

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 methyl mercaptan 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 methyl mercaptan based on toxicological studies and epidemiological investigations.

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 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.

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Although methods have been established to derive these levels (Barnes et al. 1988; EPA 1989b), 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 effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

2.2.1 Inhalation Exposure

Very little information is available on the health effects in humans or experimental animals after inhalation exposure to methyl mercaptan. Most studies of occupational exposure to methyl mercaptan in the pulp industry also involve exposure to other sulfur-containing compounds such as hydrogen sulfide, dimethyl sulfide, and sulfur dioxide as well as to methyl mercaptan (Kangas et al. 1984).

2.2.1.1 Death

A single case of death resulting from occupational exposure to methyl mercaptan has been located. A 53-year-old Black male laborer worked for about 1 week emptying tanks containing methyl mercaptan. No details of exposure level were available; however, it is assumed that both inhalation and dermal exposure were probably involved. The man was hospitalized in a coma, developed hemolytic anemia and methemoglobinemia, and died 28 days after admission (Shults et al. 1970). The immediate cause of death was determined to be a massive embolus that occluded both main pulmonary arteries.

An LC₅₀ of 675 ppm was reported for male and female rats exposed to methyl mercaptan for 4 hours (Tansy et al. 1981). However, no deaths (0/10) occurred in rats exposed to 400 ppm for 4 hours, and there was 100% mortality at 700 ppm and above. These authors also reported that no mortality was observed in male rats exposed to methyl mercaptan at doses up to 57 ppm for 3 months.

The highest NOAEL values and an LC₅₀ for rats in each duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.2 Systemic Effects

Based on the available information, effects on body weight are the only systemic effects that can be clearly associated with inhalation exposure to methyl mercaptan. No studies were located regarding musculoskeletal effects in humans or animals after inhalation exposure to methyl mercaptan.

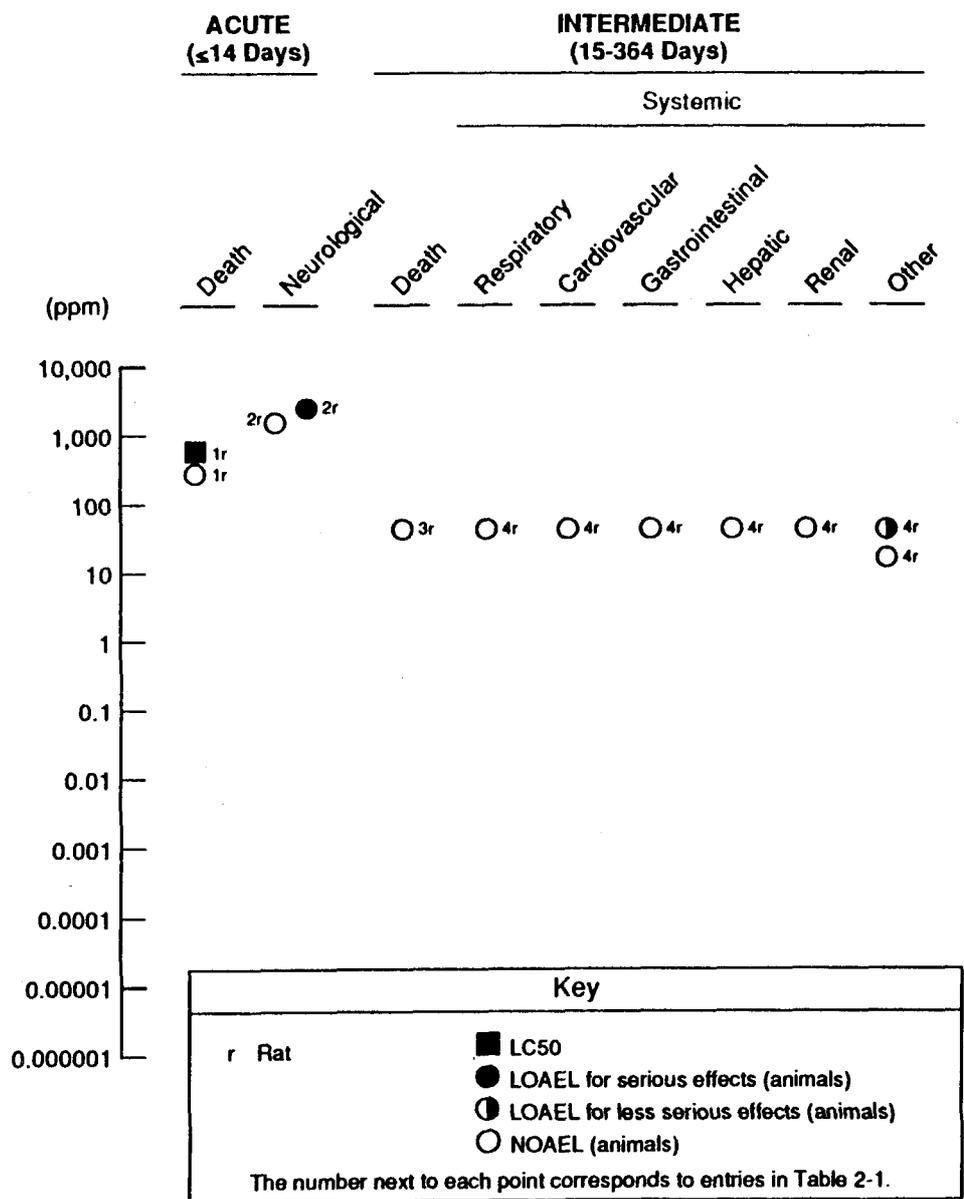
TABLE 2-1. Levels of Significant Exposure to Methyl Mercaptan - Inhalation

Key to figure ^a	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect)		Reference
					Less serious (ppm)	Serious (ppm)	
ACUTE EXPOSURE							
Death							
1	Rat	1 d 4hr/d		400		675 (LC50)	Tansy et al. 1981
Neurological							
2	Rat	1 d 15 min		1200		1400 (coma)	Zieve et al. 1984
INTERMEDIATE EXPOSURE							
Death							
3	Rat	3 mo 5d/wk 7hr/d		57			Tansy et al. 1981
Systemic							
4	Rat	3 mo 5d/wk 7hr/d	Resp Cardio Gastro Hepatic Renal Other	57 57 57 57 57 17	57 (decreased body weight)		Tansy et al. 1981

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

Cardio = Cardiovascular; d = day(s); Gastro = Gastrointestinal; hr = hour(s); LC50 = lethal concentration, 50% mortality; LOAEL = lowest-observed-adverse-effect level; min = minute(s); mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = Respiratory; wk = week(s)

FIGURE 2-1. Levels of Significant Exposure to Methyl Mercaptan – Inhalation



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A NOAEL and a reliable LOAEL for systemic effects in rats in the intermediate-duration category are recorded in Table 2-1 and plotted in Figure 2-1.

Respiratory Effects. No studies have been located that would be useful in assessing the potential effects on the respiratory system in humans breathing methyl mercaptan. Irritation of mucous membranes of the nose and respiratory tract have been reported by workers exposed to mercaptans in general (Key et al. 1977).

No compound-related histopathological changes were observed in the lungs of male rats exposed to methyl mercaptan at doses up to 57 ppm, 7 hours/day, 5 days/week, for 3 months (Tansy et al. 1981).

Cardiovascular Effects. Increased pulse rate and blood pressure were reported by Shults et al. (1970) in a 53-year-old comatose patient who had been working with tanks of methyl mercaptan. Exposure level data were not available.

No histopathological changes were found in the hearts of male rats exposed to methyl mercaptan at levels up to 57 ppm, 7 hours/day, 5 days/week, for 3 months (Tansy et al. 1981).

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans after inhalation exposure to methyl mercaptan.

No evidence of histopathological changes was found in the small intestines of male rats exposed to methyl mercaptan at levels up to 57 ppm, 7 hours/day, 5 days/week, for 3 months (Tansy et al. 1981). Intestinal transit performance, as measured by the amount of small intestine traversed in 30 minutes, was not found to be affected by exposure in this study. There was, however, a statistically significant dose-related decrease in the length of the small intestines at 17 ppm and above. However, the clinical significance of this observation is not clear, and it is not viewed as a serious adverse effect.

Hematological Effects. The only information on hematologic effects resulting from human inhalation and presumably dermal exposure to methyl mercaptan is a case report by Shults et al. (1970). A Black 53-year-old worker who had been handling and emptying tanks of methyl mercaptan for about 1 week became comatose and developed methemoglobinemia and hemolytic anemia before his death. After transfusions, these conditions were reversed. The authors postulated that the hemolysis may have been due to the oxidant effect of methyl mercaptan on erythrocytes in a person who was deficient in glucose-6-phosphate dehydrogenase (G-6-PD). An inherited deficiency of this

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enzyme may be common in American Blacks (Calabrese 1986; Goldstein et al. 1974; Shannon and Buchanan 1982). This worker was found to have some degree of G-6-PD deficiency (Shults et al. 1970).

No studies were located regarding hematological effects in animals after inhalation exposure to methyl mercaptan.

Hepatic Effects. No studies were located regarding hepatic effects in humans after inhalation exposure to methyl mercaptan.

In male rats exposed to methyl mercaptan at levels up to 57 ppm, 7 hours/day, 5 days/week, for 3 months, no compound-related histopathologic changes of the liver were noted (Tansy et al. 1981). The authors stated that results of blood chemistry studies (i.e., increased total protein with decreased serum albumin) were suggestive of liver damage, but that dehydration could not be ruled out as the cause.

Renal Effects. No studies were located regarding renal effects in humans after inhalation exposure to methyl mercaptan. Shults et al. (1970) reported that bilateral polycystic kidneys were found during the autopsy of a 53-year-old man who died after working with tanks of methyl mercaptan. However, it is possible that this was a pre-existing condition.

No compound-related histopathologic changes in the kidneys of male rats exposed to methyl mercaptan at levels up to 57 ppm, 7 hours/day, 5 days/week, for 3 months (Tansy et al. 1981).

Dermal/Ocular Effects. Irritation of the skin and eyes have been reported by workers occupationally exposed to mercaptans in general (Key et al. 1977). However, there is no available information that is specifically related to methyl mercaptan.

No studies were located regarding dermal or ocular effects in animals after inhalation exposure to methyl mercaptan.

Other Systemic Effects. No studies were located regarding other systemic effects in humans after inhalation exposure to methyl mercaptan. Male rats exposed to methyl mercaptan at 57 ppm for 7 hours/day, 5 days/week, for 3 months had significantly decreased body weights (Tansy et al. 1981). This effect was not observed in rats exposed to 17 ppm and below. Decreased levels of food consumption were not observed in rats in the 57-ppm dose group.

2.2.1.3 Immunological Effects

No studies were located regarding immunological effects in humans or animals after inhalation exposure to methyl mercaptan.

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2.2.1.4 Neurological Effects

The only available information on neurological effects in humans exposed to methyl mercaptan via inhalation is from a case study by Shults et al. (1970). A 53-year-old man went into an irreversible coma after emptying tanks of methyl mercaptan for about 1 week. Levels of exposure were not estimated. The authors also noted minimal movement in response to painful stimuli, hypoactivity of all deep tendon reflexes, and seizure activity. The patient died about one month after the onset of this coma.

Fifteen-minute exposures to methyl mercaptan at 1,400 ppm have been found to result in lethargy or coma in rats (Zieve et al. 1974). Exposures to 1,200 ppm and below did not result in either of these conditions. A methyl mercaptan concentration of 0.5 nmol/mL in the blood was identified as the level associated with coma. This study also demonstrated that the doses of intraperitoneally injected ammonium acetate or sodium octanoate needed to induce hepatic coma (coma following acute necrosis of the liver) were greatly reduced when animals were exposed to methyl mercaptan at 1,200 ppm within 1 minute after injection. (However, hepatic effects were not actually demonstrated in this study.) The authors suggested that methyl mercaptan exposure may intensify the toxic effects of ammonia and fatty acids in human hepatic failure.

These values are recorded in Table 2-1 and plotted in Figure 2-1.

No studies were located regarding the following health effects in humans or animals after inhalation exposure to methyl mercaptan:

- 2.2.1.5 Developmental Effects
- 2.2.1.6 Reproductive Effects
- 2.2.1.7 Genotoxic Effects
- 2.2.1.8 Cancer
- 2.2.2 Oral Exposure

No studies were located regarding the following health effects in humans or animals after oral exposure to methyl mercaptan:

- 2.2.2.1 Death
- 2.2.2.2 Systemic Effects
- 2.2.2.3 Immunological Effects
- 2.2.2.4 Neurological Effects
- 2.2.2.5 Developmental Effects
- 2.2.2.6 Reproductive Effects
- 2.2.2.7 Genotoxic Effects
- 2.2.2.8 Cancer

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2.2.3 Dermal Exposure

Occupational exposure as reported in the case study by Shults et al. (1970) may have involved dermal exposure since the victim's wife noted a repugnant odor on his clothes; however, there is not enough information to assess this possibility.

No studies were located regarding the following health effects in humans or animals after dermal exposure to methyl mercaptan:

- 2.2.3.1 Death
- 2.2.3.2 Systemic Effects
- 2.2.3.3 Immunological Effects
- 2.2.3.4 Neurological Effects
- 2.2.3.5 Developmental Effects
- 2.2.3.6 Reproductive Effects
- 2.2.3.7 Genotoxic Effects
- 2.2.3.8 Cancer
- 2.2.4 Other Routes of Exposure

Because the available data on the toxicity of methyl mercaptan via inhalation, oral, or dermal exposure are extremely limited, studies conducted via intraperitoneal exposure have also been considered. These studies are also limited in number and scope, and serve only to provide additional evidence that coma is associated with exposure to this chemical.

2.2.4.1 Death

No information is available on the levels of methyl mercaptan administered to animals via intraperitoneal injection that would result in death. Studies described in Section 2.2.4.4 have resulted in coma in the test animals; however, recovery and/or death in response to these injections were not among the topics of investigation.

2.2.4.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, or dermal/ocular effects in humans or animals after intraperitoneal exposure to methyl mercaptan.

2.2.4.3 Immunological Effects

No studies were located regarding immunological effects in humans or animals after intraperitoneal exposure to methyl mercaptan.

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2.2.4.4 Neurological Effects

Two studies that investigated the neurological effects of intraperitoneal administration of methyl mercaptan have been located. An injection equivalent to 4.8 mg/kg was sufficient to induce coma in 100% of treated rats in 2-4 minutes (Zieve et al. 1984). In germ-free rats administered methyl mercaptan at 9.6-28.8 mg/kg, 200 nmol/mL was the minimum blood concentration associated with coma (Al Mardini et al. 1984). It is interesting to note that this level was much higher than the blood level of 0.5 nmol/mL in comatose rats reported by Zieve et al. (1974) in inhalation studies.

In addition, an important observation was made by Al Mardini et al. (1984) who reported that blood methyl mercaptan concentrations were significantly higher in patients with hepatic encephalopathy (coma) than in normal subjects or patients with liver disease without encephalopathy. (Methyl mercaptan was not administered to any of these persons, but presumably resulted from the endogenous breakdown of methionine.) Methyl mercaptan concentrations were also higher (but not significantly) in the blood of liver disease patients without encephalopathy than in normal subjects. These findings, combined with the observations of Zieve et al. (1974) in rats with liver damage from ammonium ion or octanoate (Section 2.2.1.4), suggest that persons with existing liver damage may already have elevated blood levels of methyl mercaptan and thus may be at greater risk for the neurological effects of exposure to exogenous methyl mercaptan than would be persons with normal livers.

No studies were located regarding the following health effects in humans or animals after intraperitoneal exposure to methyl mercaptan:

2.2.4.5 Developmental Effects

2.2.4.6 Reproductive Effects

2.2.4.7 Genotoxic Effects

2.2.4.8 Cancer

2.3 TOXICOKINETICS

The only studies located on the toxicokinetics of methyl mercaptan have been conducted via the intraperitoneal route. There is indirect evidence of absorption of methyl mercaptan by humans in a human case study and by rats in a toxicity study.

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

Based on adverse effects (hemolysis, methemoglobinemia, coma, and death) reported in a 53-year-old worker exposed to methyl mercaptan via inhalation

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(Shults et al. 1970) and on the induction of coma in rats exposed to 1,400 ppm (Zieve et al. 1974), it can be inferred that absorption occurs via this route of exposure. No other data are available.

2.3.1.2 Oral Exposure

No studies were located regarding absorption in humans or animals after oral exposure to methyl mercaptan.

2.3.1.3 Dermal Exposure

No studies were located regarding absorption in humans or animals after dermal exposure to methyl mercaptan.

2.3.2 Distribution

No studies were located regarding distribution in humans or animals after exposure to methyl mercaptan via the following routes:

2.3.2.1 Inhalation Exposure

2.3.2.2 Oral Exposure

2.3.2.3 Dermal Exposure

2.3.2.4 Other Routes of Exposure

After injection of ^{14}C - or ^{35}S -labeled methyl mercaptan into rats, distribution of the radioactivity that remained in the body (from either the ^{14}C or ^{35}S label) after 6 hours was: 22.7% in plasma proteins, 17.8% in the liver, 16.7% in the intestinal mucosa, 11.5% in the lungs, 11.4% in the kidneys, 9.8% in the spleen, 8.5% in the testes, and 0% in the erythrocytes (Canellakis and Tarver 1953). No other information on the distribution of methyl mercaptan was located.

2.3.3 Metabolism

Information on the metabolism of methyl mercaptan is available only in studies in rodents using intraperitoneal administration. Susman et al. (1978) injected methyl mercaptan into one mouse and found the unchanged compound and dimethyl sulfide in the expired breath.

In rats, intraperitoneal administration of methyl mercaptan resulted in the excretion of CO_2 and volatile sulfur-containing compounds in the expired breath (Canellakis and Tarver 1953). The ^{35}S from labeled methyl mercaptan in injected rats could be found mostly (94%) as $^{35}\text{SO}_4$ in urine (Derr and Draves 1983, 1984).

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Methyl mercaptan is an intermediate in the catabolism of the amino acid methionine (Blom et al. 1988, 1989). These in vitro studies were conducted with the blood of methionine-loaded patients and with human and rat hepatocytes. Blom and Tangerman (1988) found that, in whole blood, methyl mercaptan is oxidized by the erythrocytes, the carbon-sulfur bond is split, and the resulting products are formic acid, sulfite ion, and sulfate ion.

2.3.4 Excretion

No studies were located regarding excretion by humans or animals after exposure to methyl mercaptan via the following routes:

2.3.4.1 Inhalation Exposure

2.3.4.2 Oral Exposure

2.3.4.3 Dermal Exposure

2.3.4.4 Other Routes of Exposure

The only information available on the excretion of methyl mercaptan or its metabolites is found in studies in rats conducted via intraperitoneal administration. Within 6 hours after administration of ^{14}C -methyl mercaptan, more than 40% of the administered ^{14}C was recovered as CO_2 (presumed to result solely from pulmonary excretion) (Canellakis and Tarver 1953). Another 6.4% was excreted in 1 hour in volatile sulfur compounds (route not stated), and 2.3% was excreted in the urine within 6 hours. Within 8 hours after administration of ^{35}S -methyl mercaptan, 32% of the administered ^{35}S was recovered in sulfur compounds (mostly sulfates) in the urine. Derr and Draves (1983), however, found that within 21 hours, 94% of the ^{35}S -label of ^{35}S -methyl mercaptan intraperitoneally administered to rats was excreted in the urine. No data on fecal excretion have been located.

2.4 RELEVANCE TO PUBLIC HEALTH

As discussed in Section 2.2, estimates of levels of exposure to methyl mercaptan posing minimal risk to humans (MRLs) were to have been made, where data were believed reliable, for the most sensitive noncancer effect for each route and exposure duration. However, no MRLs could be derived for methyl mercaptan. Available data on effects of acute-duration inhalation exposure to methyl mercaptan in humans or animals suggests that neurological effects may be the most sensitive indicator of toxicity, but this information does not reliably identify the threshold for this effect. Available data on effects of intermediate-duration inhalation exposure to methyl mercaptan in animals does not identify the most sensitive effect or the threshold for adverse effects. No data were located on effects of chronic-duration inhalation exposure to methyl mercaptan in humans or animals. Therefore, no inhalation MRLs were derived. No data were located on effects of acute-duration, intermediate duration, or chronic-duration oral exposure to methyl mercaptan in humans or

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animals, Therefore, no oral MRLs were derived. Acute-duration, intermediate duration, and chronic-duration dermal MRLs were not derived for methyl mercaptan due to the lack of an appropriate methodology for the development of dermal MRLs.

The observations in a single human case study, combined with the results of studies in animals, suggest that the principal health risk associated with short-term exposure to high levels of methyl mercaptan is coma. Hematological effects such as hemolytic anemia and methemoglobinemia may also result, but there is less information on this topic. In total, the available database on this chemical is so limited that the relevance of methyl mercaptan exposure to public health cannot be determined.

Death. The accidental death of a 53-year-old worker who had been handling tanks of methyl mercaptan for 1 week was reported by Shults et al. (1970). After a month in a coma and despite aggressive medical intervention, the patient died from a massive embolus that occluded both main pulmonary arteries. The exposure level was not known or estimated. An LC_{50} of 675 ppm was determined for a 4-hour exposure in rats (Tansy et al. 1981). However, no deaths (0/10) occurred at 400 ppm. Exposure to 57 ppm for 3 months also resulted in no deaths in rats. The available data indicate that high level exposure to this substance, at least by inhalation, can be lethal to exposed humans and animals.

Systemic Effects.

Hematological Effects. The major systemic effects reported in the case study of the 53-year-old Black worker who died after acute inhalation exposure to methyl mercaptan were methemoglobinemia and hemolytic anemia (Shults et al. 1970). The authors stated that the observed hemolysis may have been due to oxidant stress to erythrocyte membranes with glucose-6-phosphate dehydrogenase deficiency. In an analysis of hospital data on 14 Black children (aged 3 weeks to 11 years) with hemolytic anemia, 7 of these patients were found to be deficient in glucose-6-phosphate dehydrogenase in an initial screening test (Shannon and Buchanan 1982). Similarly, methemoglobinemia susceptibility has been attributed to this enzyme deficiency (Goldstein et al. 1974). It is obviously not possible to draw firm conclusions from the single case study presented by Shults et al. (1970) with no other studies in humans or animals to provide evidence. However, that study does provide consistent preliminary evidence for the potential for hematological effects resulting from inhalation exposure to methyl mercaptan by an individual who may also be deficient in erythrocytic glucose-6-phosphate dehydrogenase.

Other Systemic effects. The only systemic effect clearly associated with methyl mercaptan in an animal study was a significant decrease in body weight in rats exposed to methyl mercaptan by inhalation at 57 ppm for 3 months (Tansy et al. 1981). This suggests that effects on body weight may be of concern for humans exposed to methyl mercaptan.

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Immunological Effects. There is currently no information in humans or animals to suggest that exposure to methyl mercaptan is associated with immunological effects.

Neurological Effects. The main neurotoxic effect reported in a human exposed to methyl mercaptan at high levels is coma. Shults et al. (1970) reported that a 53-year-old worker who had been working with tanks of methyl mercaptan for about a week went into an irreversible coma accompanied by convulsions and died about 1 month later. Rats exposed via inhalation to methyl mercaptan at 1,400 ppm, but not 1,200 ppm or below, for 15 minutes became lethargic or comatose (Zieve et al. 1974). Intraperitoneal injections of methyl mercaptan in rats can also induce coma (Al Mardini et al. 1984; Zieve et al. 1984). Although this route of administration is not relevant to potential human exposure to this compound, these studies serve to provide additional evidence that neurological effects are a major risk when methyl mercaptan is absorbed by humans.

Developmental Effects. There is currently no information in humans or animals to suggest that exposure to methyl mercaptan is associated with developmental effects, therefore the relevance to human health is not known.

Reproductive Effects. There is currently no information in humans or animals to suggest that exposure to methyl mercaptan is associated with reproductive effects, therefore the relevance to human health is not known.

Genotoxic Effects. There is currently no information in humans or animals to suggest that exposure to methyl mercaptan is associated with genotoxic effects, therefore the relevance to human health is not known.

Cancer. There is currently no information in humans or animals to suggest that exposure to methyl mercaptan is associated with cancer effects, therefore the relevance to human health is not known.

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

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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 methyl mercaptan 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 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 impairment (e.g., DNA adducts). Biomarkers of effects caused by methyl mercaptan 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 Methyl Mercaptan

Methyl mercaptan itself and its metabolites, carbon dioxide and sulfate, can be measured in human tissues, fluid, and excreta. However, these compounds are always present in these media regardless of exposure to methyl mercaptan. Elevated blood levels of methyl mercaptan may be detected in persons who have recently been exposed to it, or in nonexposed persons with liver disease or in hepatic coma (Al Mardini et al. 1984; Challenger and Walshe 1955; Zieve 1981). In cases of liver damage, these elevated levels may be the result, rather than the cause, of liver problems.

The best indication of exposure to methyl mercaptan would probably be a combination of elevated levels of the substance itself in the breath and blood along with evidence or suspicion of exposure from environmental sources. There are currently no subtle or sensitive biomarkers of effects associated with exposure to methyl mercaptan.

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2.5.2 Biomarkers Used to Characterize Effects Caused by Methyl Mercaptan

As stated previously, no subtle or sensitive biomarkers of effects associated with exposure to methyl mercaptan have been identified.

2.6 INTERACTIONS WITH OTHER CHEMICALS

Interactions between mercaptans, including methyl mercaptan, and Ammonium acetate or sodium octanoate in the induction of coma in rats has been reported (Zieve et al. 1974). The dose of intraperitoneally injected ammonium acetate required to induce coma in 50% of the rats was 1.45 mmols without methyl mercaptan exposure but only 0.46 mmols when the animals were exposed to methyl mercaptan via inhalation at 1,200 ppm within 1 minute after the injection. Similarly, the dose of sodium octanoate decreased from 0.48 to 0.16 mmols to induce coma using the same procedures.

The condition induced in these rats was referred to as "hepatic coma" (Zieve et al. 1974) because it was demonstrated in a previous study that injection of an ammonium salt or fatty acid into rats resulted in coma accompanied by massive hepatic necrosis. In the current study of synergism, Zieve et al. (1974), hepatic damage was assumed but not demonstrated, and it is not clear if methyl mercaptan exposure resulted in increased hepatic damage in these rats. These results suggest, however, that human exposure to methyl mercaptan in conjunction with hepatotoxins may result in exacerbated liver damage and/or neurotoxicity. There is a possibility of these multiple exposures in the workplace and in the vicinity of hazardous waste sites.

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A hemolytic response to methyl mercaptan exposure, as reported in the case study by Shults et al. (1970), may be enhanced by the presence of inherited erythrocytic glucose-6-phosphate dehydrogenase (G-6-PD) deficiency. Although hemolysis may occur in any person who is exposed to a sufficiently high dose of methyl mercaptan, this enzyme deficiency may cause some persons to be unusually sensitive, since it results in an inability to maintain reduced glutathione which is needed for the integrity of the erythrocyte membrane (Goldstein et al. 1974). The incidence of the deficiency among Caucasians of European origin is relatively low, whereas there is a higher incidence among certain groups of Asians and Mediterranean (Italians, Sardinians, Greeks), and Middle Eastern populations (Shannon and Buchanan 1982). A study of hemolytic anemia in American Black children with G-6-PD deficiency by Shannon and Buchanan (1982) suggests that this is another population that may be susceptible to the hemolytic effects of methyl mercaptan exposure. Calabrese (1986) estimated that 16% of Black males are G-6-PD-deficient; Berkow et al. (1982) estimated that 10% of American Black

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males and fewer Black females have this deficiency. According to Shannon and Buchanan (1982), a syndrome of acute severe hemolysis following exposure to oxidative stress is associated with the Mediterranean variant of the deficiency, whereas the hemolytic anemia seen in American Blacks is generally mild.

The pattern of inheritance for G-6-PD deficiency is that of an autonomous sex-linked defect (Berkow et al. 1982; Goldstein et al. 1974). This is an X-linked disorder and is thus fully expressed in males who carry it on their single X chromosome and in females who carry it on both X chromosomes. Female heterozygotes (who have one normal and one defective gene for this trait) have a wide variety of values for the enzyme which suggests that other factors influence the degree to which this trait is influenced in identical genotypes (Goldstein et al. 1974).

Studies by Zieve et al. (1974) and Al Mardini et al. (1984) suggest that the major neurological effects of methyl mercaptan exposure (i.e., coma) may occur at lower levels of this compound in persons with liver disease. Methyl mercaptan levels may already be higher than normal in these persons and additional exposure may bring their blood concentrations of this compound to a more dangerous level.

2.8 MITIGATION OF EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to methyl mercaptan. 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 methyl mercaptan. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

Inhalation is the primary route of human exposure to methyl mercaptan, although dermal absorption or ingestion of small amounts in food or water may occur (see Chapter 5). General procedures following acute, high-level exposure to methyl mercaptan consist of measures to reduce or eliminate further absorption. Following inhalation exposure, these measures include removal of the victim and administration of high-flow, humidified oxygen (Bronstein and Currance 1988; Stutz and Janusz 1988). Following dermal and ocular exposure, contaminated clothing is removed and the skin and eyes thoroughly washed with water (Bronstein and Currance 1988; Stutz and Janusz 1988). Procedures used following acute, high-level oral exposure include emptying the stomach, using care to avoid pulmonary aspiration of the gastric contents, particularly in victims with severe nervous system depression or seizures. Stomach emptying is followed by administration of activated charcoal to bind the methyl mercaptan and a cathartic which may stimulate fecal excretion (Stutz and Janusz 1988).

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Supportive measures for symptoms induced by acute, high-level exposure to methyl mercaptan include administration of anticonvulsant drugs to control seizures (Stutz and Janusz 1988) and blood transfusion or alkaline diuresis to alleviate effects of hemolysis (Shannon and Buchanan 1982; Shults et al. 1970). Supportive treatment for noncardiogenic pulmonary edema, central nervous system depression, and hypertension with tachycardia may be required. In patients with methemoglobinemia of approximately 30% or greater methylene blue is administered to reduce methemoglobin levels (Ellenhorn and Barceloux 1988; Goldfrank et al. 1990). However, treatment of G-6-PD deficient individuals with methylene blue may be contraindicated.

Limited information is available regarding the retention in the body or metabolism of methyl mercaptan. Studies in animals demonstrate that carbon dioxide and sulfate are the final metabolites found in the expired breath and/or urine and that methyl mercaptan is cleared from the body within several hours (Canellkiss and Traver 1953; Derr and Draves 1983, 1984; Susman et al. 1978). Studies with human blood indicated that methyl mercaptan is oxidized in erythrocytes yielding formic acid and sulfate ion as metabolites in urine (Blom et al. 1988, 1989; Blom and Tangerman 1988). No method is commonly used to enhance the elimination of the absorbed dose of methyl mercaptan.

Acute intoxication with methyl mercaptan may cause methemoglobinemia, hemolytic anemia and neurological effects leading to lethargy, seizures, coma, and death (see Section 2.2). However, because of the lack of information regarding the mechanism of toxicity of methyl mercaptan, no specific method for reducing its toxic effects is available.

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 methyl mercaptan 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 methyl mercaptan.

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. HEALTH EFFECTS

2.9.1 Existing Information on Health Effects of Methyl Mercaptan

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to methyl mercaptan are summarized in Figure 2-2. The purpose of this figure is to illustrate the existing information concerning the health effects of methyl mercaptan. Each dot in the figure indicates that one or 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 (i.e., data gaps that must necessarily be filled).

Figure 2-2 graphically depicts the information that currently exists on the health effects that have been observed or studied in humans and animals following inhalation, oral, or dermal exposure to methyl mercaptan. There is little information available on this chemical, and, therefore, almost any additional information would probably be useful. This section, however, will attempt to focus on those areas of investigation that would appear to be the most useful for a chemical about which almost nothing is known.

2.9.2 Data Needs

Acute-Duration Exposure. The available information in humans and animals suggests that the nervous system is the major target organ following acute inhalation exposure (Shults et al. 1970; Zieve et al. 1974). However, quantitative data were available in only one study in rats (Zieve et al. 1974) and this was not considered sufficient to calculate an MRL via this route, and no studies conducted via the oral and dermal routes were available. Although any new data for this exposure duration would be useful, estimates of a lethaldose via inhalation would be most helpful, because a human death has been reported as a result of occupational exposure. Currently, LC₅₀ data are available only for the rat (Tansy et al. 1981). Because there are no data on absorption via the oral and dermal route, it is not known if toxicity studies using these routes would be useful.

Intermediate-Duration Exposure. There are no data on humans exposed to methyl mercaptan for this duration period. A 3-month study in rats exposed to methyl mercaptan via inhalation (Tansy et al. 1981) comprises virtually the entire useful database for this compound and indicates that decreased body weight is the only compound-related effect that was observed. Data were not considered sufficient to calculate an inhalation MEL for this exposure duration due to an inadequate database. There are no animal studies using the oral route, and, therefore, an intermediate oral MRL has not been calculated. Any further studies using either of these routes should use doses high enough to elicit clinically evident neurological effects and should focus on hematological effects such as hemolytic anemia and methemoglobinemia. The use of an animal model that is susceptible to these hematological effects may be

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FIGURE 2-2. Existing Information on Health Effects of Methyl Mercaptan

	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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the best choice for these tests. Dose-response information for these effects would be useful in assessing the risks of persons exposed to methyl mercaptan in the vicinity of hazardous waste sites and in the workplace. Studies via the dermal route would also be useful if pharmacologic studies have demonstrated that methyl mercaptan can be absorbed through the skin.

Chronic-Duration Exposure and Cancer. No chronic inhalation, oral, or dermal studies in any species were located for methyl mercaptan. This appears to be the most important category of duration for future study of this compound because low level chronic exposure is likely to occur via the inhalation route in occupational settings and in the vicinity of hazardous waste sites. Although the entire population is exposed via the oral route since methyl mercaptan is naturally present at low levels in certain foods, this compound has not been reported in drinking water. Since the potential for dermal exposure is not known, it is not clear if these studies would be useful.

Evaluations of its carcinogenic potential via the oral and inhalation routes would, therefore, also be useful. Studies using the dermal route would be useful if dermal exposure were first demonstrated to occur in populations living or working in the vicinity of methyl mercaptan emissions.

Genotoxicity. There are currently no genotoxicity data available in humans or animals for methyl mercaptan. A battery of *in vitro* genotoxicity tests would be useful as a preliminary step in determining its mutagenic potential and the need for further testing.

Reproductive Toxicity. There are no available data on the reproductive toxicity of methyl mercaptan in humans or animals via any route. Available data indicate that when intraperitoneally injected into rats, some methyl mercaptan is distributed to the testes (Canellakis and Tarver 1953). Based on this observation, potential effects on reproductive organs and sperm count should be considered in any future intermediate (go-day) or chronic duration studies conducted via any route. Studies via inhalation would probably be the most relevant to assessing the potential effects on the fertility of men exposed in the vicinity of hazardous waste sites or in occupational settings. This information would probably also be useful in the development of MRLs for these durations.

Developmental Toxicity. There are currently no available data on this end point in humans or animals. A study in animals exposed via inhalation would be useful in assessing the potential developmental effects on fetuses carried by women exposed to methyl mercaptan in the vicinity of hazardous waste sites and in occupational settings, since this is expected to be the main route of human exposure.

Immunotoxicity. No studies related to the immunological effects of methyl mercaptan in humans or animals have been located. Immunologic

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assessments such as effects on peripheral white blood cell counts would provide useful preliminary information on this end point, especially as a part of intermediate or chronic duration exposure studies using the inhalation route since this is the most likely route of exposure of persons in the vicinity of hazardous waste sites and in occupational settings.

Neurotoxicity. The available information in humans and animals indicates that high level exposure to methyl mercaptan via inhalation or intraperitoneal injection can result in irreversible coma (Al Mardini et al. 1984; Shults et al. 1970; Tansy et al. 1981; Zieve et al. 1984). Animal studies that describe neurological effects and assess morphological damage to the brain associated with intermediate or chronic duration inhalation exposure to methyl mercaptan at levels similar to those in the vicinity of hazardous waste sites or in occupational settings would be extremely useful, since inhalation is expected to be the main route of human exposure in those settings.

Epidemiological and Human Dosimetry Studies. Occupational exposure to methyl mercaptan, such as occurs in pulp mills, also involves exposure to other sulfur-containing compounds such as hydrogen sulfide, sulfur dioxide, and dimethyl sulfide. Epidemiological studies of such populations may not provide useful data since observed effects may not clearly be attributable to methyl mercaptan. Human dosimetry studies would be useful, however, because measurement of levels of exposure to methyl mercaptan would help to indicate whether humans were at risk for methyl mercaptan-induced effects associated with those levels (assuming that this toxicity information would eventually become available).

Biomarkers of Exposure and Effect. There are no sensitive biomarkers of methyl mercaptan exposure. This would be useful information, especially for the levels of this compound present in the vicinity of hazardous waste sites and in occupational settings. However, because methyl mercaptan is always present in the human body and blood levels can become elevated as a result of liver damage (without exogenous exposure), progress in this area may not be forthcoming.

Currently, the only effect clearly associated with methyl mercaptan toxicity is coma (Shults et al. 1970). The identification of more subtle effects that might result from chronic low-level exposure would be useful.

Absorption, Distribution, Metabolism, and Excretion. There are no toxicokinetic studies for methyl mercaptan via the inhalation, oral, or dermal routes. These studies would be valuable for tracing its metabolic fate following each route of exposure. Studies of absorption via the oral and dermal routes may be useful in helping to determine if toxicity studies using these routes are warranted.

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Comparative Toxicokinetics. There is no available information on the comparative toxicokinetics of methyl mercaptan. Although species differences in response to methyl mercaptan exposure may exist, these studies may not be useful until several other aspects of this chemical's toxicity are first investigated. These comparisons would then serve as an aid in putting the results of animal toxicity data into perspective in relation to its relevance to potential human health effects.

Mitigation of effects. Recommended methods for the mitigation of acute effects of methyl mercaptan poisoning include administration of oxygen if exposure is by inhalation, or thorough washing of the skin and flushing the eyes with water if exposure is to these organs (Bronstein and Currance 1988; Stutz and Janusz 1988). Drugs may also be administered to control seizures and transfusions to alleviate anemia. No information was located concerning mitigation of effects of lower-level or longer-term exposure to methyl mercaptan. Further information on techniques to mitigate such effects would be useful in determining the safety and effectiveness of possible methods for treating methyl mercaptan-exposed populations surrounding hazardous waste sites.

2.9.3 On-going Studies

No studies on toxicity, toxicokinetics, epidemiology, or other topics discussed in Section 2.8.2, above are known to be in progress.