is limited information available regarding the environmental fate of 3-nitrophenol. A data need exists to further characterize the environmental fate of 3-nitrophenol.

Production, Import/Export, Use, Release, and Disposal. Production methods for nitrophenols are known and there does not appear to be a need for further information. The use pattern of nitrophenols is known. Detailed information on the uses of 2-nitrophenol in industry and consumer products is available from Chemical Data Reporting (EPA 2016). Additional data on the uses of nitrophenols are not needed. TRI contains data on releases to air, water, and soil from facilities that produce nitrophenols. Additional data are needed on the environmental release of nitrophenols from uses such as rubber production and pigment/dye production to adequately assess their contribution to human exposure. More information regarding the amount of nitrophenols that are disposed of at hazardous waste sites or abandoned would be useful. No current data are available on the amount of nitrophenols disposed of annually. Methods for disposing of nitrophenols are described in the literature. Sufficient information exists on regulations pertaining to nitrophenols. Nitrophenols are regulated according to the Emergency Planning and Community Right-to-Know Act of 1986.

Environmental Fate. There is scant data available that examines the fate of 2-, 3-, and 4-nitrophenol in water and soil. More data are needed to assess the fate of these compounds in air with more confidence. Based on the compounds' photolytic behavior in water, direct photolysis in air is expected to be the primary fate process in air. Since these compounds have low vapor pressures, their potential for long range atmospheric transport is low. However, no data were available on the vapor-phase photolysis of the compounds that would permit estimation of their half-lives in the atmosphere. If degradation follows simple kinetics, these half-lives are important since they indicate the degree of persistence of a compound in a certain environmental medium.

Bioavailability from Environmental Media. No information was identified regarding absorption of 2-, 3-, or 4-nitrophenol in humans following inhalation, oral, or dermal exposure. Absorption by the inhalation route in animals could be inferred from the appearance of adverse effects after exposure to 4-nitrophenol dusts. However, oral and/or dermal absorption could also have occurred. Limited data obtained in animals indicate that 4-nitrophenol is readily and almost completely absorbed by the oral route when administered by gavage, but no data were available concerning absorption from food or drinking water. Data regarding 2-nitrophenol were not available. An ethanol solution of 4-nitrophenol was not well absorbed when applied to the skin of animals, since most of the dose could be recovered from the application site a week after dosing. It is not known whether 2-nitrophenol can be absorbed through the skin. Knowledge of the compounds' bioavailability will permit estimation of their absorption in a body organ from an environmental medium, in cases where the exposure level is known. There are no animal studies identified for exposure to 3-nitrophenol. Given the lack of literature regarding absorption of 2-, 3-, and 4-nitrophenol in humans and animals, a data need exists to further study the absorption potential of these chemicals following inhalation, oral, and dermal exposure.

Food Chain Bioaccumulation. There is limited information available on bioaccumulation of nitrophenols. Even though nitrophenols bioaccumulate in edible aquatic species, there is no current evidence indicating any transfer from plants to animals. Data for biomagnification of these chemicals are also scant. A data need exists to further study the potential for food chain bioaccumulation of 2-, 3-, and 4-nitrophenol.

Exposure Levels in Environmental Media. Data are not available to establish any ambient level of these compounds in air, drinking water, or foods. Even data on the levels of these compounds under conditions in which they are expected to show elevated values are scarce. Reliable, up-to-date monitoring data for air, drinking water, and foods would allow estimation of the extent of exposure from each of the sources.

Exposure Levels in Humans. Levels of 4-nitrophenol in the urine of general population are presented in Chapter 5. The levels of 4-nitrophenols in other tissues in the general population are unknown. There are no data available on levels 2- or 3-nitrophenol in any body tissue or fluid. No data on the levels of either compound in any body tissue or fluid for populations living near hazardous waste sites are available. More studies need to be done to better understand the exposure of nitrophenols in adults as well as levels of the compounds in populations living near hazardous waste sites.

Exposures of Children. Limited data on exposure to nitrophenols in children were identified. Li et al. (2019) measured pesticide metabolite concentrations in Australian infants and toddlers. There was a significant increase in the concentration of urinary 4-nitrophenol with age, which may suggest that exposure increases as a result of increased activity and dietary intake (Li et al. 2019). As this was the only study that studied 2-, 3-, or 4-nitrophenol exposure in children, a data need exists to further understand the potential for nitrophenols exposures in children.

6.3 ONGOING STUDIES

No ongoing studies were identified for nitrophenols (RePORTER 2022).