

TOXICOLOGICAL PROFILE FOR
NITROPHENOLS:
2-NITROPHENOL
4-NITROPHENOL

Agency for Toxic Substances and Disease Registry
U.S. Public Health Service

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FOREWORD

The Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) extended and amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare toxicological profiles for hazardous substances which are most commonly found at facilities on the CERCLA National Priorities List and which pose the most significant potential threat to human health, as determined by ATSDR and the Environmental Protection Agency (EPA). The lists of the 250 most significant hazardous substances were published in the Federal Register on April 17, 1987; on October 20, 1988; on October 26, 1989; and on October 17, 1990. A revised list of 275 substances was published on October 17, 1991.

Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the lists. Each profile must include the following content:

(A) An examination, summary, and interpretation of available toxicological information and epidemiological evaluations on the hazardous substance in order to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects.

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure which present a significant risk to human health of acute, subacute, and chronic health effects.

(C) Where appropriate, an identification of toxicological testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

This toxicological profile is prepared in accordance with guidelines developed by ATSDR and EPA. The original guidelines were published in the Federal Register on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile is intended to characterize succinctly the toxicological and adverse health effects information for the hazardous substance being described. Each profile identifies and reviews the key literature (that has been peer-reviewed) that describes a hazardous substance's toxicological properties. Other pertinent literature is also presented but described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

Foreword

Each toxicological profile begins with a public health statement, which describes in nontechnical language a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health will be identified by ATSDR, the National Toxicology Program (NTP) of the Public Health Service, and EPA. The focus of the profiles is on health and toxicological information; therefore, we have included this information in the beginning of the document.

The principal audiences for the toxicological profiles are health professionals at the federal, state, and local levels, interested private sector organizations and groups, and members of the public.

This profile reflects our assessment of all relevant toxicological testing and information that has been peer reviewed. It has been reviewed by scientists from ATSDR, the Centers for Disease Control, the NTP, and other federal agencies. It has also been reviewed by a panel of nongovernment peer reviewers. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.



William L. Roper, M.D., M.P.H.
Administrator
Agency for Toxic Substances and
Disease Registry

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1. PUBLIC HEALTH STATEMENT

This Statement was prepared to give you information about 2-nitrophenol and 4-nitrophenol and to emphasize the human health effects that may result from exposure to them. The Environmental Protection Agency (EPA) has identified 1,177 National Priorities List (NPL) sites. Nitrophenols have been found at 14 of these sites. However, we do not know how many of the 1,177 NPL sites have been evaluated for 2-nitrophenol and 4-nitrophenol. As EPA evaluates more sites, the number of sites at which nitrophenols are found may change. This information is important for you because nitrophenols may cause harmful effects and because these sites are potential or actual sources of human exposure to 2-nitrophenol and 4-nitrophenol.

When a chemical is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment as a chemical emission. This emission, which is also called a release, does not always lead to exposure. You can be exposed to a chemical only when you come into contact with it. You may be exposed to it in the environment by breathing, eating, or drinking substances containing the chemical, or from skin contact with it.

If you are exposed to a hazardous substance such as nitrophenols, several factors will determine whether harmful health effects will occur and what the type and severity of those health effects will be. These factors include the dose (how much), the duration (how long), the route or pathway by which you are exposed (breathing, eating, drinking, or skin contact), the other chemicals to which you are exposed, and your individual characteristics such as age, sex, nutritional status, family traits, life style, and state of health.

1.1 WHAT ARE 2-NITROPHENOL AND 4-NITROPHENOL?

The two nitrophenols are very similar in their chemical properties. The manufacture of one almost always produces at least a little of the other. Therefore, we include them both in one profile. 2-Nitrophenol is a light yellow solid with a peculiar aromatic smell. 4-Nitrophenol is a colorless to light yellow solid with very little odor. 2-Nitrophenol is slightly soluble in cold water, but 4-nitrophenol is moderately soluble in cold water. Neither chemical evaporates at room temperature. These are man-made chemicals with no evidence of their formation from any natural source. Therefore, humans are solely responsible for the presence of the chemicals in the environment. The main sources of the two chemicals are industrial manufacturing and processing. 2-Nitrophenol is used mainly to produce dyes, paint coloring, rubber chemicals, and substances that kill molds (fungicides). 4-Nitrophenol is used mainly to manufacture drugs, fungicides, and dyes, and to darken leather. The time needed for these two chemicals to disappear chemically in air is not known. They both break down (degrade) in water and surface soil, but the breakdown takes longer at lower soil depths and groundwater. Therefore, they are expected to stay longer in the deep soil of dump sites compared to surface

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soil and may even stay indefinitely in these soils. For more information about their use, disposal methods, and the time needed for environmental breakdown, see Chapters 4 and 5 of this profile.

1.2 HOW MIGHT I BE EXPOSED TO 2-NITROPHENOL AND 4-NITROPHENOL?

Small amounts of the two substances can be found in the air, water, and soil. Therefore, breathing air, drinking water, and eating foods grown in soils that contain these substances can expose you to them. The background levels (when no apparent sources of pollution are present) of the two nitrophenols in air are not known. However, in one case, the level of 2-nitrophenol in the air in Portland, Oregon, was 4 parts per trillion (ppt by volume). Its level in the air in Dubendorf, Switzerland, was 61 ppt. These are very small numbers, and exposure from breathing air containing such low levels of these substances may not be very harmful. Except for one case of polluted water, these two substances have not been found in U.S. public drinking waters. The background levels of these compounds in foods eaten by humans are not known either. Because the chemicals break down rapidly, any exposure from these levels will be small. 4-Nitrophenol has been found in the urine of people who did not have any known exposure to this substance. The 4-nitrophenol found in human urine comes from the breakdown within the body of a pesticide, parathion, that is commonly used on certain agricultural products that many of us eat.

Some people may be exposed to higher than background levels of nitrophenols. Workers who produce or process these chemicals may be exposed to higher doses, particularly during spills or accidents. Workers involved in cleaning up hazardous waste or spills that contain these chemicals and pesticide applicators are especially subjected to higher than background levels of exposure. People who use certain pesticides or who drink well water near farming areas where certain pesticides are used may also be exposed to higher than background levels of 4-nitrophenol. The two nitrophenols and their mixture have been found in at least 14 of the 1,177 hazardous waste sites on the National Priorities List (NPL). People who live near these sites may be subjected to exposure at higher doses than background. Except for the high levels of 4-nitrophenol found in the urine of persons exposed to the pesticide, parathion, we have no evidence of exposure to 2-nitrophenol and 4-nitrophenol that is higher than background levels. For more information on environmental levels and the possibilities for exposure to these substances, see Chapter 5 of this profile.

1.3 HOW CAN 2-NITROPHENOL AND 4-NITROPHENOL ENTER AND LEAVE MY BODY?

2-Nitrophenol and 4-nitrophenol can enter your body through your lungs and pass into the blood stream if you breathe contaminated air. If you swallow 2-nitrophenol or 4-nitrophenol, most of it probably enters your body and passes from the stomach into the blood stream very quickly (in minutes). If you spill 2-nitrophenol or 4-nitrophenol on your skin, some of it might

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pass through the skin into the blood stream, but we do not know how much or how fast. Once inside your body, 2-nitrophenol and 4-nitrophenol change (we call this change metabolism) into other chemicals that will be quickly (in hours) released from the body in your urine. We do not have enough information available to determine which will be the most likely way that 2-nitrophenol or 4-nitrophenol will enter your body if you are exposed at hazardous waste sites. For more information on how 2-nitrophenol and 4-nitrophenol can enter and leave your body, see Chapter 2.

1.4 HOW CAN 2-NITROPHENOL AND 4-NITROPHENOL AFFECT MY HEALTH?

How a chemical affects your health depends on how much you are exposed to and for how long. As the level and length of your exposure increase, the effects are likely to become more severe. Rats that breathed dusts of 4-nitrophenol for 2 weeks developed a blood disorder which reduces the ability of the blood to carry oxygen to tissues and organs. However, these abnormalities disappeared a few days after exposure stopped. Chemicals like the nitrophenols cause a similar blood disorder in humans, and so humans exposed for weeks or longer to high levels of nitrophenols may develop the same types of blood disorders that animals do. Experimental studies have shown that 4-nitrophenol is more harmful than 2-nitrophenol in animals. There is no information on the effects on human health from breathing dusts of 2-nitrophenol or 4-nitrophenol.

Some rats, mice, and rabbits that swallowed large amounts of 2-nitrophenol or 4-nitrophenol died within a few days, but we do not know the cause of death. Some rats that swallowed smaller amounts of 4-nitrophenol for a few weeks also died, but those that survived had no apparent harmful health effects. No birth defects were found in the offspring of pregnant mice that swallowed 4-nitrophenol. We do not know if swallowing very small amounts of 2-nitrophenol or 4-nitrophenol for many months or years leads to serious disease or death. There is no information on their health effects from humans who ate food or drank water contaminated with these chemicals.

Rats and rabbits that had relatively large amounts of 4-nitrophenol applied to their skin for a day or less had skin irritation. Rats that had a small amount of 4-nitrophenol on their skin for a few months also had skin irritation. 4-Nitrophenol also caused eye irritation in rabbits when it was applied to the eye. It appears that exposure of animals to very small amounts of 2-nitrophenol or 4-nitrophenol by skin contact for many months does not lead to serious disease or death. We do not know whether breathing dusts of these chemicals or spilling them on your skin can cause birth defects, affect fertility, or cause cancer. More information on how 2-nitrophenol and 4-nitrophenol can affect health can be found in Chapter 2.

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1.5 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO 2-NITROPHENOL AND 4-NITROPHENOL?

Although methods are available for measuring levels of 4-nitrophenol in the urine and blood, they are probably not useful unless the exposure was very recent. 4-Nitrophenol passes out of the body through urine within a few hours. Because the effects usually seen on the blood may also result from causes besides 4-nitrophenol, these effects alone cannot be used to prove exposure. No tests are available to tell whether you have been exposed to 2-nitrophenol. For more information, see Chapters 2 and 6.

1.6 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

In order to minimize exposure to nitrophenols by humans the Environmental Protection Agency (EPA) says that industry must tell the National Response Center when 100 pounds or more of 2-nitrophenol or 4-nitrophenol have been disposed of. For more information on federal and state recommendations, see Chapter 7.

1.7 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns not covered here, please contact your state health or environmental department or:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road, E-29
Atlanta, Georgia 30333

This agency can also provide you with information on the location of the nearest occupational and environmental health clinic. Such clinics specialize in recognizing, evaluating, and treating illnesses that result from exposure to hazardous substances.

2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of 2-nitrophenol and 4-nitrophenol and a depiction of significant exposure levels associated with various adverse health effects. It contains descriptions and evaluations of studies and presents levels of significant exposure for 2-nitrophenol and 4-nitrophenol based on toxicological studies and epidemiological investigations.

Mononitrophenols exist in three isomeric forms: 2-nitrophenol (or o-nitrophenol), 3-nitrophenol (or m-nitrophenol), and 4-nitrophenol (or p-nitrophenol). Because of a scarcity of toxicological data regarding 3-nitrophenol and because this isomer is much less prevalent in industry and in the environment, only 2-nitrophenol and 4-nitrophenol are discussed in this document.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure--inhalation, oral, and dermal--and then by health effect--death, systemic, immunological, neurological, developmental, reproductive, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods--acute (less than 15 days), intermediate (15-364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. These distinctions are intended to help the users of the document identify the levels of exposure at which adverse health effects start to appear. They should also help to determine whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the tables and figures may differ depending on the user's perspective. For example, physicians concerned with the interpretation of clinical findings in exposed persons may be interested in levels of exposure associated with "serious" effects. Public health officials and project managers concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAEL) or exposure levels below which no adverse effects (NOAEL) have been observed. Estimates

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of levels posing minimal risk to humans (Minimal Risk Levels, MRLs) may be of interest to health professionals and citizens alike.

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made, where data were believed reliable, for the most sensitive noncancer effect for each exposure duration. MRLs include adjustments to reflect human variability from laboratory animal data to humans.

Although methods have been established to derive these levels (Barnes et al. 1988; EPA 1989), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effect data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

2.2.1 Inhalation Exposure

Two studies were identified that examined the effects of inhalation exposure to nitrophenols (Hazleton 1983; Smith et al. 1988). These studies described the effects of acute- and intermediate-duration exposure to 4-nitrophenol in rats. The results are presented in relevant sections below.

2.2.1.1 Death

No studies were located regarding lethality in humans or animals following inhalation exposure to 2-nitrophenol or in humans following inhalation exposure to 4-nitrophenol.

No lethality was observed in male rats exposed to dust atmospheres of 4-nitrophenol (sodium salt) at concentrations of 4,033 mg 4-nitrophenol/m³ for a single 4-hour period (Smith et al. 1988), to 2,119 mg 4-nitrophenol/m³ for 6 hours/day for 10 days (Smith et al, 1988), or in rats (both sexes) exposed to 30 mg 4-nitrophenol dust/m³ for 6 hours/day, 5 days/week for 4 weeks (Hazleton 1983). The NOAELs are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.2 Systemic Effects

No studies were located regarding systemic effects in humans or animals following inhalation exposure to 2-nitrophenol or in humans following inhalation exposure to 4-nitrophenol.

Data regarding systemic effects of 4-nitrophenol following inhalation exposure were limited to two studies. These studies examined the effects of acute- and intermediate-duration exposure of rats to 4-nitrophenol for the following systemic categories: respiratory, cardiovascular, gastrointestinal,

TABLE 2-1. Levels of Significant Exposure to 4-Nitrophenol - Inhalation

Key to figure ^a	Species	Exposure frequency/ duration	System	NOAEL (mg/m ³)	LOAEL (effect)		Reference
					Less serious (mg/m ³)	Serious (mg/m ³)	
ACUTE EXPOSURE							
Death							
1	Rat	2 wk 5 d/wk 6 hr/d		2,119			Smith et al. 1988
2	Rat	1 d 4 hr/d		4,033			Smith et al. 1988
Systemic							
3	Rat	2 wk 5 d/wk 6 hr/d	Resp Cardio Gastro Hemato Hepatic Renal Derm/oc	2,119 2,119 2,119 26 2,119 2,119 2,119	112 (methemoglobinemia)		Smith et al. 1988
4	Rat	1 d 4 hr/d	Derm/oc		4,033 (corneal opacity)		Smith et al. 1988
INTERMEDIATE EXPOSURE							
Death							
5	Rat	4 wk 5 d/wk 6 hr/d		30			Hazleton 1983
Systemic							
6	Rat	4 wk 5 d/wk 6 hr/d	Resp Cardio Gastro Musc/sk Hepatic Renal Derm/oc Other	30 30 30 30 30 30 5 30	30 (anterior capsular cataract 11/30)		Hazleton 1983

^aThe number corresponds to entries in Figure 2-1.

d = day; Cardio = cardiovascular; Derm/oc = dermal/ocular; Gastro = gastrointestinal; Hemato = hematological; hr = hours; LOAEL = lowest-observed-adverse-effect level; mg/m³ = milligram per cubic meter; Musc/sk = musculoskeletal; NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = weeks

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ACUTE (≤14 Days)

Systemic

Death, Respiratory, Cardiovascular, Gastrointestinal, Hematological, Hepatic, Renal, Dermal/Ocular

INTERMEDIATE (15-364 Days)

Systemic

Death, Respiratory, Cardiovascular, Gastrointestinal, Musculoskeletal, Hepatic, Renal, Dermal/Ocular, Other

Y-axis: mg/m³ (log scale: 1, 10, 100, 1000)

Key

- r Rat
- LOAEL for serious effects (animals)
- ◐ LOAEL for less serious effects (animals)
- NOAEL (animals)

The number next to each point corresponds to entries in Table 2-1.

2. HEALTH EFFECTS

hematological, musculoskeletal, hepatic, renal, dermal/ocular, and other systemic. The highest NOAEL values and all reliable LOAEL values for each systemic effect are recorded in Table 2-1 and plotted in Figure 2-1.

Respiratory Effects. Rats exposed to dust atmospheres of 4-nitrophenol (sodium salt) at a concentration of 2,119 mg 4-nitrophenol/m³, 6 hours/day for 10 days showed a decrease in absolute and relative lung weights after a 14-day recovery period (Smith et al. 1988). Since no histopathological changes were noticed, the biological significance of this finding is unclear. A concentration of 292 mg/m³ was without effect. The concentration of 2,119 mg/m³, is considered a NOAEL for respiratory effects for acute-duration exposure. Male and female rats exposed to 30 mg 4-nitrophenol dust/m³ 6 hours/day, 5 days/week for 4 weeks showed no exposure-related effects on lung weight, or on gross and histological appearance of the lungs, trachea, and nasal turbinates (Hazleton 1983). This exposure level represents a NOAEL for respiratory effects for intermediate-duration exposure.

Cardiovascular Effects. No exposure-related histopathological lesions or increased weights were observed in the hearts of male rats exposed for 2 weeks to up to 2,119 mg 4-nitrophenol/m³ as dusts of the sodium salt (Smith et al. 1988). Similarly, no cardiac effects were observed in male and female rats exposed intermittently to up to 30 mg of 4-nitrophenol dust/m³ for 4 weeks (Hazleton 1983). These two exposure levels are considered NOAELs for cardiovascular effects for acute- and intermediate-duration exposure, respectively, although no further tests for cardiovascular function were performed.

Gastrointestinal Effects. Male rats exposed for 2 weeks to up to 2,119 mg 4-nitrophenol/m³ as dusts of the sodium salt had no histopathological alterations in the esophagus, stomach, small intestine, colon, and cecum (Smith et al. 1988). Similar results were reported in male and female rats exposed to up to 30 mg of 4-nitrophenol dusts/m³ for 4 weeks (Hazleton 1983).

Hematological Effects. Rats exposed to 112 mg of 4-nitrophenol/m³ as 4-nitrophenol sodium salt for 2 weeks showed a significant ($p < 0.05$) increase in methemoglobin, but exposure to 26 mg/m³ was without effect (Smith et al. 1988). After a 14-day recovery period, methemoglobin levels were reduced but had not reached preexposure values. In a similar experimental series, which used exposure concentrations of 292 and 2,119 mg 4-nitrophenol/m³, the increase in methemoglobin was dose-related. Rats exposed to up to 30 mg 4-nitrophenol dusts/m³ 6 hours/day, 5 days/week for 4 weeks showed no significant alterations in hematology parameters (Hazleton 1983). Methemoglobin values, however, determined after 2 weeks of exposure, showed great variability, and appeared to be unusually high (greater than 3%) for some unexposed animals (normal is about 0.5%).

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Musculoskeletal Effects. Rats exposed to up to 30 mg 4-nitrophenol dusts/m³ for 6 hours/day, 5 days/week for 4 weeks showed no exposure-related effects on the gross or microscopical appearance of the femur and skeletal muscles (Hazleton 1983).

Hepatic Effects. Slightly increased levels of serum glutamic oxaloacetic transaminase (SGOT) were found in rats exposed for 2 weeks to a dust of 4-nitrophenol sodium salt at concentrations of 292 and 2,119 mg 4-nitrophenol/m³ (Smith et al. 1988). However, the toxicological significance of the increase is unclear. In addition, no histological evidence of liver damage was found. No exposure-related effects on liver weight or on the gross and histological appearance of the liver was observed in rats exposed to up to 30 mg 4-nitrophenol dusts/m³, 6 hours/day for 4 weeks (Hazleton 1983). In addition, this exposure protocol did not alter serum levels of SGOT or serum glutamic pyruvic transaminase (SGPT).

Renal Effects. Rats exposed to 292 or 2,119 mg 4-nitrophenol/m³ of 4-nitrophenol dust (sodium salt) for 2 weeks had darker urine and proteinuria (Smith et al. 1988). In the absence of further information, and because no histopathological changes were noticed in the kidneys, the significance of this finding is unclear. Rats exposed to up to 30 mg 4-nitrophenol dust/m³ for 4 weeks showed no exposure-related effects on kidney weight, or on the gross and microscopical appearance of the kidneys (Hazleton 1983).

Dermal/Ocular Effects. Corneal opacity was described in 4 of 6 rats exposed to a concentration of 4,033 mg 4-nitrophenol/m³ as 4-nitrophenol dust (sodium salt) for 4 hours (Smith et al. 1988) (see Table 2-1 and Figure 2-1). The effect persisted through a 14-day observation period in one rat. This effect may be due to direct contact of 4-nitrophenol with the cornea and, as such, could also be classified under effects caused by dermal exposure. Exposure to a concentration of 2,119 mg 4-nitrophenol/m³ 6 hours/day for 2 weeks was without effect. Unilateral and bilateral diffuse anterior capsular cataracts were observed in male and female rats exposed to 30 mg 4-nitrophenol dust/m³ for 4 weeks (Hazleton 1983). This exposure level is presented as a LOAEL for intermediate duration exposure in Table 2-1. An exposure level of 5 mg/m³ was without effect.

Other Systemic Effects. No histological alterations were reported in the spleens and thyroid glands of male rats exposed for 2 weeks to up to 2,119 mg 4-nitrophenol/m³ as 4-nitrophenol dust (Smith et al. 1988), but no additional information was provided. No consistent exposure-related effects on body weight were reported in rats exposed to up to 30 mg 4-nitrophenol dust/m³ for 4 weeks (Hazleton 1983). In addition, no gross or histological alterations were observed in the urinary bladder, thyroid and parathyroid glands, pituitary, salivary glands, adrenals, pancreas, and mammary glands (Hazleton 1983).

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2.2.1.3 Immunological Effects

No studies were located regarding immunological effects in humans or animals following inhalation exposure to 2-nitrophenol or in humans following inhalation exposure to 4-nitrophenol.

No histological alterations were observed in lymph nodes, thymus, and sternal bone marrow of rats exposed for 2 weeks to up to 2,119 mg 4-nitrophenol/m³ as dust of the sodium salt (Smith et al. 1988). Similar results were reported in rats exposed to up to 30 mg 4-nitrophenol dust/m³ for 4 weeks (Hazleton 1983). However, since no immunological tests were performed in these studies, reliable NOAELs for immunological effects cannot be determined.

2.2.1.4 Neurological Effects

No studies were located regarding neurological effects in humans or animals following inhalation exposure to 2-nitrophenol or in humans following inhalation exposure to 4-nitrophenol.

No histological alterations were observed in the brains of rats exposed for 2 weeks to a dust of 4-nitrophenol sodium salt at concentrations of up to 2,119 mg 4-nitrophenol/m³ (Smith et al. 1988). Gross and histological examination of the brain, spinal cord, and peripheral nerves of rats exposed to up to 30 mg 4-nitrophenol dust/m³ for 4 weeks revealed no treatment-related effects (Hazleton 1983). However, since neurological tests were not performed in these studies, reliable NOAELs for neurological effects cannot be determined.

2.2.1.5 Developmental Effects

No studies were located regarding developmental effects in humans or animals following inhalation exposure to 2-nitrophenol or 4-nitrophenol.

2.2.1.6 Reproductive Effects

No studies were located regarding reproductive effects in humans or animals following inhalation exposure to 2-nitrophenol or in humans following inhalation exposure to 4-nitrophenol.

Male rats exposed for 2 weeks to a dust of 4-nitrophenol sodium salt at concentrations of up to 2,119 mg 4-nitrophenol/m³ showed no histological alterations in the testes and epididymides (Smith et al. 1988). Rats exposed to up to 30 mg 4-nitrophenol dust/m³ for 4 weeks showed no exposure-related effects on the gross or microscopical appearance of the prostate, seminal vesicles, ovaries, or uterus (Hazleton 1983). Nevertheless, since tests for reproductive performance were not conducted in these studies, reliable NOAELs for reproductive effects cannot be determined.

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2.2.1.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or Animals following inhalation exposure to 2-nitrophenol or 4-nitrophenol.

Genotoxicity studies are discussed in Section 2.4.

2.2.1.8 Cancer

No studies were located regarding the carcinogenic effects in humans or animals following inhalation exposure to 2-nitrophenol or 4-nitrophenol.

2.2.2 Oral Exposure

2.2.2.1 Death

No studies were located regarding lethality in humans following oral exposure to 2-nitrophenol or 4-nitrophenol.

In rats, the reported oral LD₅₀ values after gavage administration of 2-nitrophenol and 4-nitrophenol in corn oil were 2,830 and 620 mg/kg, respectively (Vernot et al. 1977). An LD₅₀ value of 230 mg/kg was reported in albino rats for 4-nitrophenol administered in propylene glycol (Monsanto 1983a); clinical observations prior to death included convulsions, prostration, and dyspnea. Twenty-three percent lethality was reported in pregnant rats administered a single dose of 667 mg 4-nitrophenol/kg on day 11 of gestation; a dose of 333 mg/kg was without effect (Kavlock 1990). Early mortality was reported in rats administered 70 mg 4-nitrophenol/kg or more by gavage in water for 13 weeks (Hazleton 1989); prostration, wheezing, and dyspnea were noticed prior to death. In mice, LD₅₀ values of 470 mg/kg (Vernot et al. 1977) and 626 mg/kg (Plasterer et al. 1985) have been reported for 4-nitrophenol and 1300 mg/kg for 2-nitrophenol (Vernot et al. 1977) after gavage administration of the chemicals in corn oil. In addition to determining an LD₅₀ in mice, Plasterer et al. (1985) reported that daily gavage doses of 400 mg of 4-nitrophenol/kg administered to pregnant mice during gestation days 7-15 caused 19% lethality. Three deaths were reported in eight female rabbits given 4-nitrophenol in single gavage doses between 182 and 322 mg/kg (Williams 1938); the lowest lethal dose was 220 mg 4-nitrophenol/kg. The cause of death was not indicated in any of these studies. Although the data regarding lethality are limited, 4-nitrophenol is apparently more lethal than 2-nitrophenol. The LD₅₀ values and other doses causing death are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.2 Systemic Effects

No studies were located regarding systemic effects in humans or animals following oral exposure to 2-nitrophenol. Data regarding systemic effects of

TABLE 2-2. Levels of Significant Exposure to Nitrophenols - Oral

Key to figure ^a	Species	Route	Exposure frequency/duration	System	NOAEL (mg/kg/day)	LOAEL (effect)		Reference	Isomer
						Less serious (mg/kg/day)	Serious (mg/kg/day)		
ACUTE EXPOSURE									
Death									
1	Rat	(GO)	NS				2830 (LD ₅₀)	Vernot et al. 1977	2-
2	Rat	(GW)	1x Gd 11		333		667 (3/13 deaths)	Kavlock 1990	4-
3	Rat	(GW)	1x		110		230 (LD ₅₀)	Monsanto 1983a	4-
4	Rat	(GO)	NS				620 (LD ₅₀)	Vernot et al. 1977	4-
5	Rabbit	(GW)	1x				220 (3/8)	Williams 1938	4-
6	Mouse	(GO)	8 d 1x/d				626 (LD ₅₀)	Plasterer et al. 1985	4-
7	Mouse	(GO)	NS				1300 (LD ₅₀)	Vernot et al. 1977	2-
8	Mouse	(GO)	8 d 1x/d				400 (19%)	Plasterer et al. 1985	4-
9	Mouse	(GO)	NS				470 (LD ₅₀)	Vernot et al. 1977	4-
Developmental									
10	Rat	(GW)	1x Gd 11		1000			Kavlock 1990	4-
INTERMEDIATE EXPOSURE									
Death									
11	Rat	(GW)	13 wk 7 d/wk		25		70 (3/13)	Hazleton 1989	4-

TABLE 2-2 (Continued)

Key to figure ^a	Species	Route	Exposure frequency/duration	System	NOAEL (mg/kg/day)	LOAEL (effect)		Reference	Isomer
						Less serious (mg/kg/day)	Serious (mg/kg/day)		
12	Rat	(GW)	13 wk 7 d/wk	Resp	25	70 (wheezing, dyspnea)		Hazleton 1989	4-
				Cardio	140				
				Gastro	140				
				Musc/sk	140				
				Hepatic	140				
				Renal	140				
				Derm/oc	140				
				Other	140				

^aThe number corresponds to entries in Figure 2-2.

Cardio = cardiovascular; d = day; Derm/oc = dermal/ocular; Gastro = gastrointestinal; Gd = gestation day; GO = gavage, oil; GW = gavage, water; LD₅₀ = lethal dose 50% kill; LOAEL = lowest-observed-adverse-effect level; Musc/sk = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory; wk = week; x = times

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4-nitrophenol following oral exposure were limited to a single study (Hazleton 1989). This study examined the effects of intermediate-duration exposure in rats in the following systemic categories: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal/ocular, and other systemic. The highest NOAEL values and all reliable LOAEL values for each systemic effect are recorded in Table 2-2 and plotted in Figure 2-2.

Respiratory Effects. No histological alterations were observed in the trachea and lungs of rats administered daily doses of up to 140 mg 4-nitrophenol/kg by gavage for 13 weeks (Hazleton 1989). However, wheezing and dyspnea were observed in rats given doses of 70 mg/kg or more that died prematurely during the study. A dose of 25 mg 4-nitrophenol/kg was without effect.

Cardiovascular Effects. No gross or histological alterations were reported in the heart and aorta of rats administered up to 140 mg 4-nitrophenol/kg/day by gavage in water for 13 weeks (Hazleton 1989).

Gastrointestinal Effects. No treatment-related effects were observed on the gross or microscopical appearance of the esophagus, stomach, duodenum, jejunum, ileum, colon, cecum, and rectum of rats administered up to 140 mg 4-nitrophenol/kg/day by gavage in water for 13 weeks (Hazleton 1989).

Hematological Effects. No significant alterations were observed in hematological and clinical chemistry parameters of rats administered up to 140 mg 4-nitrophenol/kg/day for 13 weeks (Hazleton 1989). Methemoglobin values of untreated rats determined at week 7 were unacceptably high, which led the investigators to suggest that the analytical method was not totally reliable; therefore, methemoglobin was not measured at sacrifice. Since methemoglobin formation appears to be the end point with the lowest threshold in rats following inhalation exposure to 4-nitrophenol (Smith et al. 1988), a reliable NOAEL for hematological effects due to oral exposure cannot be determined based on the findings reported by Hazleton (1989).

Musculoskeletal Effects. Rats administered up to 140 mg 4-nitrophenol/kg/day by gavage in water for 13 weeks showed no gross or histological alterations in the sternum (Hazleton 1989). In addition, no gross alterations were observed in the cranial cavity.

Hepatic Effects. Dark, enlarged, and thicker liver lobes were observed in some rats that died prematurely in a 13-week gavage study with 4-nitrophenol (Hazleton 1989). Early deaths occurred with doses of 70 mg 4-nitrophenol/kg/day or more. However, no gross or histological alterations were observed at sacrifice (13 weeks) in rats that received doses of up to 140 mg 4-nitrophenol/kg/day. Furthermore, serum levels of liver enzymes and bilirubin were unaffected by treatment with 4-nitrophenol.

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Renal Effects. Some rats that died early in a 13-week gavage study with 4-nitrophenol had kidney congestion (Hazleton 1989). Early deaths were observed at doses of 70 mg 4-nitrophenol/kg/day or more. Rats administered up to 140 mg 4-nitrophenol/kg/day, and sacrificed at week 13, however, showed no treatment-related effects on gross or histological appearance of the kidneys.

Dermal/Ocular Effects. No treatment-related ophthalmological alterations were reported throughout the experimental period in rats administered up to 140 mg 4-nitrophenol/kg/day by gavage for 13 weeks (Hazleton 1989).

Other Systemic Effects. Rats administered up to 140 mg 4-nitrophenol/kg/day by gavage for 13 weeks showed no significant effects on body weight gain, or on the gross or microscopical appearance of the salivary glands, pituitary, thyroid and parathyroid glands, adrenals, pancreas, and urinary bladder (Hazleton 1989).

2.2.2.3 Immunological Effects

No exposure-related effects were reported on spleen weight, or on the microscopical appearance of spleen, thymus, and lymph nodes of rats administered up to 140 mg 4-nitrophenol/kg/day by gavage for 13 weeks (Hazleton 1989). However, since no immunological tests were performed, a reliable NOAEL for immunological effects cannot be determined.

2.2.2.4 Neurological Effects

No exposure-related effects were reported on brain weight, or on the histological appearance of the brain and sciatic nerve of rats given up to 140 mg 4-nitrophenol/kg/day by gavage for 13 weeks (Hazleton 1989). However, since neurological tests were not performed, a reliable NOAEL for neurological effects cannot be determined.

2.2.2.5 Developmental Effects

No studies were located regarding developmental effects in humans or animals following oral exposure to 2-nitrophenol or in humans following oral exposure to 4-nitrophenol.

No significant effects on litter size, perinatal loss, pup weight, and litter biomass were observed in rats treated with a single gavage dose of up to 1,000 mg/kg of 4-nitrophenol on day 11 of gestation (Kavlock 1990). In addition, no overt malformations were observed, but the pups were not examined for internal malformations. No changes were observed in the reproductive index of pregnant mice given daily doses of 400 mg 4-nitrophenol/kg by gavage during gestation days 7-14 (Plasterer et al. 1985). The 400 mg/kg dose, however, caused 19% maternal lethality. The reproductive index was defined as

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the ratio between survivors that delivered and survivors pregnant and is a measure of prenatal lethality. Furthermore, G-nitrophenol did not affect the number of live pups or the average weight of the pups, and produced no gross anomalies. However, the pups were not examined for internal malformations. The NOAEL value of 1,000 mg/kg for developmental effects is recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.6 Reproductive Effects

No treatment-related effects were observed on testes weight, or on the histological appearance of the testes, ovaries, and uterus of rats administered up to 140 mg 4-nitrophenol/kg/day by gavage for 13 weeks (Hazleton 1989). However, since tests for reproductive performance were not conducted, a reliable NOAEL for reproductive effects cannot be determined.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals following oral exposure to 2-nitrophenol or 4-nitrophenol.

Genotoxicity studies are discussed in Section 2.4.

2.2.2.8 Cancer

No studies were located regarding cancer effects in humans or animals following oral exposure to 2-nitrophenol or 4-nitrophenol.

2.2.3 Dermal Exposure

2.2.3.1 Death

No studies were located regarding lethality in humans following dermal exposure to 2-nitrophenol or 4-nitrophenol.

No lethality was reported among rabbits when a saline suspension of 5,000 mg 4-nitrophenol/kg was applied to the abraded dorsal surface for 24 hours (Monsanto 1983b). The animals were observed for 15 days. No treatment-related deaths were observed in rats treated dermally with doses between 50 and 250 mg/kg/day of 4-nitrophenol for 120 days (Angerhofer 1985). In mice, application of a 47 mg/kg/day dose of 2-nitrophenol or 4-nitrophenol to shaved skin for 12 weeks did not alter the survival rate (Boutwell and Bosch 1959). The NOAELs are recorded in Table 2-3.

2.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculo/skeletal, hepatic, renal, dermal/ocular, or other systemic effects in humans or animals after dermal exposure to 2-nitrophenol or in humans after dermal exposure to 4-nitrophenol.

TABLE 2-3. Levels of Significant Exposure to Nitrophenols - Dermal

Species	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect)		Reference	Isomer
				Less serious (mg/kg/day)	Serious (mg/kg/day)		
ACUTE EXPOSURE							
Death							
Rabbit	24 hr		5,000			Monsanto 1983b	4-
Systemic							
Rabbit	24 hr	Derm/oc		181 (skin scabbing and scarring)		Monsanto 1983d	4-
Rabbit	4 hr	Derm/oc		147 (skin erythema and edema)		Monsanto 1984	4-
Rabbit	1x	Derm/oc			27 (corneal cloudiness)	Monsanto 1983c	4-
Rabbit	24 hr	Derm/oc		5,000 (erythema and edema)		Monsanto 1983b	4-
INTERMEDIATE EXPOSURE							
Rat	120 d		250			Angerhofer 1985	4-
Mouse	12 wk 2 d/wk		47			Boutwell and Bosch 1959	4-
Mouse	12 wk 2 d/wk		47			Boutwell and Bosch 1959	2-
Systemic							
Rat	120 d	Resp Cardio Gastro Musc/sk Hepatic Renal Derm/oc	250 250 250 250 250 250			Angerhofer 1985	4-
				50 (skin irritation)			

TABLE 2-3 (Continued)

Species	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect)		Reference	Isomer
				Less serious (mg/kg/day)	Serious (mg/kg/day)		
Developmental							
Rat	120 d		250			Angerhofer 1985	4-
Reproductive							
Rat	120 d		250			Angerhofer 1985	4-

Cardio = cardiovascular; d = day; Derm/oc = dermal/ocular; Gastro = gastrointestinal; hr = hour; LOAEL = lowest-observed-adverse-effect level; Musc/sk = musculoskeletal; NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week; x = times

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No studies were located regarding hematological effects in animals after dermal exposure to 4-nitrophenol.

Limited information is available regarding systemic effects in animals following dermal exposure to 4-nitrophenol. The highest NOAEL values and all reliable LOAEL values for each systemic effect are recorded in Table 2-1.

Respiratory Effects. No gross or histopathological alterations were observed in the lungs of rats treated dermally with doses of 50-250 mg 4-nitrophenol/kg/day for 120 days (Angerhofer 1985).

Cardiovascular Effects. No gross or histological alterations in the heart or changes in heart weight were observed in rats treated dermally with doses of 50-250 mg 4-nitrophenol/kg/day for 120 days (Angerhofer 1985).

Gastrointestinal Effects. No gross or histological alterations were seen in the gastrointestinal tract of rats treated dermally with doses of 50-250 mg 4-nitrophenol/kg/day for 120 days (Angerhofer 1985).

Musculo/Skeletal. No gross or histological alterations were seen in skeletal muscles and bones of rats treated dermally with doses of 50-250 mg 4-nitrophenol/kg/day for 120 days (Angerhofer 1985).

Hepatic Effects. No gross or histological alterations in the liver or changes in liver weight were observed in rats treated dermally with doses of 50-250 mg 4-nitrophenol/kg/day for 120 days (Angerhofer 1985).

Renal Effects. No gross or histological alterations in the kidneys or changes in kidneys weight were seen in rats treated dermally with doses of 50-250 mg 4-nitrophenol/kg/day for 120 days (Angerhofer 1985).

Dermal/Ocular Effects. Moderate to severe corneal cloudiness, blistered conjunctival tissue, and corneal neovascularization were observed in rabbits after a single application of 27 mg of solid 4-nitrophenol/kg into the conjunctival sac (Monsanto 1983c). Only in one of six rabbits the effects appeared to be reversible during a 21-day observation period. Erythema and edema at the site of application were the most prevalent signs of exposure in rabbits when a saline suspension of 5,000 mg 4-nitrophenol was applied to the abraded dorsal surface for 24 hours (Monsanto 1983b). No adverse effects were noticed in the shaved dorsal surface of rabbits after application of 147 mg of dry solid 4-nitrophenol/kg for 4 hours (Monsanto 1984). However, when the solid 4-nitrophenol was applied moistened with saline, skin erythema and edema were observed. Skin scabbing and scarring were reported in rabbits 14 days after application of 181 mg 4-nitrophenol/kg moistened with saline for 24 hours (Monsanto 1983d). Partial recovery was observed by day 21. Application of 4-nitrophenol in daily doses of 50-250 mg 4-nitrophenol/kg to the skin of rats for 120 days resulted in dose-related dermal irritation

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consisting of erythema, scaling, scabbing, and cracking of the skin (Angerhofer 1985). It is possible, however, that the solvent, ethanol, may have contributed to the development of these effects.

2.2.3.3 Immunological Effects

No studies were located regarding immunological effects in humans or animals following dermal exposure to 2-nitrophenol or 4-nitrophenol.

2.2.3.4 Neurological Effects

No studies were located regarding neurological effects in humans or animals following dermal exposure to 2-nitrophenol or in humans following dermal exposure to 4-nitrophenol.

Application of 50-250 mg/kg/day of 4-nitrophenol to the skin of rats for 120 days had no effect on the weight or the gross and microscopic appearance of the brain (Angerhofer 1985). Information regarding the areas of the brain examined was not provided. However, since neurological tests were not performed, a reliable NOAEL for neurological effects cannot be determined.

2.2.3.5 Developmental Effects

No studies were located regarding developmental effects in humans or animals following dermal exposure to 2-nitrophenol or in humans following dermal exposure to 4-nitrophenol.

In a 2-generation study, dermal application of 4-nitrophenol to rats in doses of 50-250 mg/kg/day for 120 days did not affect the appearance, behavior, or growth of the offspring (Angerhofer 1985). The NOAEL of 250 mg/kg is recorded in Table 2-3.

2.2.3.6 Reproductive Effects

No studies were located regarding reproductive effects in humans or animals following dermal exposure to 2-nitrophenol or in humans following dermal exposure to 4-nitrophenol.

Reproductive performance was assessed in rats in a 2-generation study in which 4-nitrophenol was applied to the skin of the F₀ and F₁ generations in doses of 50-250 mg/kg/day for 120 days (Angerhofer 1985). Fertility (number of pregnancies/number mated), gestation (percentage of pregnancies resulting in birth of live litters), viability (pups surviving at least to day 4 of life), and lactation (pups surviving at least to day 21 of life) were unaffected by treatment with 4-nitrophenol. Histological examination of the reproductive organs of males and females revealed no treatment-related effects. The NOAEL of 250 mg/kg is recorded in Table 2-3.

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2.2.3.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals following dermal exposure to 2-nitrophenol or 4-nitrophenol.

Genotoxicity studies are discussed in Section 2.4.

2.2.3.8 Cancer

No studies were located regarding carcinogenic effects in humans following dermal exposure to 2-nitrophenol or 4-nitrophenol.

Application of 2-nitrophenol or 4-nitrophenol (dissolved in dioxane) to the shaved backs of mice in doses of 47 mg nitrophenol/kg/day for 12 weeks did not induce skin tumors or lesions that could be considered precancerous in nature (Boutwell and Bosch 1959). These results should be interpreted with caution, since no other site was examined and the duration of the study may have been too short for evaluating carcinogenic potential.

2.3 TOXICOKINETICS

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

No studies were located regarding the rate and extent of absorption in humans or animals following inhalation exposure to 2-nitrophenol or in humans after inhalation exposure to 4-nitrophenol.

Evidence of absorption of 4-nitrophenol by the inhalation route may be inferred from the fact that rats exposed to dusts of 4-nitrophenol (sodium salt) for 2 weeks developed adverse systemic effects (Smith et al. 1988).

2.3.1.2 Oral Exposure

No studies were located regarding absorption in humans following oral exposure to 2-nitrophenol or 4-nitrophenol.

Indirect evidence of absorption of 2-nitrophenol and 4-nitrophenol has been presented in several animal studies. The sulfate conjugate of 4-nitrophenol was detected in the urine of rabbits after gavage administration of single doses between 182 and 264 mg/kg (Williams 1938). A similar finding was reported by Robinson et al. (1951a), who monitored the excretion of nitro compounds and conjugates in the urine of rabbits after gavage doses of both 2-nitrophenol (200-330 mg/kg) and 4-nitrophenol (150-200 mg/kg). Based on excretion data, it was apparent that at least 80%-90% of the dose was rapidly absorbed. In a monkey, oral absorption of 4-nitrophenol was fast since peak blood concentrations of the compound were achieved within minutes after a

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gavage dose of 20 mg/kg (Lawford et al. 1954). The extent of absorption was not determined.

2.3.1.3 Dermal Exposure

No studies were located regarding absorption in humans or animals following dermal exposure to 2-nitrophenol or in humans following dermal exposure to 4-nitrophenol.

In animals, absorption efficiency appeared to be species-specific. In rabbits and beagle dogs, 35% and 11%, respectively, of a dose of ^{14}C -labeled 4-nitrophenol dissolved in ethanol and applied to the skin under a patch, was recovered in the urine over 7 days, indicating absorption through the skin (Snodgrass 1983). In the rabbits, the absorption rate was approximately 16% of the dose/day for 2 days, whereas in the dogs the absorption rate was 3% of the dose/day for 2 days. Thus, absorption was more extensive and more rapid in rabbits than in dogs. Unabsorbed 4-nitrophenol accounted for 53% and 86% of the applied dose in the rabbits and dogs, respectively (Snodgrass 1983).

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

No studies were located regarding distribution in humans or animals following inhalation exposure to 2-nitrophenol or 4-nitrophenol.

2.3.2.2 Oral Exposure

No studies were located regarding distribution in humans or animals following oral exposure to 2-nitrophenol or 4-nitrophenol.

2.3.2.3 Dermal Exposure

No studies were located regarding distribution in humans or animals following dermal exposure to 2-nitrophenol or in humans following exposure to 4-nitrophenol.

Application of ^{14}C -labeled 4-nitrophenol to the skin of rabbits (0.12 mg/kg) and dogs (0.06 mg/kg) resulted in no detectable radioactivity in specimens of all major tissues and organs 7 days later (Snodgrass 1983). No attempt was made to determine distribution at an earlier time following exposure.

2.3.2.4 Other Routes of Exposure

Intravenous injection of ^{14}C -labeled 4-nitrophenol to rabbits (0.12 mg/kg) or dogs (0.06 mg/kg) resulted in undetectable levels of radioactivity in all major tissues and organs 7 days after treatment (Snodgrass 1983). No

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attempt was made to determine distribution at an earlier time. The study by Snodgrass (1983) suggests that following dermal or parenteral exposure, 4-nitrophenol does not bioaccumulate.

2.3.3 Metabolism

No studies were located regarding metabolism in humans following inhalation, oral, or dermal exposure to 2-nitrophenol or 4-nitrophenol. Other data, extracted from studies with cultured human cells and perfused human tissues in vitro, are discussed below.

The major metabolic route for 2-nitrophenol and 4-nitrophenol is conjugation, with the resultant formation of either glucuronide or sulfate conjugates. Conjugates are more polar than the parent compounds and, therefore, are easier to excrete in the urine. Other possible routes of metabolism include reduction to amino compounds or oxidation to dihydric nitrophenols (catechols). In humans, the evidence is indirect and comes from studies of exposure to the pesticide parathion, of which 4-nitrophenol is a metabolite (Fatiadi 1984).

The metabolism of 2-nitrophenol and 4-nitrophenol in rabbits was studied by Robinson et al. (1951a), who showed that, with oral doses of 200-300 mg/kg, conjugation with glucuronic and sulfuric acids was almost complete. With both isomers, the major conjugation product excreted in the urine was nitrophenyl-glucuronide, accounting for approximately 70% of the dose. The corresponding sulfate conjugates were also excreted. Slight reduction to amino compounds occurred, 15% of the dose for the 4-isomer and 2%-3% for the 2-isomer. Oxidation products were also found in the urine; less than 1% of the 4-nitrophenol dose was oxidized to 4-nitrocatechol, whereas less than 1% of the 2-nitrophenol dose was detected as nitroquinone.

Similar results have been obtained in rats after intravenous administration of 4-nitrophenol (Machida et al. 1982). The glucuronide and sulfate conjugates could be detected in the plasma within 1 minute after the injection of doses between 1.6 and 8.0 mg/kg. Machida et al. (1982) also demonstrated that rat liver homogenates had the greatest amount of glucuronidation activity, followed by the kidney, lung, and small intestine homogenates, in decreasing order. Sulfation, however, was detected almost exclusively in the liver. No differences in conjugation mechanisms for 4-nitrophenol between male and female rats have been reported (Meerman et al. 1987).

The metabolism of 4-nitrophenol has also been studied in perfused organ preparations. Perfusion of human kidneys (isolated from cadavers) with 4-nitrophenol resulted in the formation of the glucuronide and sulfate conjugates (Diamond et al. 1982). Sulfate conjugates were found predominantly in mice livers perfused with low concentrations (4 μ M) of 4-nitrophenol (Sultatos and Minor 1985). However, as the concentration of 4-nitrophenol was

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increased, unchanged 4-nitrophenol and the glucuronide appeared in the effluent, indicating the presence of saturation kinetics. In perfused rat livers, three factors appeared to act as rate-determining for conjugation of 4-nitrophenol: concentration of 4-nitrophenol, supply of uridine diphosphate-glucuronic acid from carbohydrates for glucuronyltransferase, and activity of the enzyme (Reinke et al. 1981). Furthermore, the extent of liver conjugation in the rat was found to be modulated by the sympathetic nervous system through the hepatic nerves (Beuers et al. 1986).

Conjugation of 4-nitrophenol also occurred in cultured skin epithelial cells from humans (Rugstad and Dybing 1975), in isolated rat hepatocytes (Araya et al. 1986; Moldeus et al. 1976; Tonda and Hirata 1983), and in microsomes isolated from dog livers (Nakano et al. 1986).

Schemes of tentative metabolic pathways for 2-nitrophenol and 4-nitrophenol are presented in Figures 2-3 and 2-4, respectively.

2.3.4 Excretion

2.3.4.1 Inhalation Exposure

No studies were located regarding excretion in humans or animals following inhalation exposure to 2-nitrophenol or 4-nitrophenol.

2.3.4.2 Oral Exposure

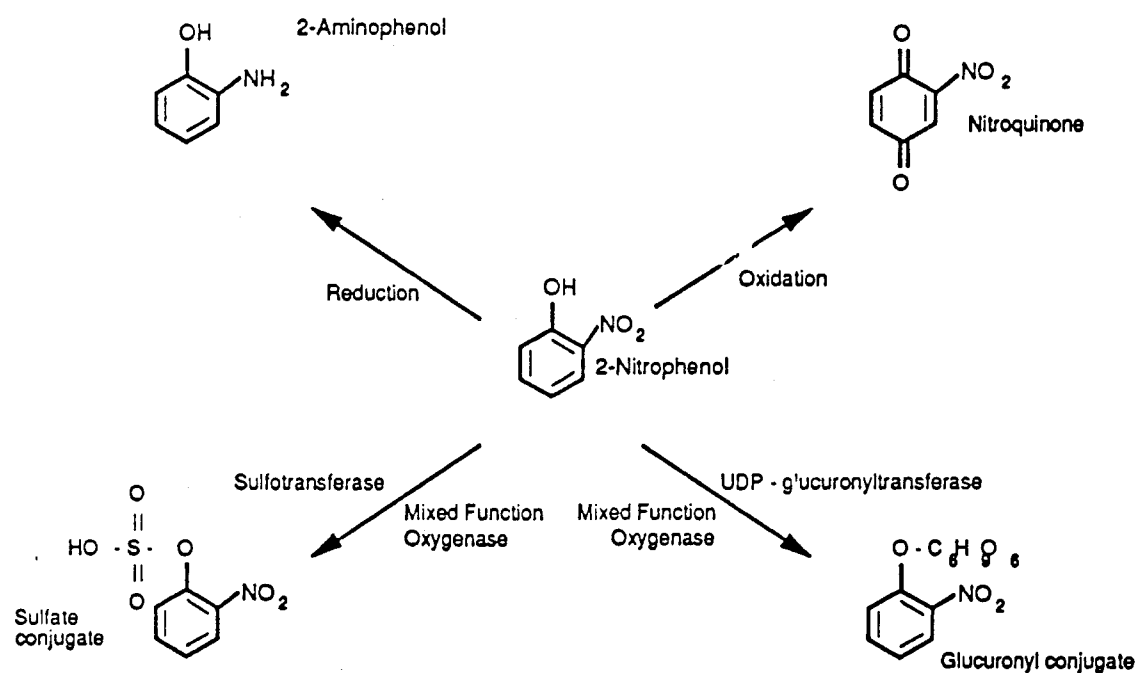
No studies were located regarding excretion in humans following oral exposure to 2-nitrophenol or 4-nitrophenol.

As part of a study to compare the extent of sulfonation between phenol and substituted phenols, Williams (1938) reported that administration of doses between 182 and 264 mg/kg of 4-nitrophenol by gavage to rabbits resulted in excretion of approximately 25% of the dose in the urine as sulfate conjugate in less than a week. This finding was later confirmed by Robinson et al. (1951a), who showed that a dose of 150-200 mg 4-nitrophenol/kg given to rabbits was excreted in the urine, 70% as glucuronide and 12-20% as ethereal sulfate. In another experimental series, Robinson et al. (1951a) showed that in rabbits the urinary excretion of nitro compounds is almost complete in 1 day after oral administration of a dose of 200 mg/kg of 4-nitrophenol by gavage. The unchanged nitro group accounted for nearly 90% of the dose, whereas approximately 15% was reduced to amino compounds. In another series, Robinson et al. (1951a) found that less than 1% of a dose of 250 mg/kg of 4-nitrophenol was excreted in the urine oxidized to 4-nitrocatechol.

Using the same experimental protocols, Robinson et al. (1951a) demonstrated that when the rabbits were given 2-nitrophenol, the unchanged nitro group accounted for approximately 80% of the dose and 2-3% was detected as amino compounds. Nearly 70% of the dose was excreted as glucuronide and

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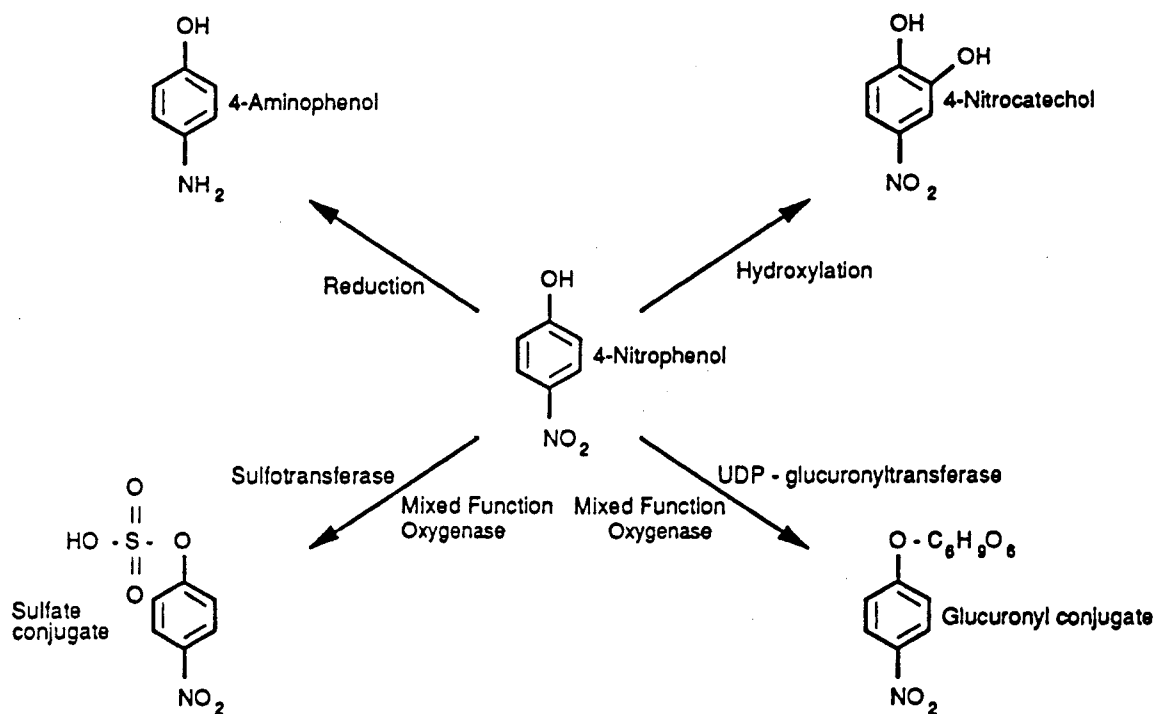
FIGURE 2-3. Proposed Metabolic Pathway for 2-Nitrophenol*



*Adapted from Robinson et al. 1951a

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FIGURE 2-4. Proposed Metabolic Pathway for 4-Nitrophenol*



*Adapted from Robinson et al. 1951a

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10% as ethereal sulfate. Less than 1% was found oxidized to nitroquinone. The rapid elimination of nitrophenols may be due to the formation of conjugates, which, by being more polar than the parent compounds, are readily excreted in the urine.

2.3.4.3 Dermal Exposure

No studies were located regarding excretion in humans or animals following dermal exposure to 2-nitrophenol or humans following dermal exposure to 4-nitrophenol.

Dermal application of ¹⁴C-labeled 4-nitrophenol to dogs resulted in 11% of the dose (radioactive label) excreted in the urine over a period of 7 days. Fecal elimination was negligible. In rabbits, 78% of an absorbed dermal dose of ¹⁴C-labeled 4-nitrophenol appeared in the urine in 1 day. As in dogs, fecal elimination accounted for less than 1% of the absorbed dose (Snodgrass 1983).

2.3.4.4. Other Routes of Exposure

Rats injected intravenously with a dose of 8.3 mg/kg of 4-nitrophenol excreted 35% of the dose as sulfate conjugate and 40% as glucuronide over a period of 24 hours (Meerman et al. 1987). No differences were noticed between males and females. Dogs given an intravenous dose (0.06 mg/kg) of ¹⁴C-labeled 4-nitrophenol excreted 92% of the dose (labeled C) in the urine in the first day (Snodgrass 1983). Radioactivity in the feces accounted for approximately 1% over a 7-day period. Snodgrass (1983) used the same protocol in rabbits and found that 78% of the dose (0.12 mg/kg) was recovered in the urine within day 1; excretion was essentially complete by day 4. Fecal elimination accounted for less than 1% of the dose.

2.4 RELEVANCE TO PUBLIC HEALTH

No information was located regarding the effects of 2-nitrophenol or 4-nitrophenol in humans after inhalation, oral, or dermal exposure. The only toxicological signs of probable relevance are hematological effects observed in animals exposed to 2-nitrophenol or 4-nitrophenol. These effects were reported in an acute duration inhalation study. Limited longer-term inhalation and oral data were available for 4-nitrophenol. Oral lethal doses for the two isomers have been identified. From acute lethality studies, it appears that 2-nitrophenol is less toxic than 4-nitrophenol, but little additional information was available regarding the 2-isomer. Aside from the hematological effects, no other specific systems or organs have been identified as targets for 2-nitrophenol or 4-nitrophenol. Dermal and ocular effects of 4-nitrophenol have been identified, but are most likely nonspecific irritation. Since no human data were available, the relevance to public health of the effects observed in animals is not known. Studies that examined the effects of nitrophenols in animals used exposure levels that are several

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orders of magnitude higher than those at which humans will be generally exposed.

Lack of adequate data precluded the derivation of an MRL for acute inhalation exposure to 4-nitrophenol. A concentration-related increase in methemoglobin was reported in rats in the acute inhalation study by Smith et al. (1988). However, inconsistencies in the values obtained in two different experimental series, the unknown toxicological significance of the methemoglobin increase, and the preliminary nature of the report were factors that greatly diminished the power of the study. Although supporting studies with 4-nitrophenol in other species were not located, nitroaromatic compounds are known inducers of methemoglobin both in humans and animals (Beard and Noe 1981; Ellenhorn and Barceloux 1988). An MRL for intermediate-duration inhalation exposure to 4-nitrophenol was not derived due to inconsistent methemoglobin values among the various subgroups of rats in the Hazleton (1983) study. Furthermore, methemoglobin was not monitored at terminal sacrifice (after 20 exposures). Since methemoglobin formation appears to be the most sensitive end point affected by 4-nitrophenol (Smith et al. 1988), other end points examined in this study were not selected for derivation of an intermediate-duration inhalation MRL. MRLs for chronic-duration inhalation exposure for 4-nitrophenol, or for any inhalation exposure duration for 2-nitrophenol are precluded by the lack of data. MRLs for acute- and chronic-duration oral exposure to 2-nitrophenol and 4-nitrophenol, and for intermediate-duration oral exposure to 2-nitrophenol could not be derived due to lack of data. Results from the study by Hazleton (1989) were not used for derivation of an MRL for intermediate-duration oral exposure to 4-nitrophenol due to uncertainty regarding the monitoring of methemoglobin. In this study, unexposed rats had unusually high methemoglobin values, suggesting that problems existed with the analytical method used. Increased methemoglobin was the most sensitive end point in rats exposed to 4-nitrophenol for 2 weeks (Smith et al. 1988). Acute-duration, intermediate-duration, and chronic-duration dermal MRLs were not derived for 2-nitrophenol or 4-nitrophenol due to the lack of an appropriate methodology for the development of dermal MRLs.

Death. No information regarding human fatalities due to inhalation, oral, or dermal exposure to 2-nitrophenol or 4-nitrophenol was located in the literature. Concentrations and doses causing death in animals have been reported for acute oral exposure to 2-nitrophenol and 4-nitrophenol, subchronic oral exposure to 4-nitrophenol, and acute dermal exposure to 4-nitrophenol. The cause of death was not reported. Acute oral toxicity data (LD₅₀) reveal that 4-nitrophenol is considerably more toxic than 2-nitrophenol. No reports of lethality related to inhalation exposure to either 2-nitrophenol or 4-nitrophenol were located. The available information on the lethality of the nitrophenols is insufficient to assess the relevance to human health.

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Systemic Effects. No studies were located regarding systemic effects in humans after inhalation, oral, or dermal exposure to 2-nitrophenol or 4-nitrophenol.

Respiratory Effects. A decrease in absolute and relative lung weight was noted in rats exposed to 2,119 mg 4-nitrophenol dust/m³ for two weeks (Smith et al. 1988). Since histological examination of the lungs failed to reveal any morphological damage, the significance of the weight change is unclear. The existing evidence suggests that the respiratory system is not a target for acute or intermediate inhalation exposure to 4-nitrophenol. Wheezing, dyspnea, and lung congestion reported in rats receiving 70 mg 4-nitrophenol/kg/day or more orally were most likely due to terminal hypoxia and not to a specific effect on the respiratory system (Hazleton 1983). This conclusion is supported by the fact that rats surviving until sacrifice (13 weeks) did not show gross or microscopical alterations in the respiratory tract. The available information on respiratory effects of 4-nitrophenol is insufficient to assess the relevance to human health.

Hematological Effects. A relevant hematological effect, observed in rats, is the induction of methemoglobinemia after acute inhalation exposure to 112 mg 4-nitrophenol dust/m³ for 2 weeks (Smith et al. 1988). Although this finding was reported in only one study, it appears relevant because aromatic amino and nitro compounds are known for causing the formation of methemoglobin in humans and animals (Beard and Noe 1981). Inconsistent methemoglobin values arising from possible analytical problems precluded a reliable assessment of hematological effects of intermediate-duration exposure of rats to 4-nitrophenol dust (Hazleton 1983) or to oral doses of 4-nitrophenol in an intermediate-duration study (Hazleton 1989).

Hepatic Effects. Rats exposed to a dust of 4-nitrophenol at concentrations of 292 and 2,119 mg 4-nitrophenol/m³ for 2 weeks had a slight increase in serum levels of SGOT (Smith et al. 1988). However, the significance of this effect is unclear. Furthermore, no histological evidence of liver damage was observed. Similar results were reported in rats exposed to 30 mg 4-nitrophenol dust/m³ for 4 weeks (Hazleton 1983) and in rats administered oral doses of up to 140 mg 4-nitrophenol/kg for 13 weeks (Hazleton 1989). The existing evidence indicates that the liver is not a target for 4-nitrophenol after acute- and intermediate-duration exposures. The available information regarding hepatic effects of 4-nitrophenol in animals is insufficient to assess the potential for hepatic effects in humans exposed to 2-nitrophenol or 4-nitrophenol.

Renal Effects. Proteinuria and darker urine were observed in rats that inhaled a dust of 4-nitrophenol at concentrations of 292 and 2,119 mg 4-nitrophenol/m³ for 2 weeks (Smith et al. 1988). These findings could not be interpreted as unequivocal evidence of kidney damage since they can also be present under unrelated conditions. Furthermore, no histological alterations

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were found in the kidneys. Similar findings were reported in rats exposed to 30 mg 4-nitrophenol dust/m³ for 4 weeks (Hazleton 1983). Kidney congestion was reported in rats that died prematurely in a 13-week gavage study (Hazleton 1989), but this effect was most likely caused by terminal hypoxia, since rats that survived did not exhibit kidney lesions at sacrifice. The available information regarding renal effects of 4-nitrophenol in animals is insufficient to assess the potential for renal effects in humans exposed to 2-nitrophenol or 4-nitrophenol.

Dermal/Ocular Effects. Two studies were located that described dermal/ocular effects in rats after inhalation exposure. In one study, rats exposed to 4,033 mg 4-nitrophenol dust/m³ for 4 hours developed corneal opacity (Smith et al. 1988). The second study reported anterior capsular cataracts in rats exposed to 30 mg 4-nitrophenol dust/m³ for 4 weeks (Hazleton 1983). Corneal opacity was also reported in rabbits after a single local application of 27 mg 4-nitrophenol/kg (Monsanto 1983c). It is, therefore, possible that the effect seen in the Smith et al. (1988) study was caused by direct contact of the 4-nitrophenol dusts with the cornea rather than by inhalation of the 4-nitrophenol. Similarly, cataracts reported by Hazleton (1983) are likely to have been caused by direct contact with 4-nitrophenol; however, a systematic effect cannot be totally excluded. Application of single doses of 147 mg 4-nitrophenol or more to the skin of rabbits (Monsanto 1984), or of 50 mg 4-nitrophenol/kg/day or more for 120 days to the skin of rats (Angerhofer 1985) resulted in skin irritation. It is important to point out that 4-nitrophenol was much more toxic to the skin when applied moistened with saline than when the dry solid was used. The evidence available suggests that 4-nitrophenol may cause dermal and eye irritation when applied locally in humans.

Neurological Effects. No information was identified regarding neurological effects in humans or animals following exposure to 2-nitrophenol or in humans following exposure to 4-nitrophenol. Inhalation exposure of rats to 2,119 mg 4-nitrophenol dust/m³ (sodium salt) for 2 weeks (Smith et al. 1988) or to 30 mg 4-nitrophenol dust/m³ for 4 weeks (Hazleton 1983) did not affect brain weight or the gross or histological appearance of the central and peripheral nervous system. Similar lack of effects were reported in rats administered oral doses of 140 mg 4-nitrophenol/kg/day for 13 weeks (Hazleton 1989). It must be mentioned, however, that none of these studies conducted tests for neurological function. The available information is insufficient to assess the potential for neurological effects in humans exposed to 2-nitrophenol or 4-nitrophenol.

Developmental Effects. No studies were located that examined the developmental effects of 2-nitrophenol in humans or animals or 4-nitrophenol in humans. In a 3-generation study, dermal application of 4-nitrophenol to rats, in doses of 50-250 mg/kg for 120 days that included the gestation period, did not affect the appearance, behavior or growth of the offspring

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(Angerhofer 1985). Oral administration of 400 mg/kg of 4-nitrophenol to mice during gestation did not alter the reproductive index, a measure of prenatal death (Plasterer et al. 1985). However, in the latter study, the teratogenic potential of 4-nitrophenol could not be dismissed. In the absence of further information, no inference regarding possible effects in humans can be made.

Reproductive Effects. It is not known whether 2-nitrophenol or 4-nitrophenol could cause reproductive effects in humans. Rats exposed to 30 mg 4-nitrophenol/m³ for 4 weeks (Hazleton 1983) or administered 140 mg 4-nitrophenol/kg/day for 13 weeks (Hazleton 1989) had no treatment-related effects on the weight or histopathology of the reproductive organs, but reproductive performance was not assessed. In a 2-generation study in rats, dermal application of 4-nitrophenol in doses of 50-250 mg/kg for 120 days did not alter reproductive performance. The relevance of this information to human health is not known. Data regarding the reproductive effects of 2-nitrophenol were not available.

Genotoxic Effects. No studies were located regarding the genotoxic effects of 2-nitrophenol or 4-nitrophenol in humans or animals by inhalation, oral, or dermal routes. 4-Nitrophenol was not mutagenic in vivo as judged by the dominant lethal assay and the host-mediated assay in mice (Buselmaier et al. 1973). No information was available regarding mutagenicity of 2-nitrophenol in vivo.

As indicated in Table 2-4, 2-nitrophenol did not increase the frequency of reverse mutations in Salmonella typhimurium or in Escherichia coli in the presence or absence of metabolic activation, nor did it induce DNA damage when tested in Bacillus subtilis. No data were available regarding genotoxic properties of 2-nitrophenol in eukaryotic organisms.

The in vitro genotoxicity of 4-nitrophenol has been investigated in prokaryotic organisms and in mammalian cell systems. The overall evidence indicates that 4-nitrophenol is not mutagenic in the presence or absence of activating systems in S. typhimurium and E. coli (Table 2-5). One positive result was reported by Shimizu and Yano (1986), who showed that 4-nitrophenol induced DNA damage when tested in B. subtilis by the ret assay. According to the authors (Shimizu and Yano 1986), this assay appears to be more sensitive for nitro compounds in general than the standard Ames Test. Weaker genotoxic effects were reported in two studies (Adler et al. 1976; Garrett and Lewtas 1983). The hypothesis that reduction of the nitro group is required to observe mutagenic effects was tested by Dellarco and Prival (1989). These authors did not observe an increase in mutagenicity when 2-nitrophenol or 4-nitrophenol was incubated in the presence of S-9 and flavin mononucleotide mixture in S. typhimurium. 4-Nitrophenol was not mutagenic when tested in mammalian cells with or without metabolic activation. The In vitro and in vivo information, negative data or lack of data, respectively, would suggest that 2-nitrophenol or 4-nitrophenol does not pose a genotoxic threat to humans.

TABLE 2-4. Genotoxicity of 2-Nitrophenol In Vitro

Species (test system)	End point	Result		Reference
		With activation	Without activation	
Prokaryotic organisms:				
<u>Salmonella typhimurium</u> (plate incorporation)	Gene mutation	No data	-	Chiu et al. 1978
<u>S. typhimurium</u> (plate incorporation)	Gene mutation	-	-	Suzuki et al. 1983
<u>S. typhimurium</u> (plate incorporation)	Gene mutation	-	-	Dellarco and Prival 1989
<u>S. typhimurium</u> (plate incorporation)	Gene mutation	-	-	Shimizu and Yano 1986
<u>Escherichia coli</u> sd-4-73 (spot test)	Gene mutation	No data	-	Szybalski 1958
<u>Bacillus subtilis</u> (plate incorporation)	DNA damage	No data	-	Shimizu and Yano 1986

- = negative result

TABLE 2-5. Genotoxicity of 4-Nitrophenol In Vitro

Species (test system)	End point	Result		Reference
		With activation	Without activation	
Prokaryotic organisms:				
<u>Salmonella typhimurium</u> (plate incorporation)	Gene mutation	-	-	Suzuki et al. 1983
<u>S. typhimurium</u> (plate incorporation)	Gene mutation	-	-	Probst et al. 1981
<u>S. typhimurium</u> (plate incorporation)	Gene mutation	-	-	Haworth et al. 1983
<u>S. typhimurium</u> (plate incorporation)	Gene mutation	-	-	Shimizu and Yano 1986
<u>S. typhimurium</u> (plate incorporation)	Gene mutation	-	-	Dellarco and Prival 1989
<u>Escherichia coli</u> (plate incorporation)	Gene mutation	-	-	Probst et al. 1981
<u>E. coli</u> (spot test)	Gene mutation	-	-	Szybalski 1958
<u>E. coli</u> (plate incorporation)	Prophage induction	-	No data	Ho and Ho 1981
<u>Proteus mirabilis</u> (plate incorporation)	DNA damage	No data	(+)	Adler et al. 1976
<u>E.coli</u> (disc assay)	DNA repair	No data	-	Rashid and Mumma 1986
<u>S. typhimurium</u> (disc assay)	DNA repair	No data	-	Rashid and Mumma 1986
<u>Bacillus subtilis</u> (plate incorporation)	DNA damage	No data	+	Shimizu and Yano 1986
Mammalian cells:				
Rat hepatocytes (culture)	DNA repair	No data	-	Probst et al. 1981
Mouse lymphoma cells	Forward mutation	-	-	Oberly et al. 1984
Mouse lymphoma cells	Forward mutation	-	No data	Amacher and Turner 1982
Chinese hamster ovary cells (culture)	Inhibition of DNA synthesis	No data	(+)	Garrett and Lewtas 1983

+ = positive result

- = negative result

(+) = weakly positive result

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Cancer. No studies were located regarding the carcinogenic potential of 2-nitrophenol or 4-nitrophenol in humans by any route of exposure or in animals by the inhalation or oral route. Neither isomer induced tumors when applied to the backs of mice in doses of 47 mg/kg/day for 12 weeks (Boutwell and Bosch 1959). However, since no other site was examined and the duration of the study was only 12 weeks, the results should be interpreted with caution. The relevance of this information to human health is unknown. NTP (1991) recently conducted a review of a 2-year skin painting study with 4-nitrophenol in mice. The panel concluded that under the conditions of the study, there was no evidence of carcinogenic activity in male or female Swiss-Webster mice receiving doses of up to 160 mg 4-nitrophenol/kg for 78 weeks.

2.5 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time biologic samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to 2-nitrophenol and 4-nitrophenol are discussed in Section 2.5.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are often not substance specific. They also may not be directly adverse, but can indicate potential health

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impairment (e.g., DNA adducts). Biomarkers of effects caused by 2-nitrophenol and 4-nitrophenol are discussed in Section 2.5.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, biologically effective dose, or target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.7, "POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE."

2.5.1 Biomarkers Used to Identify and/or Quantify Exposure to 2-Nitrophenol and 4-Nitrophenol

No studies were located regarding levels of 2-nitrophenol or 4-nitrophenol in human tissues, fluids, or excreta that were associated with exposure to nitrophenols. To assess exposure to the pesticide parathion, of which 4-nitrophenol is a metabolite, several methods have been developed to monitor 4-nitrophenol in human urine (Arterberry et al. 1961; Fatiadi 1984). In general, it is agreed that these methods are not suitable indicators for studying the severity of the intoxication caused by parathion (or perhaps nitrophenols) or the appearance of toxic signs; rather, these methods indicate acute exposure to the pesticide (or nitrophenols) (Arterberry et al. 1961; Pena-Egido et al. 1988). The reason is that 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-nitrophenol or 4-nitrophenol (or their conjugates) can be associated quantitatively with exposure to these chemicals.

2.5.2 Biomarkers Used to Characterize Effects Caused by 2-Nitrophenol and 4-Nitrophenol

No toxic signs specific to 2-nitrophenol or 4-nitrophenol exposure have yet been identified. However, nitro aromatic and amino compounds in general are known to induce formation of methemoglobin in humans and experimental animals (Beard and Noe 1981). Although response varies considerably among species, it appears that 2-nitrophenol and 4-nitrophenol are not among the most potent methemoglobin inducers. Furthermore, methemoglobinemia can also be caused by inherited disorders and a number of drugs including sulfonamides and benzocaine.

2.6 INTERACTIONS WITH OTHER CHEMICALS

No studies were located regarding interactions of 2-nitrophenol or 4-nitrophenol with other chemicals in vitro or regarding interactions of 2-nitrophenol with other chemicals in vivo. However, it was reported that, in ethanol-treated rats, 4-nitrophenol is rapidly metabolized to 4-nitrocatechol, which competes with 4-nitrophenol for the formation of sulfate and glucuronide conjugates (Reinke and Moyer 1985). This prevention of the conjugation of

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4-nitrophenol may lead to the formation of amino derivatives, which can then induce methemoglobinemia.

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

Human populations that have experienced health effects from exposure to 2-nitrophenol or 4-nitrophenol have not been identified, but little research has been conducted on this subject. Based on results from animal studies, as described in Section 2.6, it is possible that individuals who consume ethanol may have slower rates of clearance of 4-nitrophenol. This subpopulation, if exposed to 4-nitrophenol, may be considered potentially susceptible. Furthermore, newborn infants utilize fetal hemoglobin, which has reduced oxygen-carrying capacity, and also have low levels of nicotinamide adenine dinucleotide diaphorase, which continuously reduces methemoglobin; therefore, infants (as well as individuals congenitally deficient in this enzyme) may represent unusually susceptible subpopulations. Data regarding health effects in humans exposed to 2-nitrophenol were not available.

2.8 MITIGATION OF EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to nitrophenols. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to nitrophenols. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. No studies were located regarding health effects induced by nitrophenols in humans. However, studies in animals exposed to nitrophenols (Smith et al. 1988) and data regarding toxicity of other related compounds (nitrates/nitrites) in humans and animals (see ATSDR 1991) indicate that the major effect of absorption of high amounts of nitrophenols would be an increased formation of methemoglobin in red blood cells. Methemoglobin results from iron in the ferrous state being oxidized to the ferric state. Methemoglobin is unable to combine reversibly with oxygen and carbon dioxide and also causes a shift in the oxygen dissociation curve toward increased oxygen affinity, preventing the transfer of oxygen from the blood to the tissues. Clinical effects of methemoglobinemia are closely related to the percentage of methemoglobin in the blood (see ATSDR 1991). Concentrations up to 20% cause central cyanosis, but are usually asymptomatic. With higher methemoglobin concentrations, CNS depression (headache, dizziness, fatigue, lethargy) and dyspnea may develop. Methemoglobin levels over 45% lead to hypotension, cardiac arrhythmias, metabolic acidosis, and shock. Further CNS depression may cause convulsions, coma, and eventually death. Newborn infants are especially susceptible to methemoglobin induced effects (see Section 2.7).

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In addition, ethanol consumers and individuals with certain enzyme deficiencies may be susceptible (see Section 2.6 and 2.7). The initial steps following removal of the individual from the exposure source are skincleansing, if dermal exposure is suspected. A caution should be employed with the administration of emetics (syrup of ipecac) in cases when ingestion of nitrophenols is suspected (Ellenhorn and Barceloux 1988; Stutz and Janusz 1988). Emesis has been suggested to be followed by administration of a suspension of activated charcoal in water to bind any toxicant remaining in the gastrointestinal tract. Subsequent steps have been aimed at chemically reducing methemoglobin back to oxyhemoglobin. A commonly used intervention for reducing methemoglobin is intravenous infusion of a solution of methylene blue (Ellenhorn and Barceloux 1988). Methylene blue acts as a cofactor to increase the chemical reduction of methemoglobin in the red blood cells in the presence of nicotinamide adenine dinucleotide (NADPH) (Ellenhorn and Barceloux 1988). Methylene blue is oxidized to leukomethylene blue, which donates electrons for the nonenzymatic reduction of methemoglobin to oxyhemoglobin. Administration of oxygen has been suggested in all cases of nitrophenols poisoning. In addition, standard control for convulsions and arrhythmias has been proposed. In life-threatening situations, hyperbaric oxygen therapy and blood transfusion have been recommended (see ATSDR 1991).

2.9 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 2-nitrophenol and 4-nitrophenol is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of 2-nitrophenol and 4-nitrophenol.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met, would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

2.9.1 Existing Information on Health Effects of 2-Nitrophenol and 4-Nitrophenol

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to 2-nitrophenol and 4-nitrophenol are summarized in Figures 2-5 and 2-6, respectively. The purpose of these figures is to illustrate the existing information concerning the health effects of 2-nitrophenol and 4-nitrophenol. Each dot in the figure indicates that one or

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more studies provide information associated with that particular effect. The dot does not imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as "data needs" information.

As seen from Figures 2-5 and 2-6, no information is available regarding the health effects of either 2-nitrophenol or 4-nitrophenol in humans. The only information available regarding 2-nitrophenol is provided by two studies that determined the oral LD₅₀ in rats and mice, and a dermal cancer study. Data are available in animals for lethality after inhalation, oral, or dermal exposure to 4-nitrophenol. One study reported effects of 4-nitrophenol after acute inhalation exposure; however, assessing the significance of most of the effects, such as immunological, neurological, and developmental (or Lack thereof), is difficult due to the incomplete examination of some end points. Data were available for systemic effects after oral exposure to 4-nitrophenol, and one pilot study examined developmental effects of this isomer. A limited number of dermal studies provided information concerning lethality, systemic effects after intermediate exposure, and developmental and reproductive effects of 4-nitrophenol. Information regarding the carcinogenicity of 4-nitrophenol was available from a single dermal study.

2.9.2 Data Needs

Acute-Duration Exposure. No data were Located indicating specific organs or systems as targets for 2-nitrophenol or 4-nitrophenol in humans by any route of exposure. However, amino and nitro aromatic compounds in general have been known to induce methemoglobinemia in humans (Beard and Noe 1981). The data in experimental animals were insufficient to derive oral and inhalation MRLs.

Information is lacking regarding the cause of death in the acute-duration studies, most of which have been conducted in rats. The significance of the renal effects, identified in the only acute-duration inhalation study available (Smith et al. 1988), could be clarified with a better designed acute inhalation study. Additional acute-duration studies by the oral and dermal routes would provide information on interspecies differences seen for dermal absorption and on the mechanisms of lethality, as well as on the thresholds for systemic toxicity due to acute-duration exposure for both 2-nitrophenol and 4-nitrophenol, particularly 2-nitrophenol.

Careful dose-response studies on the effect of nitrophenols on the development of methemoglobinemia, in multiple species, both sexes, and at multiple doses, would provide information on an effect that is relevant to humans. Studies in rabbits could provide data on what appears to be the most sensitive species, as judged by data on acute lethality by the oral route (Williams 1938). The limited pharmacokinetic data do not suggest routespecific target organs. Because 2-nitrophenol and 4-nitrophenol are rapidly removed from the circulation and excreted (see Chapter 2.3), they will not

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FIGURE 2-5. Existing Information on Health Effects of
2-Nitrophenol

	SYSTEMIC									
	Death	Acute	Intermed.	Chronic	Immunologic	Neurologic	Developmental	Reproductive	Genotoxic	Cancer
Inhalation										
Oral										
Dermal										
HUMAN										

	SYSTEMIC									
	Death	Acute	Intermed.	Chronic	Immunologic	Neurologic	Developmental	Reproductive	Genotoxic	Cancer
Inhalation										
Oral	●									
Dermal										●
ANIMAL										

● Existing Studies

2. HEALTH EFFECTS

FIGURE 2-6. Existing Information on Health Effects of 4-Nitrophenol

	SYSTEMIC									
	Death	Acute	Intermed.	Chronic	Immunologic	Neurologic	Developmental	Reproductive	Genotoxic	Cancer
Inhalation										
Oral										
Dermal										

HUMAN

	SYSTEMIC									
	Death	Acute	Intermed.	Chronic	Immunologic	Neurologic	Developmental	Reproductive	Genotoxic	Cancer
Inhalation	●	●	●		●	●		●		
Oral	●	●	●		●	●	●	●		
Dermal	●	●	●		●	●	●	●		●

ANIMAL

● Existing Studies

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accumulate. This is particularly important in intermittent-exposure studies and in occupational settings and applies to intermediate- and chronic-duration studies, as well. However, additional studies that use continuous exposure would provide information relevant to potential exposure by populations surrounding hazardous waste sites.

Intermediate-Duration Exposure. No data were located that identified target organs in humans following intermediate-duration exposure to 2-nitrophenol or 4-nitrophenol by any route. An intermediate-duration study by the dermal route was conducted in rats, but some of the effects could be attributed to the vehicle used (Angerhofer 1985). Therefore, a dermal study with different vehicles would provide information on the effects that can be attributed to 4-nitrophenol and those attributed to the solvents used. Intermediate-duration studies by the inhalation (Hazleton 1983) and oral (Hazleton 1989) routes were conducted in rats. However, these studies could not define reliable NOAELs and LOAELs for methemoglobin formation, a sensitive end point in rats, due to analytical problems. Repeating these studies would eliminate the uncertainty regarding the threshold-effect level for this and other end points. There are no pharmacokinetic data that would suggest route-specific target organs. No data were available in animals regarding 2-nitrophenol. Intermediate-duration exposure studies with 2-nitrophenol would provide information on the thresholds for systemic toxicity for this isomer, as well as information regarding reproductive effects. Intermediate-duration studies in other species might provide information that could be relevant to human exposure, especially populations surrounding hazardous waste sites where humans might be exposed for similar durations.

Chronic-Duration Exposure and Cancer. Chronic inhalation, oral, or dermal studies are not available for either 2-nitrophenol or 4-nitrophenol. Studies using well-designed experiments using complete dose and time protocols, and measuring all sensitive toxicological end points, would provide information on the health effects associated with long-term exposure to 2-nitrophenol and 4-nitrophenol. These studies could provide information on subtle toxicological changes in organs associated with long-term exposure to low levels of 2-nitrophenol or 4-nitrophenol. No pharmacokinetic data suggest route-specific target organs. Inhalation and dermal studies are particularly relevant to individuals in occupational settings and to populations surrounding hazardous waste sites where humans might be exposed for similar durations.

No data were located regarding the carcinogenic potential of 2-nitrophenol or 4-nitrophenol in humans exposed by the inhalation, oral, or dermal route. A single dermal study assessed the carcinogenicity of 2-nitrophenol and 4-nitrophenol in mice (Boutwell and Bosch 1959). However, in this study, mice were exposed to only one dose level of 2-nitrophenol or 4-nitrophenol, and the duration of the study was inappropriate. In addition, only the site where the chemicals were applied was examined. Since

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4-nitrophenol is a metabolite of the pesticide parathion, a chronic-duration study by the oral (diet and drinking water) and inhalation routes would provide information relevant to possible exposure in humans. Furthermore, since it is generally agreed that reduction of the nitro group to the amino group transforms the molecule into a more reactive (more electrophilic) one, studies with the reduced nitrophenols would provide information on the potential carcinogenicity of the metabolites. However, according to pharmacokinetic data, the extent of reduction of nitrophenols to amino compounds is minimal. NTP (1991) conducted a 2-year skin-painting study with 4-nitrophenol in mice; after reviewing the report, a peer review panel concluded that under the conditions of the study, there was no evidence of carcinogenic activity in male or female Swiss-Webster mice receiving doses of up to 160 mg 4-nitrophenol/kg 3 times/week for 78 weeks (see Section 2.9.3).

Genotoxicity. No studies were identified that evaluated genotoxic effects in humans or animals following inhalation, oral, or dermal exposure to 2-nitrophenol or 4-nitrophenol. Several In vitro studies suggest that 2-nitrophenol is not mutagenic in bacterial systems (Table 2-4); therefore, additional In vitro studies would add little to the database. No studies were identified regarding genotoxicity of 2-nitrophenol in eukaryotic organisms and mammalian cells. Such studies would provide information regarding the genotoxicity of 2-nitrophenol in those systems.

The available In vitro genotoxicity studies regarding 4-nitrophenol indicate that this isomer is not mutagenic in bacterial systems or in mammalian cells (Table 2-5). Further studies using the CHO/HGPRT mutation assay would help interpret the weak positive result reported by Garrett and Lewtas (1983) with this assay. Studies in eukaryotic organisms would certainly complement the existing information in prokaryotes.

Reproductive Toxicity. No data on the effects of 2-nitrophenol on the reproductive system for any time period or route of exposure are available. Such data, if available, would provide information on the potential toxic effects of 2-nitrophenol on the reproductive system of animals, information which, in turn, may be relevant to humans. The effects of 4-nitrophenol on reproductive performance have been examined in rats treated dermally (Angerhofer 1985). This study found no adverse effects. Available pharmacokinetic data do not suggest route-specific target organs. Studies were available that examined the subchronic effects of 4-nitrophenol on the gross and histological appearance of reproductive organs in rats after inhalation (Hazleton 1983) and oral (Hazleton 1989) exposure. However, reproductive performance was not assessed in these studies, therefore, a multigeneration study by the oral and inhalation routes would add information that could be relevant to humans.

Developmental Toxicity. No information was available indicating that 2-nitrophenol affects development in humans or animals following inhalation,

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oral, or dermal exposure. The data regarding 4-nitrophenol were limited to one pilot study in which no gross abnormalities were observed in the offspring of mice dosed orally during pregnancy (Plasterer et al. 1985). In this study, however, a complete examination of the pups for possible teratogenic effects was not performed. It is not known whether 2-nitrophenol or 4-nitrophenol crosses the placenta, but the low molecular weight suggests that it (or its metabolites) does. Available pharmacokinetic data do not suggest routespecific target organs. Developmental studies in mammals treated orally, dermally, or by inhalation would provide information on possible fetotoxic and teratogenic effects that might be relevant to humans.

Immunotoxicity. No information was available indicating that, in humans or animals, the immune system is a target for either 2-nitrophenol or 4-nitrophenol. No histopathological effects were observed in organs and tissues involved in immunological functions of rats exposed by inhalation to 4-nitrophenol for 2 weeks (Smith et al. 1988) or 4 weeks (Hazleton 1983). Similar lack of effects was reported in rats treated dermally with 4-nitrophenol in an intermediate-duration study (Angerhofer 1985) or in rats administered 4-nitrophenol orally for 13 weeks (Hazleton 1989). However, none of these studies conducted tests for immunocompetence. In general, the immune system does not appear to be a target for nitro aromatic compounds. Dermal sensitization studies in animals might provide information on whether 2-nitrophenol or 4-nitrophenol are likely to cause an allergic response.

Neurotoxicity. No studies were located regarding the neurotoxic effects of 2-nitrophenol or 4-nitrophenol in humans, by any route of exposure. The limited data available in animals suggest that the nervous system is not a target for either 2-nitrophenol or 4-nitrophenol. No histopathological effects were observed in the central or peripheral nervous system of rats exposed by inhalation to 4-nitrophenol for 2 weeks (Smith et al. 1988) or 4 weeks (Hazleton 1983). Similar negative findings were reported in rats after subchronic dermal treatment with 4-nitrophenol (Angerhofer 1985) and in rats administered 4-nitrophenol orally for 13 weeks (Hazleton 1989). However, none of these studies tested neurological functions. Available pharmacokinetic data do not suggest route-specific target organs. Studies in other species and by the oral route of exposure, as well as tests for neurological impairment in animals, might provide information that could be relevant to humans.

Epidemiological and Human Dosimetry Studies. Health effects from humans exposed to 2-nitrophenol or 4-nitrophenol have not been reported. As discussed in Chapter 5, the potential for environmental exposure to 2-nitrophenol or 4-nitrophenol is considered low, although individuals living near waste sites where 2-nitrophenol and 4-nitrophenol have been identified represent a subpopulation with potential exposure to these chemicals. Moreover, individuals involved in the manufacture or processing of 2-nitrophenol and 4-nitrophenol clearly represent a potentially exposed

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subpopulation. Epidemiology studies of people living in areas where nitrophenol has been detected in ambient and drinking water, near industries releasing nitrophenols, or near hazardous waste sites and of people occupationally exposed could provide information on whether nitrophenols produce effects in humans similar to those seen in animals or produce other toxic effects.

Biomarkers of Exposure and Effect. Information regarding populations exposed specifically to 2-nitrophenol or 4-nitrophenol is not available. However, data derived from animal studies indicate that unchanged 2-nitrophenol or 4-nitrophenol or the sulfate and/or glucuronide conjugates monitored in the urine represent biomarkers of exposure. The same would probably occur in humans. This assumption is based on studies in populations exposed to the pesticide parathion, of which 4-nitrophenol is a metabolite. Individuals exposed to parathion excreted 4-nitrophenol and conjugates in the urine (Fatiadi 1984). G-Nitrophenol is also a metabolite of pesticides other than parathion. (Fatiadi 1984) and of nitrobenzene (Piotrowski 1967; Robinson et al. 1951b). However, because 2-nitrophenol and 4-nitrophenol and their metabolites are rapidly excreted in the urine, these biomarkers are only valuable in evaluating acute situations, as demonstrated by Arterberry et al. (1961) in humans exposed to parathion. Hence, the development of methods to detect alternative biomarkers, the presence of which in body fluid or tissues can be associated with chronic exposure levels of nitrophenol, would be useful.

Information regarding populations exposed specifically to 2-nitrophenol or 4-nitrophenol is not available. Consequently, no specific alteration has been identified. Nonetheless, nitro aromatic and amino compounds in general induce formation of methemoglobin in humans and experimental animals (Beard and Noe 1981). However, it appears that 2-nitrophenol and 4-nitrophenol are not among the most potent methemoglobin inducers. In humans, methemoglobin in blood must reach a level of approximately 40% (normal levels are less than 1%) for serious symptoms such as cyanosis, coma, or stupor, to appear; these blood levels of methemoglobin are reached only with very high doses of nitro compounds. Therefore, identification of signs and symptoms associated with low levels of exposure would aid in the early detection of exposure. Furthermore, methemoglobinemia can also be caused by inherited disorders and a number of drugs, including sulfonamides and benzocaine.

Absorption, Distribution, Metabolism, and Excretion. No studies were located regarding absorption, distribution, metabolism, or excretion of 2-nitrophenol or 4-nitrophenol in humans by any route of exposure, or in animals by the inhalation route. Indirect evidence indicates that absorption of 2-nitrophenol and 4-nitrophenol by the oral route is fast and almost complete (Robinson et al. 1951a). However, only 35% and 11% of a dermally applied dose of 4-nitrophenol was absorbed in rabbits and dogs, respectively, over a 7-day period (Snodgrass 1983). Limited data regarding distribution

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showed that dermal or intravenous dosing of 4-nitrophenol to rabbits and dogs results in undetectable amounts of the chemical in major organs and tissues 7 days after dosing (Snodgrass 1983). Examination of the distribution at earlier times could provide important information regarding possible target organs and tissues. Data regarding 2-nitrophenol were not available. Although the metabolism of 2-nitrophenol and 4-nitrophenol has been examined only after oral dosing, a number of In vitro studies support the findings obtained in vivo. The excretion of 2-nitrophenol and 4-nitrophenol has been quantitated after oral, dermal, and intravenous dosing. Studies in which a range of doses are applied would provide information regarding possible saturation phenomena.

Comparative Toxicokinetics. Data were not available regarding the toxicokinetics of 2-nitrophenol or 4-nitrophenol in humans. In vivo toxicokinetic studies have been performed in rabbits (oral and dermal routes) and dogs (dermal route), with qualitatively similar results regarding absorption rates, metabolic pathways, and excretion rates (Robinson et al. 1951a, Snodgrass 1983; Williams 1938). These studies, however, have used single doses; therefore, it is not known if the similarities would persist over a range of doses. The limited size of the database precludes the identification of an animal species that could serve as the best model for extrapolating results to humans. Data obtained in humans after exposure to the pesticide parathion, of which 4-nitrophenol is a metabolite, suggest that conjugation is also the predominant metabolic route, and that 4-nitrophenol is also rapidly excreted in the urine, but quantitative data are not available. Due to the lower expense and wider usage of rats and mice, these should do well as study species, unless other ones are shown to be of more interest. Once reliable end points are determined in other species, it should be important to verify that primates are affected in a similar manner, in order to ensure that no unforeseen health effect might occur in humans.

Mitigation of Effects. The most prevalent sign of nitrophenol poisoning is increased formation of methemoglobin (Ellenhorn and Barceloux 1988). The most widely used antidote for treating methemoglobinemia is methylene blue, although other reducing agents such as ascorbic acid have been used with questionable results. Therefore, studies identifying alternate antidotes for the treatment of methemoglobinemia would be useful in providing a therapeutic choice for mitigation of this adverse effect. This is particularly relevant in view of the fact that methylene blue is poorly absorbed from the gastrointestinal tract and high intravenous doses produce unwanted side effects (Ellenhorn and Barceloux 1988).

2.9.3 On-going Studies

NTP (1991) conducted an 18-month skin-painting study with 4-nitrophenol in Swiss-Webster mice. In this study, 4-nitrophenol in acetone was applied to the interscapular skin of mice at concentrations of 0, 40, 80, and 160 mg/kg

2. HEALTH EFFECTS

3 days/week for 78 weeks. Administration of 4-nitrophenol did not affect body weight gain. Starting at week 60, high mortality occurred in all groups of mice, including controls. Swiss-Webster mice have an expected life span of only approximately a year, and the natural deaths of the control mice severely limited the statistical power of the study. Gross and microscopical examination of all major tissues and organs at necropsy revealed no significant neoplastic or non-neoplastic alterations that could be attributed to treatment with 4-nitrophenol. Hematological and clinical chemistry end points were not monitored. This study recently (July 9, 1991) underwent review by a peer review panel; the panel concluded that under the conditions of the study there was no evidence of carcinogenic activity in male or female Swiss-Webster mice.

NTP (1991) also conducted genotoxicity studies with 4-nitrophenol. 4-Nitrophenol was not mutagenic in S. typhimurium strains TA98, TA100, TA1535, and TA1537 in concentrations of up to 3,333 µg/plate with or without metabolic activation. 4-Nitrophenol did not induce sister chromatid exchange in Chinese hamster ovary cells in the absence or presence of metabolic activation at concentration levels of up to 500 µg/mL, but induced chromosomal aberrations in Chinese hamster ovary cells, in the presence of S-9, at concentrations that delayed cell cycle (1,500 µg/mL). No evidence of mutagenicity was found in germ cells of male Drosophila melanogaster administered 4-nitrophenol in feed (7,500 ppm) or by injection (1,500 ppm). The peer review comments regarding these studies were not available at the time of this writing.

The NIEHS has sponsored a carcinogenicity study with 4-nitrophenol to be conducted FY 1990 by Litton Bionetics, Inc. (NTP 1990). In addition, NIEHS sponsored a mutagenesis/genetic toxicity study with 4-nitrophenol to be completed FY 1990; the performing organization was not specified (NTP 1990). An acute/chronic toxicity study on 4-nitrophenol sponsored by the FDA was to be completed FY 1990 (NTP 1990). 4-Nitrophenol has been selected for a pharmacokinetics/metabolism study by EPA (NTP 1990); this research is to be conducted at the Health Effects Research Laboratory.

No on-going studies were identified regarding 2-nitrophenol.

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

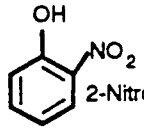
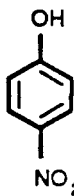
Mononitrophenols exist in three isomeric forms: 2-nitrophenol (or ortho- or o-), 3-nitrophenol (or meta- or m-), and 4-nitrophenol (or para- or p-). In this document, the two high-production-volume chemicals, 2-nitrophenol and 4-nitrophenol will be discussed. Data pertaining to the chemical identities of these two nitrophenols are listed in Table 3-1.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

The physical and chemical properties of the two nitrophenols are presented in Table 3-2. Both the nitrophenols are weak acids compared to carboxylic acids, but the nitro substitution makes them both stronger acids than phenol. 2-Nitrophenol is volatile in steam, but 4-nitrophenol is not. The nitrophenols can be converted to their water-soluble salts by alkaline hydroxides. The OH-group in these compounds is susceptible to substitution reactions with the formation of ethers and esters. The nitro group can be reduced to the amino group under strong reducing conditions. The nitrophenols may also undergo ring substitution reactions (EPA 1985; Morrison and Boyd 1969).

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-1. Chemical Identities of 2-Nitrophenol and 4-Nitrophenol

Characteristic	2-Nitrophenol	4-Nitrophenol	Reference
Chemical name	2-Nitrophenol	4-Nitrophenol	
Synonyms	2-Hydroxynitro- benzene o-nitrophenol	4-Hydroxynitro- benzene p-nitrophenol, PNP	HSDB 1989
Trade names	Atonik	No data	OHM/TADS 1989
Chemical formula	$C_6H_5NO_3$	$C_6H_5NO_3$	HSDB 1989
Chemical structure	 2-Nitrophenol	 4-Nitrophenol	Windholz 1983
Identification numbers:			HSDB 1989
CAS registry	88-75-5	100-02-7	
NIOSH RTECS	21000	22750	
EPA hazardous waste	No data	U170	
OHM/TADS	7800021	7800022	
DOT/UN/NA/IMCO shipping	UN1663;IMO6.1	UN1663;IMO6.1	
HSDB	1133	1157	
NCI	No data	C55992	

CAS = Chemical Abstracts Service

DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code

EPA = Environmental Protection Agency

HSDB = Hazardous Substances Data Bank

NCI = National Cancer Institute

NIOSH = National Institute for Occupational Safety and Health

OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System

RTECS = Registry of Toxic Effects of Chemical Substances

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-2. Physical and Chemical Properties of 2-Nitrophenol and 4-Nitrophenol

Property	2-Nitrophenol	4-Nitrophenol	Reference
Molecular weight	139.11	139.11	
Color	Light yellow	Colorless to light yellow	HSDB 1989
Physical state	Crystalline solid	Crystalline solid	HSDB 1989
Melting point	44-45°C	113-114°C	HSDB 1989
Boiling point	216°C	297°C	HSDB 1989
Density	1.495 g/cc at 14°C	1.270 g/cc at 20°C	HSDB 1989
Dissociation constant (pKa)	7.21-7.23	7.08-7.18	Pearce and Simkins 1968; Polster et al. 1986; Schwarzenbach et al. 1988
Odor	Peculiar aromatic	Slight odor	HSDB 1989; Verschueren 1963
Odor threshold:			
Water	no data	2.5 mg/L	Verschueren 1983
Air	0.0012 mg/m ³	2.3 mg/m ³	Verschueren 1983
Solubility:			
Distilled water	1400 mg/L at 25°C; 2100 mg/L at 25°C	16,000 mg/L at 25°C	Leuenberger et al. 1985; Verschueren 1983
Sea water	1160 mg/L at 20°C	10,795 mg/L at 20°C	Hashimoto et al. 1984
Organic solvents	Soluble in benzene, CS ₂ , alkali hydroxides, ethanol, ethyl ether, and acetone	Soluble in toluene, ethanol, chloroform, ethyl ether, and alkali hydroxides	HSDB 1989
Partition coefficients:			
Log octanol/water	1.79	1.91	Hansch and Leo 1985
Log K _{oc}	2.06	2.18-2.42	Boyd 1982; Hodson and Williams 1938
Vapor pressure (mmHg)	0.12; 0.11 at 25°C	0.0003 at 30°C	Leuenberger et al. 1985; McCrady et al. 1985; Scala and Banerjee 1982
Henry's law constant	1.6x10 ⁻⁵ atm-m ³ /mol at 25°C	3.5x10 ⁻⁹ atm-m ³ /mol at 25-30°C	Leuenberger et al. 1985; McCrady et al. 1985
Autoignition temperature	No data	No data	HSDB 1989
Flashpoint	73.5°C	No data	OHM/TADS 1989
Flammability limits	No data	No data	HSDB 1985
Conversion factors:			
ppm (v/v) to mg/m ³	1 ppm = 5.783 mg/m ³	1 ppm = 5.783 mg/m ³	
in air at 20°C			
mg/m ³ to ppm (v/v)	1 mg/m ³ = 0.173 ppm	1 mg/m ³ = 0.173 ppm	
in air at 20°C			
Explosive limits	no data	no data	

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

4.1 PRODUCTION

2-Nitrophenol was produced commercially in the United States by Monsanto Co. in Sauget, Illinois (SRI 1989; USITC 1989). According to TRI89 (TRI 1989), between 1 and 9 million pounds of 2-nitrophenol was produced in the United States in 1989. 4-Nitrophenol is currently manufactured in the United States by DuPont Co. in Deepwater, New Jersey, and Monsanto Co. in Anniston, Alabama (SRI 1989; USITC 1989). The yearly production capacity is 10 million pounds for the former and 36 million pounds for the latter (CMR 1987; SRI 1989). According to SRI (1989), Monsanto Co. captively (used on-site) uses part of the 4-nitrophenol that it produces. The U.S. demand for 4-nitrophenol, including exports, was 23 million pounds in 1987 and the projected demand is 25 million pounds in 1991. If Hoechst-Celanese commercializes an alternate acetaminophen (N-acetyl-4-aminophenol) production process, it could reduce the consumption of 4-nitrophenol toward the end of the decade (CMR 1987). Besides the facilities that manufacture the nitrophenols, the companies that process these compounds are listed in Table 4-1. Table 4-1 also shows the intended use and the maximum amounts of each chemical stored on site.

2-Nitrophenol is produced either by the catalytic hydrolysis of 2-nitrochlorobenzene with NaOH or by the action of dilute HNO_3 on phenol with subsequent steam distillation for separation from 4-nitrophenol (EPA 1985; HSDB 1989). 4-Nitrophenol is produced either by the catalytic hydrolysis of 4-nitrochlorobenzene or by the reaction of dilute HNO_3 on phenol and subsequent steam distillation to separate the 4- from the 2- isomer (EPA 1985; HSDB 1989).

4.2 IMPORT/EXPORT

In 1977, FMC Corp. and Rhone-Poulenc, Inc. imported between 1 and 11 million pounds of 2-nitrophenol into the United States (TSCAPP 1989). Imports of 2-nitrophenol through principal U.S. customs districts in 1983 were 3.56 million pounds (EPA 1985). Imports of 4-nitrophenol into the United States are negligible. Export of 4-nitrophenol in 1987 was 35% of its United States demand of 23 million pounds (CMR 1987).

4.3 USE

2-Nitrophenol is used mainly as an intermediate for the production of dyestuffs, pigments, rubber chemicals, and fungicides. Small amounts are used as an acid-base indicator and as a reagent for glucose (EPA 1985; HSDB 1989). The current use pattern of 4-nitrophenol is as follows: production of N-acetyl-4-aminophenol, 55%; exports, 35%; miscellaneous other uses including leather tanning, insecticides (methyl and ethyl parathion), dyestuff and oxydianiline manufacture, 10% (CMR 1987; HSDB 1989). Small amounts of 4-nitrophenol are used as a laboratory reagent (e.g., phosphatase and

TABLE 4-1. Facilities that Manufacture or Process Nitrophenols^a

Facility	Location	Maximum amount on site (lbs)	Use	Isomer ^b
Monsanto Company	Anniston, AL	1,000,000-9,999,999	Produce for sale/ distribution	4-NP
Monsanto Company	Sauget, IL	1,000,000-9,999,999	Produce for sale/ distribution	2-NP
Monsanto Company	Sauget, IL	1,000-9,999	Produce; as a byproduct	4-NP
Monsanto Company	Luling, LA	100,000-999,999	As a reactant	4-NP
Ciba-Geigy Corporation	St. Gabriel, LA	10,000-99,999	As a reactant	2-NP
FMC Corporation-Baltimore plant	Baltimore, MD	100,000-999,999	As a reactant	2-NP
Mallinckrodt, Inc.	St. Louis, MO	10,000-99,999	As a byproduct; as a reactant	4-NP
Monsanto Company	St. Louis, MO	100-999	Produce; as an impurity	4-NP
Kollsman	Merrimack, NH	0-99	As a manufacturing aid	2-NP
Tennessee Eastman Company	Kingsport, TN	10,000-99,999	As a reactant	4-NP

^aProduction information for 1989 derived from TRI 1989^b4-NP = 4-nitrophenol; 2-NP = 2-nitrophenol

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

carboxyesterase determinations) and as a fungicide in military footwear. It is registered with the EPA for fungicidal use (Angerhofer 1985; HSDB 1989).

4.4 DISPOSAL

Incineration under controlled conditions (to attain complete combustion) appears to be the best method of disposal for both the nitrophenols (HSDB 1989; OHM/TADS 1989). The waste containing nitrophenols can be incinerated either with a rotary kiln incinerator at 820-1600°C with a residence time of hours or in a fluidized bed incinerator at 450-980°C with a residence time of seconds for liquids and gases, longer for solids. Incineration of large quantities may require scrubbers to control the emission of NO_x gases (HSDB 1989). Biological treatment with powdered activated carbon and activated sludge has been used for liquid wastes (HSDB 1989). Oxidation by passing air at 275°C through the aqueous waste destroys 99.6% of 4-nitrophenol (Heimbuch and Wilhelmi 1985). A resin absorption (Ambelite XAD-7) method for the removal of 4-nitrophenol has been used for industrial waste water. Waste residues including waste sludge can be disposed of by land treatment or burial in specified landfills (HSDB 1989).

A guideline for maximum daily effluent discharge of 2.13 mg of total toxic organics (including both nitrophenols) per liter of waste water was set for electroplating plants that discharge less than 10,000 gallons of waste water per day (EPA 1988a). Similarly, the limitations for daily effluent discharge from electrical and electronic industries is set at 1.37 mg/L of total toxic organics (EPA 1988a). Information regarding pretreatment standards and effluent guidelines and standards may be found in Section 7.

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5.1 OVERVIEW

There are no known natural sources of 2-nitrophenol and 4-nitrophenol in the environment (HSDB 1989). The primary anthropogenic sources of the two compounds in air are probably industrial manufacturers and processors. Manufacturing and processing industries release an estimated total of 33,000 pounds of 2-nitrophenol and 5,500 pounds of 4-nitrophenol in the air (TRI 1989). Very little of these compounds is directly released to surface waters or soil. About 21,500 pounds of 2-nitrophenol and 250 pounds of 4-nitrophenol are disposed of in off-site landfills by the industries. In addition, about 7,000 pounds of 4-nitrophenol are disposed of by underground injection (TRI 1989). The nitrophenols can also be formed in the air as a result of the atmospheric photochemical reactions of several aromatic compounds formed from anthropogenic sources. They are also formed in vehicular exhausts as a result of the thermal reaction of fuel with oxides of nitrogen. 4-Nitrophenol is formed as a degradation product and it is an impurity in parathion formulations (HSDB 1989; Nojima et al. 1976, 1980).

In the air, both photolysis and physical removal processes such as gravitational settling of aerosols and wet deposition by rain and snow will probably determine the fate of 2-nitrophenol and 4-nitrophenol. The atmospheric half-lives of these compounds are not known. In water, both photolysis and biodegradation will be important fate processes. Photolysis will be more important in near-surface water; where attenuation of sunlight is usually minimal. The half-life of the nitrophenols may range between 1 and 8 days in fresh water and may range between 13 and 21 days in sea water. In soils, biodegradation may be the most important fate process for these nitrophenols. In top-soil, the half-life of 4-nitrophenol may be about 1-3 days under aerobic conditions and around 14 days under anaerobic conditions. In subsoils, the half-life of 4-nitrophenol may be about 40 days under aerobic conditions and even slower under anaerobic conditions. The half-life of 2-nitrophenol may be about 12 days under aerobic conditions (Bourquin et al. 1982; Bourquin 1984; EPA 1985; HSDB 1989; Kincannon and Lin 1985; Loekke 1985). However, other studies have found that the rate of disappearance of nitrophenols, both in water and soil, may not be first-order, and evaluation of a biodegradation half-life may not be meaningful (Hoover et al. 1986; Jones and Alexander 1986, 1988; Scow et al. 1986, 1989; Zaidi et al. 1988, 1989). The products of biodegradation have also been studied with pure cultures of microorganisms. Catechol, beta-keto adipic acid, and nitrite have been identified as products of aerobic biodegradation of 2-nitrophenol (Zeyer and Kearney 1984) and 4-nitrocatechol, hydroquinone, gamma-hydroxymuconic semialdehyde, and nitrite from 4-nitrophenol (Raymond and Alexander 1971; Spain et al. 1979). On the other hand, 2-aminophenol and 4-aminophenol have been isolated from anaerobic biodegradation of 2-nitrophenol and 4-nitrophenol, respectively (Adhya et al. 1981; Villanueva 1961).

Monitoring data for the nitrophenols in any environmental medium were limited. The average concentration of 2-nitrophenol in the gas phase during

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seven rainfalls in Portland, Oregon, in 1984 was $0.024 \mu\text{g}/\text{m}^3$. The corresponding concentration in rain water was $0.059 \mu\text{g}/\text{L}$ (Leuenberger et al. 1985). The nitrophenols have been identified in effluents from several industries at a median concentration of less than $10 \mu\text{g}/\text{L}$ (Staples et al. 1985). 4-Nitrophenol was detected in the potable water supply of Ames, Iowa, at a concentration of $0.2 \text{ mg}/\text{L}$. The source of the compound was probably the contamination of well water from coal gas plant wastes (EPA 1980). No other report of detection of either nitrophenol in U.S. drinking waters was found in the literature. The two nitrophenols and their mixture have been detected in 14 NPL waste sites (View 1989). The frequency of these sites within the United States can be seen in Figure 5-1.

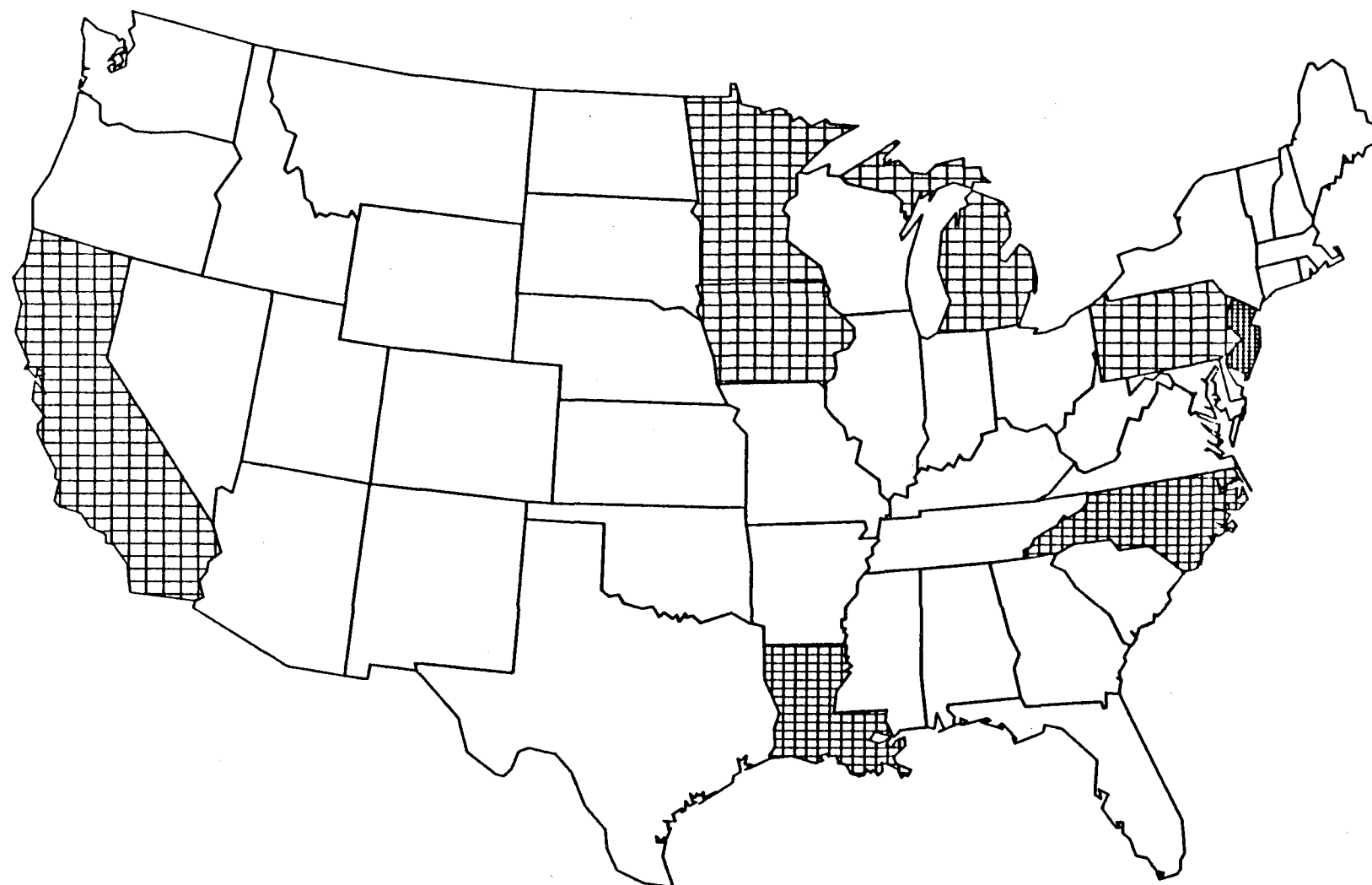
No report on the detection of either nitrophenol in any food was found in the literature. In a Health and Nutrition Survey conducted by the National Center for Health Statistics, 4-nitrophenol (as its glucuronide or sulfate conjugate) was quantifiable in 2.4% of urine samples of the general population, with a geometric mean value of less than $10 \mu\text{g}/\text{L}$. It was speculated that the 4-nitrophenol originated from the pesticides methyl and ethyl parathion (Carey and Kutz 1985; Kutz 1983). Although no experimental data are available, it is likely that people who live near landfills that contain these compounds, applicators of certain pesticides,, and those people who consume contaminated drinking water from groundwaters adjacent to parathion-treated farmlands are potentially exposed to doses higher than the background level.

5.2 RELEASES TO THE ENVIRONMENT

5.2.1 Air

There is no evidence of the formation of 2-nitrophenol and 4-nitrophenol from natural sources in the environment (HSDB 1989). The primary anthropogenic sources of the two compounds in air are probably industrial manufacturers and processors. The manufacturing and processing industries release an estimated total of 33,000 pounds of 2-nitrophenol and about 5,500 pounds of 4-nitrophenol in the air (TRI 1989). These facilities and the amount of individual atmospheric emissions are shown in Table 5-1. Monsanto Co. disposes of a large amount (about 175,000 pounds) of 4-nitrophenol and 4,000 pounds of 2-nitrophenol by incinerator/thermal processes (TRI 1989). It should be mentioned that the TRI (1989) release data in these sections are quantities released to the environment in 1987. Since the efficiencies of the incinerator/thermal processes are less than 100%, a small amount of undegraded nitrophenols will be released into the air during these processes. The nitrophenols can also be formed in the air as a result of atmospheric photochemical reactions of nitrobenzene, aromatic hydrocarbons (e.g., benzene and toluene) and bromobenzene primarily formed from anthropogenic sources with nitrogen oxides present in the air (HSDB 1989; Nojima et al. 1976, 1980;

FIGURE 5-1. FREQUENCY OF NPL SITES WITH NITROPHENOLS CONTAMINATION *



FREQUENCY  1 SITE  2 SITES  5 SITES

* Derived from View 1989

TABLE 5-1. Releases to the Environment from Facilities
that Manufacture or Process Nitrophenols^a

Facility	Location	Release in lbs							Isomer
		Air	Underground injection	Water	Land	Total environment	POTW transfer	Off-site transfer	
Monsanto Company	Anniston, AL	500	0	0	250	750	250	0	4-NP
Monsanto Company	Sauget, IL	27,000	0	0	0	27,000	120,000	4,000	2-NP
Monsanto Company	Sauget, IL	2,200	0	0	0	2,200	92,000	175,000	4-NP
Monsanto Company	Luling, LA	2,250	6,800	0	0	9,050	0	250	4-NP
Ciba-Geigy Corporation	St. Gabriel, LA	0	0	250	0	250	0	0	2-NP
FMC Corporation - Baltimore Plant	Baltimore, MD	6,149	0	0	0	6,149	7,684	21,553	2-NP
Mallinckrodt, Inc.	St. Louis, MO	0	0	0	0	0	1,200	0	4-NP
Monsanto Company	St. Louis, MO	500	0	0	0	500	90,000	0	4-NP
Kollsman	Merrimack, NH	0	0	0	0	0	0	0	2-NP
Tennessee Eastman Company	Kingsport, TN	2	0	0	0	2	0	0	4-NP

^aDerived from TRI 1989 and release data for 1987

2-NP = 2-nitrophenol

4-NP = 4-nitrophenol

Off-site = waste containing nitrophenols are transferred away from plant site for incineration, land, or other modes of disposal

POTW = publicly owned treatment works

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Rippen et al. 1987). The nitrophenols are released from exhausts of both gasoline- and diesel-powered vehicles (Nojima et al. 1983). 4-Nitrophenol is a degradation product of parathion and is one of the impurities in parathion formulations (HSDB 1989). Therefore, small amounts of 4-nitrophenol may be released in local windblown dusts in areas where these pesticides are used. A quantitative estimate of atmospheric release of 2-nitrophenol and 4-nitrophenol from any of the last three indirect pathways (photochemical formation, vehicular exhaust, parathion use) is not available.

5.2.2 Water

The estimated total direct industrial releases of 2-nitrophenol and 4-nitrophenol in U.S. surface waters are 250 and 0 pounds, respectively (TRI 1989). The facilities that emit and the amount of individual emissions in water are shown in Table 5-1. Much larger amounts of the two compounds from direct manufacturing and processing industries are released into publicly owned treatment works (POTWs). The releases of 2-nitrophenol and 4-nitrophenol to POTWs have been estimated to be 128,000 pounds and 184,000 pounds, respectively (see Table 5-1). The parathion formulations contain small amounts of 4-nitrophenol as impurities, and the hydrolysis and biodegradation of the pesticide can produce 4-nitrophenol (Gomaa and Faust 1972). Therefore, application of the pesticide formulations may release 4-nitrophenol into surface water as a result of runoff from land. Small amounts of 4-nitrophenol conjugates are excreted in the urine of people exposed to parathion formulations (Carey and Kutz 1985; Kutz 1983). This could be a minor route of entry of 4-nitrophenol into POTWs. Effluents from the textile industry may also release both 2-nitrophenol and 4-nitrophenol into surface water and POTWs (EPA 1981). In addition, the two nitrophenols were found in treated waste waters from the following industries: iron and steel manufacturing (nitrophenols formed during the coke making process); foundries (nitrophenols formed during the coke making process); pharmaceutical manufacturing; rubber processing; and electrical/electronic components production (EPA 1981).

5.2.3 Soil

It is estimated that only a small amount (250 pounds) of 4-nitrophenol and no 2-nitrophenol is discharged directly to on-site land from facilities in the United States that manufacture or process these chemicals (TRI 1989). However, about 21,500 pounds of 2-nitrophenol and 250 pounds of 4-nitrophenol are disposed of in off-site landfills by these industries (TRI 1989) (see Table 5-1). In addition, about 7,000 pounds of 4-nitrophenol is disposed of by underground injection (see Table 5-1). Therefore, manufacturing and processing industries are sources of the nitrophenols in soils and may cause groundwater contamination near the disposal sites. As has been discussed in Section 5.2.2, the application of parathion formulations to foliage could be an additional source of 4-nitrophenol in soil. Atmospheric to terrestrial transfer, primarily through rainwater and snow, will be secondary sources of

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the nitrophenols in water and soil (Luenberger et al. 1988). Deposition of vehicular exhaust on roadways is another source of nitrophenols in soil. No quantitative estimate of the amounts of the two nitrophenols released into soil from the latter three sources is available.

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

The fate and distribution of 4-nitrophenol in different environmental compartments were assessed with a nonsteady-state equilibrium model (Yoshida et al. 1983). The model predicted the following distribution: air, 0.0006%; water, 94.6%; soil, 0.95%; sediment, 4.44%; and biota, 0.00009%. Therefore, only a very small fraction of this compound released from various sources is expected to remain in the air. The atmospheric concentration of 2-nitrophenol is expected to be higher than the 4-isomer because it has a Henry's law constant value that is four orders of magnitude higher (see Table 3-2). Based on the 4-nitrophenol data given by Yoshida et al. (1983), the fraction in air is still expected to be small for 2-nitrophenol.

The partitioning of a chemical from the atmosphere to land and water depends on its physical state and physico-chemical properties. For example, gravitational settling may be more important than other transport processes for partitioning of suspended particulate matters from air to land and water, whereas wet deposition via rainwater or snow may be more important for chemicals that exist in the vapor phase in air. From the vapor pressure data (see Table 3-2), both these chemicals are expected to be present predominantly in the vapor phase in the atmosphere (Eisenreich et al. 1981), although they have been detected in particulates collected over Yokohama, Japan (Nojima et al. 1983). Because of their significant water solubilities (see Table 3-2) and expected existence in the vapor phase, partitioning of these chemicals from air to surface waters and land via wet deposition is expected to occur. The detection of both these nitrophenols in rainwater by a few authors (Luenberger et al. 1988; Rippen et al. 1987) supports this partitioning mechanism.

The intramedia transport of the two compounds from their points of emission to locations farther away in the air will depend on the lifetime of the compounds in air. Because of their significantly long half-life (days) in the air (Section 5.3.2), these compounds are expected to undergo atmospheric transport from polluted areas to less polluted or pristine areas. However, there is no experimental evidence to confirm the long-range transport of the nitrophenols.

The partitioning of 2-nitrophenol and 4-nitrophenol from water to air and different aquatic phases will depend on its volatility from water to air and its distribution between water, sediment, and biota. Experimental volatilization rates for either of the compounds from water are unavailable.

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The modeling data based on nonsteady-state equilibrium predict that volatilization of 4-nitrophenol will be insignificant (Yoshida et al. 1983). The Henry's law constant (H) values for these two compounds (see Table 3-2) and the volatility characteristics associated with various H values (Thomas 1982) can be used to predict that volatilization from water will not be important. The dissociation constant (pKa) values of the two compounds (see Table 3-2) indicate that significant fractions of these nitrophenols will be dissociated at pHs above 6. Since ionic species do not volatilize significantly from water, the ionization may further limit volatilization.

The partitioning of the nitrophenols between water and sediment is expected to depend on the pH of the water. Two sorption mechanisms may be operating: one is the normal hydrophobic sorption common to hydrophobic organic compounds, and which can be correlated with organic carbon content of sediments. The other is chemical bonding (probably hydrogen bonding) between the sediment and the chemical (Boyd 1982; Isaacson 1985). The fact that sorption of 4-nitrophenol was correlated with iron oxide, clay, and silt contents of soils (Artiola-Fortuny and Fuller 1982) confirms these hypotheses. The log K_{oc} values of 2.06-2.42 (see Table 3-2) can be used to predict that the two nitrophenols would not be sorbed appreciably to sediments. On the basis of the K_{oc} value, the nonsteady-state equilibrium model (Yoshida et al. 1983) predicts that only 4.4% of 4-nitrophenol will remain in sediment, compared to 94.6% in water. The sorption will be higher for sediments with high organic content, iron oxide and montmorillonite or other clay minerals. Experimental data with an estuarine sediment show that, once 4-nitrophenol is sorbed to reduced estuarine sediment, the desorption of the compound from sediment back to the water column will be insignificant (Siragusa and Delaune 1986).

The bioconcentration factor (BCF) (wet-weight basis) for 4-nitrophenol in a species of green algae (Chlorella fusca) was 30 (Geyer et al. 1984). In golden orfe fish (Leuciscus idus melanotus), the whole-body BCF after 3 days of exposure was 57 (Freitag et al. 1982). With ^{14}C radiolabeled test compound, the mean plateau whole-body ^{14}C BCF for 4-nitrophenol in the fathead minnow (Pimephales oromelas) was 180. Only 2.7% of the tissue contained the parent compound after 28 days of depuration, and the compound was eliminated with a mean depuration half-life of 150 hours. 4-Aminophenol was identified as a metabolite (Call et al. 1980). Other authors have estimated a BCF of 126 for 4-nitrophenol from its octanol/water partition coefficient and various regression equations (Isnard and Lambert 1988; Schueuermann and Klein 1988). Based on available BCFs, 4-nitrophenol would biomagnify from lower to higher tropic levels in both aquatic and terrestrial organisms (Loehr and Krishnamoorthy 1988).

The transport and partitioning of nitrophenols in soils will depend on their sorption and volatilization characteristics. The sorption characteristics will be similar to those described in sediments. The measured log K_{oc} values for 2-nitrophenol and 4-nitrophenol in a clay loam soil of

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5.1% organic matter content and a pH of 5.7 were 2.06 and 1.72, respectively (Boyd 1982). Other authors have reported log K_{oc} values in the range 2.18-2.42 for 4-nitrophenol (Hodson and Williams 1988). These K_{oc} values indicate that nitrophenols will not strongly adsorb to soils. Although sorption of 4-nitrophenol to soil is weak, the sorption increases with the hydrogen bonding capacity of soils/sediments (Artiola-Fortuny and Fuller 1982; Isaacson 1985). Therefore, in the absence of significant degradation, nitrophenols may leach from soil and may be found in the leachate of landfills.

In a laboratory study in which a test system was constructed to simulate a typical terrestrial ecosystem in terms of air flow (over soil), percolating water (through soil), and vegetation cover, the fate of nitrophenols was studied with radiolabeled compounds added to soil. Of the total radioactivity applied to soils, only 1.6% in the case of 4-nitrophenol and 45.3% in the case of 2-nitrophenol were recovered in the gas phase after 30 days that were not attributable to CO_2 formed from biodegradation or other mineralization processes. Although the portions of the gas phase that were not attributable to CO_2 were not identified (i.e., they could be the nitrophenols or their metabolites other than CO_2), this study indicates that volatilization from soil will be insignificant for 4-nitrophenol but may be significant for 2-nitrophenol. In the same terrestrial ecosystem study, 35.7% and 12.7% of the applied radioactivities were recovered in plants when 4-nitrophenol and 2-nitrophenol, respectively, were used (Figge et al. 1983). This indicates that a significant portion of nitrophenols (or their metabolites) may be transferred from soil to plant. However, this transfer may not indicate bioaccumulation in plants because of the possible metabolism in plants.

5.3.2 Transformation and Degradation

5.3.2.1 Air

The two processes that are likely to degrade nitrophenols in air are direct photolysis and reactions with free radicals in the air. Very few studies are available on photolysis of nitrophenols in the air. When 4-nitrophenol was coated on silica gel and irradiated with an ultraviolet (UV) lamp of wavelengths greater than 290 nm in the presence of an air current, 39% of the starting material photomineralized to CO_2 after 17 hours (Freitag et al. 1982; Korte and Klein 1982). No experimental data on the vapor-phase photolysis of the nitrophenols are available. Photolysis experiments in water (Section 5.3.2.2) can be used to predict that photolysis of the nitrophenols in air will be a significant degradation process.

The rate constant for the gas-phase reaction of 2-nitrophenol with OH radicals is 9.0×10^{-13} cm^3 -molecule/sec at 21°C (Atkinson 1985) and 8.95×10^{-13} cm^3 -molecule/sec at 27°C (Gusten et al. 1984). Assuming that a 24-hour average concentration of OH radicals in a normal atmosphere is 5×10^5 radicals/ cm^3 (Atkinson 1985), the atmospheric half-life of 4-nitrophenol

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due to this reaction is an estimated 18 days, and the reaction may not be an important fate determining process in the atmosphere.

5.3.2.2 Water

Chemical oxidation reactions of the two nitrophenols by singlet oxygen and alkyl peroxy radicals formed as a result of sunlight-induced photochemical reactions in water are too slow to be significant (EPA 1985; Scully and Hoigne 1987). OH radicals in water attack 2-nitrophenol and 4-nitrophenol at the 2- and 4-carbon positions, resulting in the formation of a variety of products including 1,4-benzoquinone, 1,4-dihydroxybenzene and 4-nitrocatechol (4-nitro-1,2-dihydroxybenzene) (Suarez et al. 1970). 4-Nitrophenol photoreacts quite rapidly in water in the presence of nitrate or nitrite (EPA 1985). This is not surprising, since nitrate and nitrite in water produce elevated concentrations of OH when irradiated by sunlight.

The photolytic behavior of nitrophenols in water is well studied. The irradiation of 4-nitrophenol in neutral or acidic aqueous solution in the presence of air at wavelength 365 nm produced primarily hydroquinone and HNO_2 , together with small amounts of benzoquinone and 4-nitrocatechol (HSDB 1989). Other authors have determined the phototransformation quantum yield to be in the range 3.3×10^{-6} to 8.3×10^{-6} at pH 9.0 (ECETOC 1984; Lemaire et al. 1985). From the quantum yield data, the half-life of 4-nitrophenol in near-surface water was an estimated 27.5 hours at pH 5.5 under sunlight conditions equivalent to noontime, summer conditions in Chicago (EPA 1985). Hustert et al. (1981), on the other hand, used the EPA test procedure and determined the photolytic half-lives of 5.7 days at pH 5, 6.7 days at pH 7, and 13.7 days at pH 9.

The biodegradability of nitrophenols in water has been studied extensively with pure cultures of microorganisms, mixed microorganisms and standardized screening test methods (Blok et al. 1985; Boatman et al. 1986; Chambers et al. 1963; Frietag et al. 1982; Gericke and Fischer 1979; Jones and Alexander 1986; Kitano 1978; Kool 1984; Korte and Klein 1982; McCormick et al. 1976; Means and Anderson 1981; Neujahr and Varga 1970; Neujahr et al. 1974; Patterson and Kodukala 1981; Pitter 1976; Rott et al. 1982; Sudhakar-Barik et al. 1976; Tabak et al. 1981; Wilderer 1981; Zaidi et al. 1988). Depending on test conditions, the results from these tests vary considerably, some predicting that 4-nitrophenol is not easily biodegradable and others predicting easy biodegradability. It has been established that the nitrophenols have a lag period before the onset of biodegradation (Haller 1978).

Several authors have used natural waters to study the aerobic biodegradability of 4-nitrophenol and concluded that, after a few days of adaptation, it will rapidly biodegrade in many of these waters (Bourquin et al. 1982; Spain et al. 1980; Spain and Van Veld 1983; Spain et al. 1984). The half-life of biodegradation in natural water (parent compound disappearance)

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reported or estimated from experimental results are as follows: about 3.5 days in a river (Bourquin et al. 1982; Bourquin 1984); a mean of 3.2 days for five pond and river waters (Vaishnav and Korthals 1988); and a mean of less than 1 day for five pond and river waters based on the concentration of degrader microorganisms of 10^{+6} organisms/ml (Paris et al. 1983). Compared to these fresh waters, the half-life of 4-nitrophenol in sea water may be longer, and the experimental half-life may range between 13 and 21 days (Bourquin et al. 1982; Bourquin 1984; Van Veld and Spain 1983). The rate and extent of degradation of 4-nitrophenol in natural water also depend on the initial concentration of the substance, the nature and concentration of nutrients, the activities of the organisms, and the presence or absence of predators or inhibitors of degrader organisms (Hoover et al. 1986; Jones and Alexander 1988; Rubin and Alexander 1983; Rubin et al. 1982; Subba-Rao et al. 1982; Wiggins and Alexander 1988; Zaidi et al. 1989). Other investigators have found that the rate of biodegradation of nitrophenols may follow complex kinetics and the derivation of a half-life based on simple first-order kinetics in such cases would not be appropriate (Jones and Alexander 1986, 1988; Zaidi et al. 1988).

Biodegradation studies of the two nitrophenols with digested sludge under methanogenic conditions have shown that the compounds are not easily biodegraded and that 4-nitrophenol at high concentration is inhibitory to methanogenic microorganisms (Battersby and Wilson 1989; Horowitz et al. 1982). The anaerobic biodegradation of 4-nitrophenol in bottom sediments of lakes and rivers is also a slow process (Siragusa and DeLaune 1986). However, in anaerobic screening tests using digester sludge inocula, 4-nitrophenol completely disappeared in 1 week in one study (Boyd et al. 1983), and over 75% mineralized in 56 days in another (Shelton and Tiedje 1984). Under anaerobic conditions in two flooded soils, over 50% degradation of 2-nitrophenol and 4-nitrophenol was observed in 10 days (Sudhakar-Barik and Sethunathan 1978).

5.3.2.3 Soil

Data regarding the chemical degradation of nitrophenols in soils are lacking. Oxides of Mn (+3/+4) undergo reductive dissolution by substituted phenols. However, nitrophenols are among the most resistant substituted phenols for this reaction, which will be quite slow at neutral and alkaline PH. At low pHs, the nitrophenols may degrade at an appreciable rate, forming dimeric and polymeric oxidation products, since the dissolution rate of one form of Mn_xO_y with 4-nitrophenol was less than 10^{-9} mol/L-min at a pH of 4.4 (Stone 1987). The significance of this reaction under environmental conditions where the concentration of nitrophenols will be expected to be much lower than that used (10^{-2} M) in the experiment of Stone (1987) is likely to be low. The photolytic reaction of nitrophenols will not be significant beyond the surface layer of soil because light attenuation will reduce the light intensity to insignificant levels. The most important fate determining process for nitrophenols in soils is expected to be biodegradation. A number of studies discussed in the following paragraph support this conclusion.

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Several pure cultures isolated from soils degraded nitrophenols (EPA 1985). As in the case of water, adaptation of soil to 4-nitrophenol was a prerequisite for biodegradation; the presence of a critical number of degrader microorganisms was necessary for the initiation of biodegradation. However, unlike in natural water, the mineralization of low concentrations of 4-nitrophenol proceeds with little or no initial acclimation period (Scow et al. 1986). Addition of specific nutrients from pristine aquifer also resulted in more rapid adaptation (Aelion et al. 1987; Swindoll et al. 1988), and the rate of biodegradation was concentration-dependent (Scow et al. 1986). The biodegradation of 2-nitrophenol by soil microorganisms is comparatively slower than that of 4-nitrophenol (Alexander and Lustigman 1966; Figge et al. 1983). In a study designed to simulate biodegradation of chemicals under natural land disposal conditions, the half-life of 2-nitrophenol in sandy loam soil was estimated to be 12 days under aerobic conditions (Kincannon and Lin 1985). In topsoil, the half-life of 4-nitrophenol was about 1 day under aerobic conditions and 14 days under anaerobic conditions. Addition of certain nutrients reduced the anaerobic half-life of 4-nitrophenol. In subsoils, the half-life of 4-nitrophenol was 40 days under aerobic conditions and even slower under anaerobic conditions (Loecke 1985). From a laboratory microcosm study simulating coastal wetlands, the half-life of 4-nitrophenol was predicted to be 2-3 days (Portier 1985).

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

Monitoring data for nitrophenols in U.S. air are limited. Therefore, monitoring data for these compounds in ambient air, rainwater and vehicular exhausts from both inside and outside of the United States are presented. Nitrophenols were detected but not quantified in the urban air and rainwater of a Japanese city in 1975 (Rippen et al. 1987). Concentrations of 2-nitrophenol (less than 0.05-3.9 $\mu\text{g/g}$) and 4-nitrophenol (5.1-42 $\mu\text{g/g}$) were detected in the air particulate matter collected in a Japanese city in 1982. Under engine idling conditions, the concentrations of 2-nitrophenol and 4-nitrophenol in vehicular exhaust gases were 3.1 ppb (17.9 $\mu\text{g/m}^3$) and less than 0.5 ppb (less than 2.9 $\mu\text{g/m}^3$), respectively, for a gasoline engine (2,600 cc) and 6.4 ppb (37 $\mu\text{g/m}^3$) and 2.5 ppb (14.5 $\mu\text{g/m}^3$), respectively, for a diesel engine (7,000 cc) (Nojima et al. 1983). The average concentration of 2-nitrophenol in the gas phase during seven rainfalls in Portland, Oregon, in 1984 was 0.024 $\mu\text{g/m}^3$. The corresponding concentration in rainwater was 0.059 $\mu\text{g/L}$ (Leuenberger et al. 1985). The concentrations of 2-nitrophenol in air and rainwater at Dubendorf, Switzerland, in 1985 were 0.35 $\mu\text{g/m}^3$ (one rainfall) and 0.1-0.8 $\mu\text{g/L}$ (several rainfalls), respectively (Leuenberger et al. 1988). 2-Nitrophenol was also detected in rainwater at a concentration of 0.031 $\mu\text{g/L}$ in Azusa, California, and at 0.1-1.4 $\mu\text{g/L}$ in different locations in West Germany. 4-Nitrophenol was also detected in rainwater at concentrations of 2-24 $\mu\text{g/L}$ in different locations in West Germany. Extremely high values of

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4-nitrophenol (up to 50 µg/L) have been found in rainwater from a thunderstorm after a hot and sunny period (Rippen et al. 1987).

5.4.2 Water

The nitrophenols have been identified in effluents from several industries. 2-Nitrophenol has been detected in effluents from photographic and electronics industries (Burse and Pellizzari 1982). Nitrophenols (isomer unidentified) at a concentration of 5 mg/L was detected in oil shale retort water (Dobson et al. 1985). Nitrophenols have been identified in effluents from other chemical plants, as well. 4-Nitrophenol has been identified in effluent from a pesticide plant (EPA 1985). Both 2-nitrophenol and 4-nitrophenol were detected in the final effluent from the waste water of a petroleum refining industry (Snider and Manning 1982). Nitrophenols have also been identified in primary and secondary effluents of municipal waste water treatment plants. For example, both nitrophenols were identified in the secondary effluent from a waste water treatment plant in Sauget, Illinois, (Ellis et al. 1982), and 4-nitrophenol was detected in both primary and secondary effluent from a waste water treatment plant in Los Angeles, California, in secondary effluent from a waste water treatment plant in Orange County, California, and in primary effluent from a San Diego, California, waste water treatment plant (Young 1978). Based on data from EPA's STORET database from 1980 to January 1984 (to assure better quality, data from earlier years have been excluded), 2-nitrophenol and 4-nitrophenol have been detected in 1.8% (total samples, 1318) and 3.3% (total samples, 1322) of effluent samples for the respective isomer at various locations in the United States. The median concentrations of both nitrophenols in these samples were less than 10 µg/L (Staples et al. 1985). 4-Nitrophenol was found in stormwater runoffs from four (Long Island, New York; Washington, District of Columbia; Little Rock, Arkansas; and Eugene, Oregon) of 15 cities at concentrations ranging from 1 to 19 µg/L (Cole et al. 1984).

Neither of the nitrophenols was detected in water from Lake Erie and Lake Michigan (Great Lakes Water Quality Board 1983). Based on data from EPA's STORET database since 1980 (to assure better data quality), neither of the nitrophenols was detected in any of the over 800 ambient surface water samples analyzed (Staples et al. 1985). 4-Nitrophenol at a concentration of 0.2 mg/L was detected in the potable water supply of Ames, Iowa. The source of the compound was speculated to be the contamination of well water from the wastes of a coal gas plant after the plant ceased operation around 1930 (EPA 1980). No other detection of either nitrophenol in U.S. drinking waters was reported.

5.4.3 Soil

The monitoring program conducted by EPA at Love Canal (Niagara Falls, New York) in 1980 qualitatively detected the presence of both nitrophenols in sediment/soil samples (Hauser and Bromberg 1982). Brown and Donnelly (1988)

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compiled leachate data from several landfills in the United States. The concentration range for 2-nitrophenol in a few unspecified municipal landfill leachates was reportedly 8.6-12.0 mg/L. The presence of 2-nitrophenol in the leachates suggests that the compound was also present in the soil, although no soil monitoring data were reported. 2-Nitrophenol was detected at a concentration of 76 mg/L in one of 1,131 samples taken from drums, tanks, or other containers from 221 hazardous waste disposal sites in 41 states and one territory (Blackman et al. 1984). The nitrophenols have not been monitored in all of the 1,177 hazardous waste sites listed on the NPL. In the sites monitored so far, the two isomers and their mixture were found at 14 sites (View 1989). Additionally, 2-nitrophenol and 4-nitrophenol were found in 15 and 29 matrices (surface water, groundwater, and soil), respectively, in the Contract Laboratory Statistical Program Database (CLPSD 1988). Note that the Contract Laboratory Program Statistical Database includes data from both NPL and non-NPL sites.

5.4.4 Other Environmental Media

No data in the literature demonstrated the presence of the nitrophenols in foods. The production of 4-nitrophenol from degradation or metabolism of several pesticides, including parathion and fluoridifen, on plant leaves or in soil may result in the contamination of food crops following application of these pesticides. When spinach fields were sprayed with 0.5-1.0 pound (active ingredient) of parathion/acre, the 4-nitrophenol residues 7 days following application of the pesticide at recommended application rate did not exceed the unsprayed spinach. The source of 4-nitrophenol in unsprayed spinach was not stated. Since the recommendations for parathion application call for harvesting at least 14 days following application, 4-nitrophenol may not be found in harvested spinach (because it was not found in spinach on the 7th day following application) (EPA 1980). As of September 1991, EPA has reached a settlement agreement with registrants of the insecticide to limit the use of parathion to nine field crops (alfalfa, corn, canola, cotton, sorghum, soybeans, sunflower, and wheat) and intends to issue a Notice of Intent to Cancel (NOIC) the field use of parathion in the near future. The EPA decision is based on concerns about unacceptable risks of exposure to agricultural workers, the general public, birds, and aquatic invertebrates (EPA 1991).

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The general population may be exposed to nitrophenols through the inhalation of ambient air and ingestion of contaminated foods and drinking water. Although limited air monitoring data are available, low levels (less than 1 $\mu\text{g}/\text{m}^3$) of 2-nitrophenol are expected to exist in the air. Because of photochemical formation of G-nitrophenol in smog and thermochemical formation of both nitrophenols in vehicular exhausts, the levels are expected to be higher in urban and suburban air than in rural air. Nitrophenols have been detected rarely in drinking water and foods. Whether this is because of a lack of effort directed at monitoring these compounds or because they are

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present at undetectable levels is not known. Therefore, exposure from these two sources, although plausible, remains to be demonstrated with actual monitoring data. The detection of 4-nitrophenol in human urine 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 (Piotrowski 1967; Robinson et al. 1951b).

4-Nitrophenol conjugates have been detected in human urine. Based on the analysis of 6,990 samples collected from the general population during 1976-1980 via the National Health and Nutrition Survey II (NHANES II) conducted by the National Center for Health Statistics, 4-nitrophenol was quantifiable in 2.4% of the samples, with a high value of 143 µg/L and a geometric mean value of less than 10 µg/L. 4-Nitrophenol originated in the urine from the pesticides methyl and ethyl parathion (Carey and Kutz 1985; Kutz 1983). Based on concerns about unacceptable risk of exposure, EPA intends to issue a Notice of Intent to Cancel (NOIC) the use of parathion on field crops (EPA 1991).

A National Occupational Exposure Survey (NOES) conducted by NIOSH from 1981 to 1983 estimated that 2,155 workers, including 1,553 female workers, are potentially exposed to 4-nitrophenol in the United States (NIOSH 1989). The NOES database does not contain data on the frequency, duration, concentration or route of exposure of workers to 4-nitrophenol. This survey provides only estimates of the number of workers potentially exposed to 4-nitrophenol in the workplace. No reports of actual measured exposure levels under any occupational situation were found in the literature.

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Besides workers involved in the manufacture or use of 2-nitrophenol and 4-nitrophenol and applicators of certain pesticides, members of the general population who live near landfill sites that contain these compounds may be exposed to the compounds at higher than background levels via inhalation. Children playing in and around these landfill sites may be exposed dermally. Another sector of the general population, those in agricultural areas that use parathion and related pesticides for crop protection, may be exposed to 4-nitrophenol at higher than background levels via the consumption of drinking water from groundwater and possibly via the consumption of foods. No experimental data either on background levels of human exposure from any route or evidence of higher than background levels of exposure were found in the literature.

5.7 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 2-nitrophenol and 4-nitrophenol is available. Where

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adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of 2-nitrophenol and 4-nitrophenol.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met, would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

5.7.1 Data Needs

Physical and Chemical Properties. As can be seen from Table 3-2, the physical and chemical properties of 2-nitrophenol and 4-nitrophenol have been sufficiently characterized to permit estimation of its environmental fate. However, there are considerable variations in the reported values of some of the physical data, such as water solubility and vapor pressure, in the literature. Knowledge of more accurate vapor pressure and water solubility data are important in predicting the volatility of the nitrophenols from water and soil.

Production, Import/Export, Use, and Disposal. No data on the production volume for 2-nitrophenol in the United States were available in the literature. The availability of this data is important because the risk of human exposure to a chemical is often related to its production volume. The import/export data for these chemicals are known (CMR 1987; EPA 1985). The data on usage (CMR 1987; HSDB 1989) indicates that the potential for general population exposure to nitrophenols from consumer products or the environment is low. More detailed site- and medium-specific (e.g., air, water, or soil) release data than given in Table 5-1 are necessary to assess the potential for exposure to these compounds from different sources.

According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The Toxic Release Inventory (TRI), which contains this information for 1987, became available in May of 1989. This database is updated yearly and should provide a list of industrial production facilities and emissions.

Although some data are available on the methods of disposal of these compounds (HSDB 1989; OHM/TADS 1989), more data are needed to assess the impact of disposal on the possible levels of human exposure.

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Environmental Fate. Data in the existing literature are sufficient to allow assessment of the environmental fate of 4-nitrophenol in water and soil. Data on 2-nitrophenol are sparse (see Section 5.1). More data are needed to assess the fate of these compounds in air with more confidence. Based on the compounds' photolytic behavior in water (see Section 5.3.2.2), direct photolysis in air is expected to be the primary fate process in air. 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 located regarding absorption of 2-nitrophenol and 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 (see Section 2.3.1) 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.

Food Chain Bioaccumulation. Although some data on bioconcentrations of these chemicals in edible aquatic organisms and transfer of the chemicals from soil to edible plants are available (see Section 5.3.1), it has not yet been firmly established whether food chain bioaccumulation occurs. There is also a lack of data on plant-to-animal transfer. Data on the biomagnification of these chemicals in the food chain are scant. Significant food chain bioaccumulation would indicate the possibility of significant human exposure to these chemicals from the consumption of aquatic and terrestrial foods.

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. The levels of 4-nitrophenol in the urine of the general population are known (Carey and Kutz 1985; Kutz 1983). However, the data are outdated and need to be updated to establish contemporary background levels of this compound in human urine. The levels of

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4-nitrophenol in other body tissues of the general population (although its levels in the plasma of parathion sprayers have been determined) are not known, possibly because of its quick excretion from the body. The level of 2-nitrophenol in any body tissue or fluid has not yet been determined (Piotrowski 1967). No data on the levels of either compound in any body tissue or fluid for populations living near hazardous waste sites are available.

Exposure Registries. No exposure registries for 2-nitrophenol or 4-nitrophenol were located. This compound is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. This compound will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to the exposure to this compound.

5.7.2 On-going Studies

No on-going studies regarding the environmental fate, environmental levels, food chain bioaccumulation, or exposure levels in humans for either 2-nitrophenol or 4-nitrophenol were found in the literature.

As part of the Third National Health and Nutrition Evaluation Survey (NHANES III), the Environmental Health Laboratory Sciences Division of the Center for Environmental Health and Injury Control, Centers for Disease Control, will be analyzing human urine samples for 2-nitrophenol and 4-nitrophenol and other phenolic compounds. These data will give an indication of the frequency of occurrence and background levels of these compounds in the general population.

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting and/or measuring and monitoring 2-nitrophenol and 4-nitrophenol in environmental media and in biological samples. The intent is not to provide an exhaustive list of analytical methods that could be used to detect and quantify 2-nitrophenol and 4-nitrophenol. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used to detect 2-nitrophenol and 4-nitrophenol in environmental samples are the methods approved by federal agencies such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that refine previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

6.1 BIOLOGICAL MATERIALS

The analytical methods for determining nitrophenol in biological matrices are given in Table 6-1. The methods for handling biological samples are given by Fatiadi (1984). No promulgations concerning methods officially approved for use by federal or private trade groups could be located for 2-nitrophenol or 4-nitrophenol. All the methods presented in Table 6-1 are for determining 4-nitrophenol in plasma or urine. Since 4-nitrophenol is a well known urinary metabolite in parathion-exposed subjects (Kirby et al. 1979), it is not surprising that the methods attempt to quantify 4-nitrophenol. However, there is no reason to believe that the methods applicable to 4-nitrophenol will not be applicable to 2-nitrophenol. The detection limit and accuracy will change for the two isomers for the same method (Section 6.2). The nitrophenols are not very volatile, and the determination of these compounds by GC usually requires derivatization to more volatile products. On the other hand, determination of these compounds by HPLC does not require derivatization. Among the commonly used methods, GC with electron capture detection of fluorinated derivatives using heptafluorobutyric anhydride is probably the most sensitive method (Kirby et al. 1979). Other less commonly used methods, such as the Hall electroconductivity detector (HECD), dropping-mercury electrode, pulse polarography, and an enzymatic procedure are given by Fatiadi (1984) and Kirby et al. (1979).

4-Nitrophenol is excreted in urine entirely as glucuronide and sulfate conjugates (Fatiadi 1984). The sequential analysis of hydrolyzed (enzymatically or by acid) and unhydrolyzed urine provides a measure of the conjugated and unconjugated levels of the compound. Derivatization subsequent to acid hydrolysis of urine and quantification by gas chromatography with electron capture detection provides one of the most sensitive methods for 4-nitrophenol (Fatiadi 1984).

TABLE 6-1. Analytical Methods for Determining 2-Nitrophenol and 4-Nitrophenol in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Urine	Acid hydrolysis, extraction, derivatization, silica gel chromatography (for 4-NP)	GC-EC	20 µg/L	85-98	Shafik et al. 1973
Urine	Diluted in distilled water (4-NP and its conjugates)	HPLC-UV	no data	>98 (4-NP) >95 (conjugates)	Diamond and Quebbemann 1979
Plasma	Vortexed with methanol and supernatant concentrated (4-NP and its conjugates)	HPLC-UV	no data	>98 (4-NP) >95 (conjugates)	Diamond and Quebbemann 1979
Urine	4-Ethoxynitrobenzene obtained by method of Shafik et al. (1973) reduced and converted to amide by heptafluorobutyric anhydride (4-NP)	GC-EC	10 µg/L	No data	Kirby et al. 1979
Urine	Acid hydrolysis, extraction, and complexation with o-cresol in presence of $TiCl_3$ (4-NP)	spectrophotometric	30 µg in sample	92-100	Fatiadi 1984

GC-EC = gas chromatography-electron capture detection

HPLC-UV = high-pressure liquid chromatography-ultraviolet detection

4-NP = 4-nitrophenol

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6.2 ENVIRONMENTAL SAMPLES

Analytical methods for determining 2-nitrophenol and 4-nitrophenol in environmental samples are given in Table 6-2. The handling methods for environmental samples are given in EPA, 1982. The nitrophenols probably exist predominantly in the vapor phase in the air (see Chapter 5.3.1), but small amounts of both compounds have been detected in the particulate phase (Leuenberger et al. 1985; Nojima et al. 1983). Therefore, the best method for collecting nitrophenols in air is to use an air sampler that uses glass-fiber filters to collect the particulate matter, followed by adsorption cartridges for trapping the volatile components (Leuenberger et al. 1985). Methods that are designed for multicomponent analysis use sample extraction with organic solvent(s) under both acidic and basic conditions. Nitrophenols, being acidic, are found in the acidic extract. In a recent evaluation of the EPA-approved method 625, a single continuous extraction at pH 2 was most efficient for determining both acidic and basic/neutral components in a sample. Additionally, the use of fused silica capillary columns may enhance both the efficiency and detection limits of various components, including nitrophenols, in multicomponent analytical methods such as the EPA method 625 (Valkenburg et al. 1989).

Among the commonly used methods, GC with electron capture detection of the heptafluorobutyryl derivative provides the greatest sensitivity. However, the GC-MS method has the most versatility and is more suitable where multicomponent analysis is required. Several other less commonly used methods are available for determining 2-nitrophenol and 4-nitrophenol in environmental samples. Some of these methods are spectrometric measurement in the presence of crown ethers (Papadoyannis et al. 1983), coulometric measurement with methylviologen radical cation (Lozano et al. 1989), HPLC-surface-enhanced resonance Raman scattering (Ni et al. 1989), GC-FID (flame ionization detector) with a special graphitized carbon black as the GC stationary phase (Mangani et al. 1986), remote fluorescence analysis of ground water with UV lasers and fiber optics (Chudyk et al. 1985), HPLC with diode-array UV-visible - detector (Nielen et al. 1985), and cyclic voltammetric determination by the addition of α -cyclodextrin (Matsue et al. 1981).

6.3 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 2-nitrophenol and 4-nitrophenol is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of 2-nitrophenol and 4-nitrophenol.

TABLE 6-2. Analytical Methods for Determining 2-Nitrophenol and 4-Nitrophenol in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Thermal desorption of cartridge	FSCC-MS/DS	No data	No data	Leuenberger et al. 1985
Air	Extract filter, clean extract, treated with diazomethane and concentrated	GC-MS	No data	No data	Nojima et al. 1983
Waste water	Extract, clean extract, derivatized with pentafluorobenzyl bromide	GC-EC (EPA Method 604)	0.77 µg/L (2-NP) 0.70 µg/L (4-NP)	67 (2-NP) 45 (4-NP)	EPA 1982
Water	Extract, concentrated and mixed with hexadecyltrimethylammonium bromide and K ₂ CO ₃	HPLC-UV	1 µg/L (4-NP)	81-88	Roseboom et al. 1981
Water	Resin sorption, desorption, and concentration	HPLC-UV	0.18 µg/L (for 10 mL)	97.4-105.7	Borys 1981
Water	Sample reacted with iodine monobromide, extract	Absorbance at 240 nm (4-nitrophenol)	3 µg/L	No data	Bosch et al. 1987
Water	Extract, derivatized with heptafluorobutyl anhydride and concentrate	GC-EC	0.01 µg/L (2-NP) 0.01 µg/L (4-NP)	73 (2-NP) 40-43 (4-NP)	Bengtsson 1985
Water	Extract, clean extract, concentrate	GC-MS/DS	1 µg/L (2-NP) 5 µg/L (4-NP)	No data	Sporstoel et al. 1985
Water, waste water	Extract, concentrate	GC-MS (EPA Method 625)	3.6 µg/L (2-NP) 2.4 µg/L (4-NP)	75 both in water and waste water (for 2-NP) 41 in water and 43 in waste water (for 4-NP)	EPA 1982
Sediment/soil	Extract, concentrate, and clean-up	GC-MS (EPA CLP method)	330 µg/kg (2-NP) 1600 µg/kg (4-NP)	No data	EPA 1988b

CLP = contract laboratory program; EC = electron capture detection; FSCC-MS/DS = fused silica capillary, mass spectrometry/data system; GC = gas chromatography; HPLC-UV = high-resolution liquid chromatography - ultraviolet detection; 2-NP = 2-nitrophenol; 4-NP = 4-nitrophenol

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The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met, would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.3.1 Data Needs

Methods for Determining Biomarkers of Exposure and Effect. No biomarker that can be associated quantitatively with exposure to 2-nitrophenol or 4-nitrophenol has been identified (see Section 2.5). If a biomarker for these compounds in a human tissue or fluid were available and a correlation were found to exist between the level of biomarker and exposure/health effect, the biomarker could be used as an indication of health effects caused by the exposure of these chemicals.

No specific effects of 2-nitrophenol or 4-nitrophenol exposure have yet been identified (see Section 2.5.2).

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Analytical methods with good sensitivity and specificity for determining the two compounds in contaminated water and soil are available (see Table 6-2). Dr. Milton Lee of Brigham Young University has recently developed an analytical method for the quantification of femtogram quantities of nitrophenols in air using time-of-flight mass spectrometer (Sin et al. 1991). Besides this method, analytical methods for the determination of low levels of nitrophenols found in ambient air and data on the accuracies, precisions, and sensitivities of such methods are lacking. The levels of these two compounds in drinking water have very rarely been measured. It is not clear whether this limitation in data is due to lack of effort directed to measure the levels, lack of method sensitivity, or the presence of these compounds at extremely low levels. Analytical methods are available for determining most of the final biodegradation and photodegradation products of these compounds (Raymond and Alexander 1971; Sethunathan 1973; Zeyer and Kearney 1984). However, the accuracy and precision of these methods have rarely been established. The intermediate products remain unknown or unidentified in many cases. The levels of the parent compounds in different environmental media can be used to indicate exposure to these compounds by humans through the inhalation of air and ingestion of foods and drinking water, when the typical volume of air inhaled and drinking water consumed daily and the daily average amount and composition of adult total diet samples are known (Gartell et al. 1986). If a correlation between the levels of these compounds in human tissue and the levels of exposure could be found, the exposure levels from different environmental sources could be used to estimate human body burden. Similarly, determining degradation products is important because it may assist in the need for evaluating the toxicity of the products

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and determining the persistence of the parent compound. In instances where the products of an environmental reaction are more toxic than the parent compound, it is important that the level of the degradation products in the environment be known.

6.3.2 On-going Studies

The Environmental Health Laboratory Sciences Division of the Center for Environmental Health and Injury Control, Centers for Disease Control, is developing methods for the analysis of 2-nitrophenol and 4-nitrophenol and other phenolic compounds in urine. These methods use high resolution gas chromatography and magnetic sector mass spectrometry which gives detection limits in the low parts per billion range.

No other on-going studies pertaining to the determination of the nitrophenols in biological or environmental media were found.

7. REGULATIONS AND ADVISORIES

Table 7-1 summarizes national and state regulations and guidelines on human exposure to 2-nitrophenol and 4-nitrophenol.

The Clean Water Effluent Guidelines regulate 2-nitrophenol and 4-nitrophenol for the following industrial point sources: electroplating, organic chemicals production, steam electric power generation, asbestos product manufacturing, timber products processing, metal finishing, paving and roofing, ink formulating, carbon black manufacturing, and electrical and electronic components manufacturing (EPA, 1988a). In addition, 4-nitrophenol is regulated for the following industrial point sources: metal molding and casting, paint formulating, and gum and wood chemicals manufacturing (EPA 1988a).

7. REGULATIONS AND ADVISORIES

TABLE 7-1. Regulations and Guidelines Applicable to 2-Nitrophenol and 4-Nitrophenol

Agency	Description	Information	References
<u>NATIONAL</u>			
a. Water:			
EPA OWRS	Priority pollutant effluent limitations and pretreatment standards for BAT, NSPS and PSES		EPA 1988c (40 CFR 414)
	Maximum for any 1 day (2-nitrophenol)	231 µg/L	
	Maximum monthly average (2-nitrophenol)	65 µg/L	
	Maximum for any 1 day (4-nitrophenol)	576 µg/L	
	Maximum monthly average (4-nitrophenol)	162 µg/L	
b. Other:			
EPA OERR	Reportable quantity, final rule (2-nitrophenol and 4-nitrophenol)	100 lb	EPA 1988d (40 CFR 302.4)
EPA OSW	Designation of Hazardous Substances (mixture)	Yes	EPA 1988e (40 CFR 116.4)
	Listing as hazardous waste: Discarded commercial chemical products off-specification species, container residues, and spill residues thereof (4-nitrophenol)	Yes	EPA 1988f (40 CFR 261.33)
	Listing as Hazardous Waste Constituent (4-nitrophenol)	Yes	EPA 1988f (40 CFR 261, Appendix VIII)
EPA OTS	Toxic Chemical Release Reporting; Community Right-to-Know (2-nitrophenol and 4-nitrophenol)	Yes	EPA 1988g (40 CFR 372.65)
<u>STATE</u>			
Regulations and Guidelines:			
a. Air:	Acceptable ambient air concentrations		
New York (4-nitrophenol)		0.03 µg/m ³ (1 yr avg)	NATICH 1988
South Carolina (4-nitrophenol)		0.00 µg/m ³ (24 hrs)	NATICH 1988
b. Water:	Drinking water quality standards		
Kansas (2-nitrophenol)		290 µg/L	FSTRAC 1988
Kansas (4-nitrophenol)		290 µg/L	FSTRAC 1988
Maine (mixture)		83 µg/L	FSTRAC 1988

BAT = Best Available Technology; EPA = Environmental Protection Agency; NSPS = New Source Performance Standards; OERR = Office of Emergency and Remedial Response; OSW = Office of Solid Waste; OTS = Office of Toxic Substances; OWRS = Office of Water Regulations and Standards; PSES = Pretreatment Standards for Existing Sources

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9. GLOSSARY

Acute Exposure -- Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption Coefficient (K_{oc}) -- The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (K_d) -- The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Bioconcentration Factor (BCF) -- The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Cancer Effect Level (CEL) -- The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen -- A chemical capable of inducing cancer.

Ceiling Value -- A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure -- Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Developmental Toxicity -- The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Embryotoxicity and Fetotoxicity -- Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurred. The terms, as used here, include malformations and variations, altered growth, and in utero death.

EPA Health Advisory -- An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

9. GLOSSARY

Immediately Dangerous to Life or Health (IDLH) -- The maximum environmental concentration of a contaminant from which one could escape within 30 min without any escape-impairing symptoms or irreversible health effects.

Intermediate Exposure -- Exposure to a chemical for a duration of 15-364 days as specified in the Toxicological Profiles.

Immunologic Toxicity -- The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

In vitro -- Isolated from the living organism and artificially maintained, as in a test tube.

In vivo -- Occurring within the living organism.

Lethal Concentration_(Lo) (LC_{Lo}) -- The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration₍₅₀₎ (LC₅₀) -- A calculated concentration of a chemical in air to which exposure or a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose_(Lo) (LD_{Lo}) -- The lowest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals.

Lethal Dose₍₅₀₎ (LD₅₀) -- The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time₍₅₀₎ (LT₅₀) -- A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL) -- The lowest dose of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Malformations -- Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level -- An estimate of daily human exposure to a chemical that is likely to be without an appreciable risk of deleterious effects (noncancerous) over a specified duration of exposure.

9. GLOSSARY

Mutagen -- A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

Neurotoxicity -- The occurrence of adverse effects on the nervous system following exposure to chemical.

No-Observed-Adverse-Effect Level (NOAEL) -- The dose of chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow}) -- The equilibrium ratio of the concentrations of a chemical in n-octanol and water, in dilute solution.

Permissible Exposure Limit (PEL) -- An allowable exposure level in workplace air averaged over an 8-hour shift.

ql* -- The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The ql* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually $\mu\text{g/L}$ for water, mg/kg/day for food, and $\mu\text{g/m}^3$ for air).

Reference Dose (RfD) -- An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the NOAEL (from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ) -- The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are (1) 1 lb or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity -- The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

9. GLOSSARY

Short-Term Exposure Limit (STEL) -- The maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily TLV-TWA may not be exceeded.

Target Organ Toxicity -- This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen -- A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV) -- A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a TWA, as a STEL, or as a CL.

Time-Weighted Average (TWA) -- An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose (TD₅₀) -- A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Uncertainty Factor (UF) -- A factor used in operationally deriving the RfD from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

APPENDIX A

USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in nontechnical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or substance release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the substance.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-1, 2-2, and 2-3) and figures (2-1 and 2-2) are used to summarize health effects by duration of exposure and endpoint and to illustrate graphically levels of exposure associated with those effects. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed- Adverse-Effect Levels (LOAELs) for Less Serious and Serious health effects, or Cancer Effect Levels (CELs). In addition, these tables and figures illustrate differences in response by species, Minimal Risk Levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper-bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. The LSE tables and figures can be used for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text.

The legends presented- below demonstrate the application of these tables and figures. A representative example of LSE Table 2-1 and Figure 2-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 2-1

- (1). Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exist,

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three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-1) and oral (LSE Figure 2-2) routes.

- (2). Exposure Duration Three exposure periods: acute (14 days or less); intermediate (15 to 364 days); and chronic (365 days or more) are presented within each route of exposure. In this example, an inhalation study of intermediate duration exposure is reported
- (3). Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table.
- (4). Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to define a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in Figure 2-1).
- (5). Species The test species, whether animal or human, are identified in this column.
- (6). Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to [substance x] via inhalation for 13 weeks, 5 days per week, for 6 hours per day.
- (7). System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated in this study.
- (8). NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote ``c'').
- (9). LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest exposure level used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose, A brief description of the specific end point used to

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quantify the adverse effect accompanies the LOAEL. The "Less Serious" respiratory effect reported in key number 18 (hyperplasia) occurred at a LOAEL of 10 ppm.

- (10). Reference The complete reference citation is given in Chapter 8 of the profile.
- (11). CEL A Cancer Effect Level (GEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiological studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses which did not cause a measurable increase in cancer.
- (12). Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "c" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND**See LSE Figure 2-1**

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure levels for particular exposure duration.

- (13). Exposure Duration The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.
- (14). Health Effect These are the categories of health effects for which reliable quantitative data exist. The same health effects appear in the LSE table.
- (15). Levels of Exposure Exposure levels for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure levels are reported on the log scale "y" axis. Inhalation exposure is reported in mg/m³ or ppm and oral exposure is reported in mg/kg/day.
- (16). NOAEL In this example, 18r NOAEL is the critical end point for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates a NOAEL for the test species (rat). The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).
- (17). CEL Key number 38r is one of three studies for which Cancer Effect Levels (CELs) were derived. The diamond symbol refers to a CEL for the test species (rat). The number 38 corresponds to the entry in the LSE table.

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- (18). Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q1*).
- (19). Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

SAMPLE

1 → TABLE 2-1. Levels of Significant Exposure to [Chemical x] - Inhalation

Key to figure ^a	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect)		Reference
					Less serious (ppm)	Serious (ppm)	
2 →	INTERMEDIATE EXPOSURE						
3 →	Systemic	5	6	7	8	9	10
4 →	18	Rat	13 wk 5d/wk 6hr/d	Resp	3 ^b	10 (hyperplasia)	Nitschke et al. 1981
<hr style="border-top: 1px dashed black;"/>							
CHRONIC EXPOSURE							
Cancer							
38	Rat	18 mo 5d/wk 7hr/d				11 20 (CEL, multiple organs)	Wong et al. 1982
39	Rat	89-104 wk 5d/wk 6hr/d				10 (CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79-103 wk 5d/wk 6hr/d				10 (CEL, lung tumors, hemangiosarcomas)	NTP 1982

^a The number corresponds to entries in Figure 2-1.

12 → ^b Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5×10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

CEL = cancer effect level; d = day(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

SAMPLE

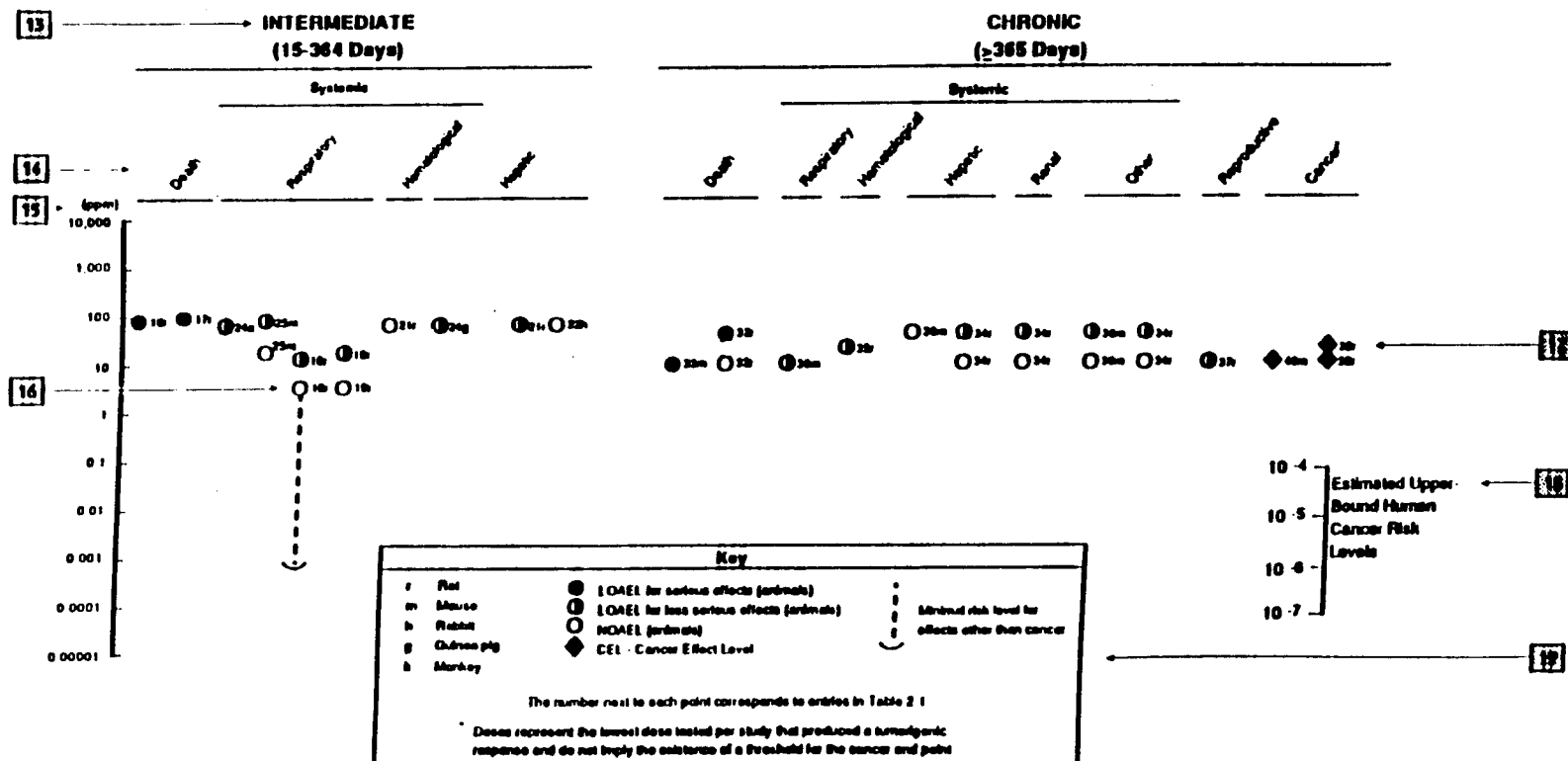


FIGURE 2-1. Levels of Significant Exposure to [Chemical X]-Inhalation

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Chapter 2 (Section 2.4)**Relevance to Public Health**

The Relevance to Public Health section provides a health effects summary based on evaluations of existing toxicological, epidemiological, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions.

1. What effects are known to occur in humans?
2. What effects observed in animals are likely to be of concern to humans?
3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The section discusses health effects by end point. Human data are presented first, then animal data. Both are organized by route of exposure (inhalation, oral, and dermal) and by duration (acute, intermediate, and chronic). In vitro data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this section. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. MRLs for noncancer end points if derived, and the end points from which they were derived are indicated and discussed in the appropriate section(s).

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Identification of Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information was available, MRLs were derived. MRLs are specific for route (inhalation or oral) and duration (acute, intermediate, or chronic) of exposure. Ideally, MRLs can be derived from all six exposure scenarios (e.g., Inhalation - acute, -intermediate, -chronic; Oral - acute, -intermediate, -chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a substance emission, given the concentration of a contaminant in air or the estimated daily dose received via food or water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

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MRL. users should be familiar with the toxicological information on which the number is based. Section 2.4, "Relevance to Public Health," contains basic information known about the substance. Other sections such as 2.6, "Interactions with Other Chemicals" and 2.7, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology used by the Environmental Protection Agency (EPA) (Barnes and Dourson, 1988; EPA 1989a) to derive reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential effects (e.g., systemic, neurological, and developmental). In order to compare NOAELs and LOAELs for specific end points, all inhalation exposure levels are adjusted for 24hr exposures and all intermittent exposures for inhalation and oral routes of intermediate and chronic duration are adjusted for continuous exposure (i.e., 7 days/week). If the information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. The NOAEL is the most suitable end point for deriving an MRL. When a NOAEL is not available, a Less Serious LOAEL can be used to derive an MRL, and an uncertainty factor (UF) of 10 is employed. MRLs are not derived from Serious LOAELs. Additional uncertainty factors of 10 each are used for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the adjusted inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

APPENDIX B

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BSC	Board of Scientific Counselors
CDC	Centers for Disease Control
CEL	Cancer Effect Level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
CLP	Contract Laboratory Program
cm	centimeter
CNS	central nervous system
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DOL	Department of Labor
ECG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
EKG	see ECG
FAO	Food and Agricultural Organization of the United Nations
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
f ₁	first generation
fpm	feet per minute
ft	foot
FR	Federal Register
g	gram
GC	gas chromatography
HPLC	high performance liquid chromatography
hr	hour
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
Kd	adsorption ratio
kg	kilogram
Koc	octanol-soil partition coefficient
Kow	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC _{Lo}	lethal concentration low
LC ₅₀	lethal concentration 50 percent kill
LD _{Lo}	lethal dose low
LD ₅₀	lethal dose 50 percent kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter

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mg	milligram
min	minute
mL	milliliter
mm	millimeters
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectroscopy
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
nm	nanometer
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPL	National Priorities List
NRC	National Research Council
NTIS	National Technical Information Service
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportional mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
RfD	Reference Dose
RTECS	Registry of Toxic Effects of Chemical Substances
sec	second
SCE	sister chromatid exchange
SIC	Standard Industrial Classification
SMR	standard mortality ratio
STEL	short-term exposure limit
STORET	<u>STORAGE</u> and <u>RETRIEVAL</u>
TLV	threshold limit value
TSCA	Toxic Substances Control Act
TRI	Toxic Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
WHO	World Health Organization
>	greater than
≥	greater than or equal to

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=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
δ	delta
γ	gamma
μm	micron
μg	microgram

APPENDIX C

PEER REVIEW

A peer review panel was assembled for 2- and 4-nitrophenol. The panel consisted of the following members: Dr. Martin Alexander, Professor, Department of Agronomy, Cornell University, Ithaca, New York; Dr. Gary Booth, Professor, Department of Zoology, Brigham Young University; Dr. Samuel Cohen, Professor and Vice Chair, Department of Pathology and Microbiology, University of Nebraska Medical Center, Omaha, Nebraska; Dr. Loren Koller, Professor and Dean, College of Veterinary Medicine, Oregon State University, Corvallis, Oregon; and Dr. Frederick Oehme, Director, Comparative Toxicology Laboratories, Kansas State University, Manhattan, Kansas. These experts collectively have knowledge of 2- and 4-nitrophenol's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in the Comprehensive Environmental Response, Compensation, and Liability Act of 1986, Section 104.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

