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16. ABSTRACT

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with specific chemicals or compounds. The Office of Emergency and Remedial Response (Superfund) uses these documents in preparing cost-benefit analyses under Executive Order 12991 for decision-making under CERCLA. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data are available. The interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed. Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval. The RfD is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan. For compounds for which there is sufficient evidence of carcinogenicity, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

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HEALTH EFFECTS ASSESSMENT FOR NITROPHENOLS

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PREFACE

This report summarized and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with nitrophenols. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the Chemical Abstracts, TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to June, 1986. Secondary sources of information have also ben relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980. Ambient Water Quality Criteria Document for Nitrophenols. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC. EPA 440/5-80-063. NTIS PB81-117749.

U.S. EPA. 1983a. Reportable Quantity Document for 2-Nitropenol. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC.

U.S. EPA. 1983b. Reportable Quantity Document for p-Nitrophenol. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC.

U.S. EPA. 1983c. Reportable Quantity Document for Nitrophenol (Mixed). Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC.

U.S. EPA. 1985. Health and Environmental Effects Profile for Nitrophenols. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, D.C.

The intent in these assessments is to suggest acceptable exposure levels for noncarcinogens and risk cancer potency estimates for carcinogens whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard or risk associated with exposure to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S (formerly AIS) or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used, or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for RFD_S estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure. These values are developed for both inhalation (RfD_{SI}) and oral (RfD_{SO}) exposures.

The RfD (formerly AIC) is similar in concept and addresses chronic exposure. It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980) for a discussion of this concept]. The RfD is route-specific and estimates acceptable exposure for either oral (RfD_O) or inhalation (RfD_I) with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for identifying reportable quantities and the methodology for their development is explained in U.S. EPA (1983).

For compounds for which there is sufficient evidence of carcinogenicity RfD_S and RfD values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. For carcinogens, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

ABSTRACT

Data were insufficient for quantitative risk analysis of the nitrophenols. Recommendations for further testing await the outcome of the NTP (1986) skin-painting oncogenicity study with 4-nitrophenol in mice.

The acute toxicity data available do not indicate either a target organ or system for these isomers. Both the acute toxicity and the mechanisms of toxicity appear to vary with each isomer. It does not appear that the risk assessment of an isomer may prudently be based on analogy to another, or to closely related compounds such as 2,4-dinitrophenol, because of marked differences in mechanisms of toxicity.

ACKNOWLEDGEMENTS

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LIST OF ABBREVIATIONS

DNA	Deoxyribonucleic acid
LD_{50}	Dose lethal to 50% of recipients
ppm	Parts per million

1. ENVIRONMENTAL CHEMISTRY AND FATE

Selected physical properties and the available data on the environmental fate of the nitrophenols are summarized in Table 1-1. Nitrophenols can be classified as nitroaromatic hydrocarbons.

Available data regarding the environmental fate of the nitrophenols pertain primarily to 4-nitrophenol. It is assumed that the environmental fate is similar for 2-, 3- and 4-nitrophenol. Monitoring data indicate that 4-nitrophenol is removed from the atmosphere by wet and dry deposition (U.S. EPA, 1985). Direct photolysis or reaction with photochemically generated hydroxyl radicals are also potential removal mechanisms. The estimated atmospheric removal half-life of the nitrophenols that is due to rainfall is 3 weeks and the estimated hydroxyl reaction half-life of 2-nitrophenol is 9 days (U.S. EPA, 1985). The half-lives of 2- and 3-nitrophenols in water could not be located in the available literature. U.S. EPA (1985) reported that 4-nitrophenol reacts quite rapidly with hydroxyl radicals in water in the presence of sunlight and that the nitrophenols are capable of undergoing significant biodegradation in various ambient surface waters. The observed photolysis half-life of 4-nitrophenol in aqueous solution is reported to vary from 16 hours to 5.7 days at pH 5, 6.7 days at pH 7 and 13.7 days at pH 11.5 (U.S. EPA, 1985). The soil half-life of 4-nitrophenol was estimated using a decay rate constant of 0.105/day measured in a model soil ecosystem. Soil microorganisms are capable of degrading the nitrophenols and the nitrophenols may be susceptible to leaching in certain soil types, although biodegradation may occur rapidly enough to prevent extensive leaching (U.S. EPA, 1985).

TABLE 1-1

Physical Properties and Environmental Fate of Nitrophenols*

Properties	2-Nitrophenol	3-Nitrophenol	4-Nitrophenol
CAS Registry number:	88-75-5	554-84-7	100-02-7
Molecular weight:	139.11	139.11	139.11
Vapor pressure:	0.23 at 20°C 0.152 at 20°C 0.11 at 25°C	0.75 at 20°C	0.75 at 20°C
Water solubility:	21,000 mg/ℓ at 20°C	13,500 mg/ℓ at 20-25°C	16,000 mg/ℓ at 25°C
Log octanol/water partition coefficient:	1.79	2.00	1.85-1.91
pKa:	7.23	2.00	7.156
Bioconcentration factor:	8-13.5 (estimated)	3-19.5 (estimated)	11-30 green algae (Chlorella fusca) 57-180, fish
Soil adsorption coefficient:	113.52, clay loam	52.83, clay loam	55.25, clay loam 133-400 clay soils
Half-life in			
Air:	<9 days	NR	NR
Water:	NR	NR	16 hours to >6.7 days
Soil:	NR	NR	6.6 days (estimated)

*Source: U.S. EPA, 1985

NR = Not reported

4-Nitrophenol is produced as a metabolite by microbial and hydrolytic decomposition of the pesticides parathion, methyl parathion and fluorodifen (U.S. EPA, 1985). Occupational exposure that is due to dermal contact with 4-nitrophenol may result from handling crops treated with these pesticides. The general public may be exposed by ingestion of food containing 4-nitrophenol residues as suggested by the identification of 4-nitrophenol on spinach that was treated with parathion (U.S. EPA, 1985). 2-Nitrophenol and 4-nitrophenol have been detected in atmospheric particulates; thus, exposure from inhalation potentially exists (U.S. EPA, 1985). The relatively low vapor pressures for these compounds at ambient temperatures suggest that volatilization would be minimal and that exposure by the oral route may be more relevant.

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

Pertinent quantitative data regarding the absorption of nitrophenols after oral or inhalation exposure could not be located in the available literature.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. ACUTE, SUBCHRONIC AND CHRONIC TOXICITY

Pertinent data regarding subchronic or chronic oral and inhalation toxicity of nitrophenols in man or experimental animals could not be located in the available literature.

Table 3-1 lists oral LD_{50} values for the nitrophenols in rats and mice. From these data it appears that 4-nitrophenol may be more toxic to rats and mice than the 2- and 3-isomers. Mice appear to be more sensitive than rats to 2-nitrophenol and rats may be more sensitive than mice to 3-nitrophenol. Methemoglobin formation was reported after acute 4-nitrophenol administration to cats (von Oettingen, 1941) and after 4-nitrophenol administration to mice (Smith et al., 1967) (route of administration not reported in secondary sources) but not after oral administration of 3- or 4-nitrophenol to rats (Grant, 1959). The U.S. EPA (1980) concluded that methemoglobinemia may be dependent upon the nitroreductase activity of the organism, which is not extensive in most species. Ogino and Yasukura (1957) reported cataract formation in 4-nitrophenol treated vitamin C-deficient guinea pigs, but it was unclear whether this effect was primarily from the vitamin deficiency itself (U.S. EPA, 1980).

Since 2,4-dinitrophenol is an uncoupler of oxidative phosphorylation (U.S. EPA, 1980), several investigators have explored the possibility that mononitrophenols act similarly. Cameron (1958) found substantial differences in the effect of mononitrophenol on the metabolic activity of rats. Carbon dioxide output was increased by 4-nitrophenol, oxygen consumption was depressed by 3-nitrophenol and 2-nitrophenol had no effect on either parameter. Of the mono- and di-nitrophenols tested, only 2,4-dinitrophenol

TABLE 3-1

Acute Toxicity of Orally Administered Nitrophenols*

Isomer	Species	LD_{50} (mg/kg)	Reference
2-Nitrophenol	rat	2830	Vernot et al., 1977
	mouse	1300	
3-Nitrophenol	rat	930	Vernot et al., 1977
	mouse	1410	
4-Nitrophenol	rat	620	Vernot et al., 1977
	rat	350	Fairchild, 1977
	mouse	470	Vernot et al., 1977

*Source: U.S. EPA, 1985

stimulated both carbon dioxide output and oxygen consumption. Based on these results, the U.S. EPA (1980) concluded that the mononitrophenols were not potent uncouplers of oxidative phosphorylation.

The findings of direct binding of 3-nitrophenol to erythrocyte membranes, leading to the formation of ghost cells (Mackleidt et al., 1972) and 2- and 4-nitrophenol inhibition of chloride transport in erythrocytes (Motais et al., 1978) suggest that these agents may act directly on the cell membrane. Species were unspecified and no further details were given.

An abstract of a Russian study (Makhinya, 1969) stated that administration of 2-, 3- or 4-nitrophenol caused gastritis, enteritis, colitis, hepatitis, neuritis, splenic hyperplasia and inhibited oxidation processes in an unspecified species. Details were limited.

3.2. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

In a preliminary developmental toxicity test in groups of 10 mice, Plasterer et al. (1985) found that oral administration of 400 mg/kg 4-nitrophenol, from days 7-14 of gestation, had no adverse effects on indices of fetal survival, birth weights or the incidence of gross malformations. Maternal survival and weight gain, however, were significantly decreased. The oral LD_{50} for adult mice when administered daily for 8 days was calculated to be 625.7 mg/kg in this study.

3.3. TOXICANT INTERACTIONS

Reinke and Moyer (1985) found that ethanol pretreatment caused rapid microsomal metabolism of 4-nitrophenol to 4-nitrocatechol, which in turn competed with 4-nitrophenol for conjugation with glucuronic acid or sulfate. Much slower rates of metabolic induction were effected by interactions with phenobarbital and β-napthoflavone.

4. CARCINOGENICITY

4.1. HUMAN DATA

Data regarding the carcinogenicity of the nitrophenols to humans could not be located in the available literature.

4.2. BIOASSAYS

Pertinent data regarding oral or inhalation oncogenicity in experimental animals could not be located in the available literature.

4.3. OTHER RELEVANT DATA

Boutwell and Bosch (1959) conducted skin-painting assays in female mice using 25 µl of 2- or 4-nitrophenol in dioxane, twice weekly for 12 weeks. The incidence of any tumor type was not increased as a result of treatment with either compound. The U.S. EPA (1985) considered this study inadequate for assessment of the oncogenic potency of nitrophenol.

The NTP (1986) is currently conducting a chronic skin-painting study with 4-nitrophenol in mice.

The results of mutagenicity testing of the nitrophenol isomers have been summarized by U.S. EPA (1985). For the most part, 2-, 3- or 4-nitrophenol did not increase the frequency of reverse mutations in either Salmonella typhimurium or Escherichia coli (Taylor, 1979a,b; Haworth et al., 1983; Suzuki et al., 1983; Probst et al., 1981). Fahrig (1974) reported that 4-nitrophenol also did not increase the frequency of forward mutations in E. coli or Serratia marcescens, or recessive lethal mutations in Drosophila melanogaster; however, increases in the frequency of mitotic gene conversion, probably indicative of DNA single-strand breaks were found in Saccharomyces cerevisiae with 4-nitrophenol (Fahrig, 1974). In confluent human fibroblast cultures, 4-nitrophenol inhibited both repair and replicative DNA synthesis (Poirier et al., 1975).

4.4. WEIGHT OF EVIDENCE

The nitrophenols should be classified as IARC Group 3 or EPA Group D (U.S. EPA, 1986). These classifications apply to chemicals with inadequate relevant carcinogenicity data.

5. REGULATORY STANDARDS AND CRITERIA

Pertinent guidelines and standards including EPA ambient water and air quality criteria, drinking water standards, HAs, AADIs and ACGIH, NIOSH or OSHA occupational exposure limits could not be located in the available literature. The U.S. EPA (1980) defined organoleptic detection thresholds for nitrophenols of 0.24-389 mg/ℓ based upon the Soviet literature. U.S. EPA (1980) stated that the absence of chronic toxicity data precluded derivation of water criteria for the nitrophenols.

The tolerance for the herbicide fluorodifen and its metabolites (including 4-nitrophenol) on peanut hulls, peanuts and peanut vine hay is 0.2 ppm (CFR, 1982). For soybean forage, soybeans, and seed and pod vegetables and their forages, the tolerance is 0.1 ppm (CFR, 1982).

6. RECOMMENDATIONS

Results from a limited number of mutagenicity tests in prokaryotic systems indicate that the nitrophenols are not potent mutagens, although effects on DNA synthesis in human fibroblasts with 4-nitrophenol (Poirier et al., 1975) are cause for concern. Both 2- and 4-nitrophenol were negative in skin-painting studies using mice; 4-nitrophenol is currently being retested in this system by the NTP (1986). Recommendations for further carcinogenicity testing of these compounds await the results of the NTP (1986) study in progress.

If the results of this study do not suggest a carcinogenic role for the nitrophenols, subchronic threshold toxicity testing would be in order, initially by oral exposure. The oral LD_{50} data suggest different thresholds of toxicity for the different isomers of nitrophenol in different species (U.S. EPA, 1985). Other acute toxicity data indicate that the different isomers may have different mechanisms of toxicity. Cameron (1958), for example, observed marked differences in the impact of the various isomers on the metabolic activity of rats. 4-Nitrophenol has been associated with cataract formation in guinea pigs (Ogino and Yasukura, 1957) and methemoglobinemia in cats (von Oettingen, 1941) and mice (Smith et al., 1967). An abstract of a Russian study (Makhinya, 1969) associates gastritis, enteritis, colitis, hepatitis, neuritis, splenic hyperplasia and inhibited oxidation processes with each of the nitrophenol isomers. These data are insufficient to suggest a target organ for these compounds and these data suggest that risk assessment for one isomer should not be based by analogy on data obtained with another isomer. Similarly, risk assessment

of the nitrophenols should not be based on analogy to 2,4-dinitrophenol since these chemicals appear to differ markedly in their mechanisms of toxicity (U.S. EPA, 1980).

Although 4-nitrophenol had no apparent effects on reproductive indices or gross malformation in mice treated during gestation (Plasterer et al., 1985), the small number of animals/test group and the limited parameters of developmental toxicity measured render this study inadequate to serve as the sole basis for evaluating the reproductive toxicity of this compound. It is recommended that the developmental toxicity of all three isomers be evaluated more completely and that animals from subchronic studies be evaluated to determine potential effects of these compounds on reproductive performance.

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