CHAPTER 6. ADEQUACY OF THE DATABASE

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

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

6.1 Information on Health Effects

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

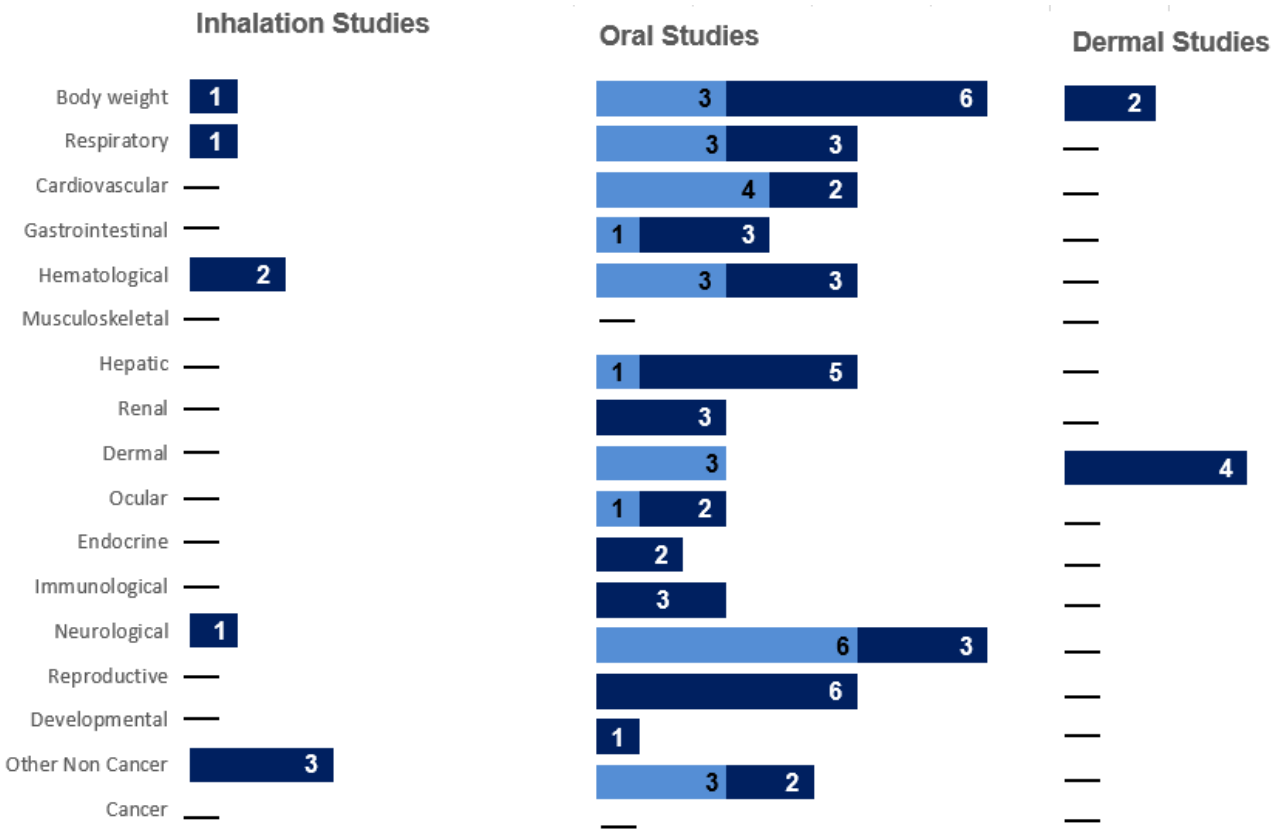
6.2 Identification of Data Needs

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

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

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

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



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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

6.3 Ongoing Studies

No ongoing studies were identified for DNOC.