DRAFT REPORT

SUPPORT FOR CHEMICAL NOMINATION AND SELECTION PROCESS OF THE NATIONAL TOXICOLOGY PROGRAM

NIEHS CONTRACT No. NO1-ES-85218

EXECUTIVE SUMMARY OF DATA

FORMAMIDE
(75-12-7)

November 18, 1988

Submitted to:

National Toxicology Program
National Institutes of Health
Building 31, Room 2B-55
Bethesda, Maryland 20205

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FORMAMIDE*

I. Chemical and Physical Information

A. Synonyms: Formic acid, amide

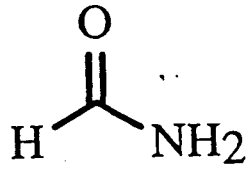
Methanamide

Carbamaldehyde

B. CAS No.: 75-12-7

C. Molecular Formula: CH_3NO

D. Structural Formula:



E. Molecular Weight: 45.04

F. Physical Properties:

1. Physical State: Slightly viscous, odorless, colorless liquid (Windholz, 1983)

2. Melting Point: 2.55°C (Windholz, 1983)

3. Boiling Point: 210.5°C at 760 mm Hg (partial decomposition to CO and NH_3 beginning at 180°C at atmospheric pressure) (Windholz, 1983)

4. Flash Point: 310°F (154°C) (open cup) (Windholz, 1983)

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*Formamide was nominated for genotoxicity and reproductive effects testing by the Environmental Defense Fund and carcinogenicity testing by the National Cancer Institute.

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5. Vapor Pressure: 29.7 mm Hg at 129.4°C (measured); 0.014 mm Hg at 20°C [calculated using equation 2.4 from Riddick et al. (1986)]

6. Specific Gravity: 1.13340 at 20°C (referred to water at 4°C) (Windholz, 1983)

7. Refractive Index: n_D^{20} = 1.44754 (Windholz, 1983)

8. Solubility in Water: Infinite (Riddick et al., 1986)

9. Solubility in Organic Solvents: Miscible in methanol, ethanol, acetone, acetic acid, dioxane, ethylene glycol, U.S.P. glycerol, phenol; very slightly soluble in ether, benzene (Windholz, 1983)

10. Log Octanol/Water Partition Coefficient: -1.51 (recommended value) (Hansch and Leo, 1985)

11. Henry's Law Constant: 1.4×10^{-7} atm-m^3/mol (estimated) (Hine and Mookerjee, 1975)

12. Other: Industrial grades may have a faint odor of ammonia (Windholz, 1983)

II. Production/Use/Exposure/Environmental/Regulatory Data

A. Production

1. Manufacturing Process

Formamide is manufactured by one of two continuous processes. In the first process, ammonia and carbon monoxide are reacted in methanolic sodium methoxide at elevated temperature and pressure. The second is a two-step synthesis in which carbon monoxide and methanol are reacted in the presence of catalytic sodium methoxide to form methyl formate, which is then reacted with ammonia at elevated temperature and pressure to yield formamide (Kirk-Othmer, 1980).

2. Volume

The public portion of the Toxic Substances Control Act Chemical Substance Inventory (TSCA Inventory) reported two companies as domestic producers of formamide (USEPA, 1988a). One of these companies reported zero production, and the other company reported production volume between 1 and 10 million pounds in 1977.

The Chemical Economics Handbook (CEH) did not report domestic production volume of formamide (CEH, 1988), nor did the U.S. International Trade Commission (USITC) for the years 1985 and 1986 (USITC, 1986, 1987).

The 1987 and 1988 Directory of Chemical Producers did not report the domestic production of formamide (SRI International, 1987, 1988).

The TSCA Inventory reported the importation of between 100,000 and 1 million pounds of formamide in 1977 by one company (USEPA, 1988a).

In 1982, one company reported to the U.S. Environmental Protection Agency (USEPA) the importation of between 1 and 11 million pounds of formamide per year (USEPA, 1986).

The CEH did not report the importation of formamide (CEH, 1988), nor did the U.S. Department of Commerce (USDOC) for the years 1983 and 1984 (USDOC, 1984, 1985).

3. Producers and Importers

Producers

The following companies have been listed as domestic producers of formamide:

American Cyanamid Company Bound Brook, NJ	(USEPA, 1988a)
E.I. du Pont de Nemours & Co. Belle, WV	(USEPA, 1988a)

Importers

The following company has been listed as an importer of formamide:

BASF Wyandotte Corp. Parsippany, NJ	(USEPA, 1986, 1988a)

4. Technical Product Composition

Formamide is available in several grades. Spectrophotometric and reagent grades are 99% pure and contain less than 0.03% water. Formamide concentrations in commercial grades may range from 75 to 99.5% (NCI, 1987a; Kirk-Othmer, 1980). The 99.5% product contains 0.1% water, 0.1% methanol, and 0.1% ammonium formate (Kirk-Othmer, 1980).

B. Use

Formamide is used in the manufacture of a wide variety of pharmaceutical, chemical, and agrichemical products, and as a solvent.

The pharmaceutical industry uses approximately 82% of the imported formamide (USEPA, 1986); in the early 1980's, it was used mainly in the production of the antiulcer drug, cimetidine NCI, 1987a). Formamide is also used as a monomer in the production of polymers such as heat-resistant coatings (NCI, 1987a; USEPA, 1986). Formamide is utilized as an intermediate in the large-scale production of formic acid, as well as in the synthesis of hydrogen cyanide, imidazoles, pyrimidine, and 1,3,5-triazines (Kirk-Othmer, 1980).

Formamide has a wide range of solvent applications (Kirk-Othmer, 1980; NCI, 1987a; USEPA, 1986). The major use under TSCA is in petroleum production, where it acts as a carrier for drilling mud corrosion-inhibiting additives pumped into wells during drilling operations (USEPA, 1986). It is also used in soil stabilization, as an ink solvent in fiber, plastic, and felt-tip pens and markers, and in laboratory applications (USEPA, 1986). Formamide is used as a solvent in the manufacture and processing of plastics, nonaqueous electrolysis, crystallization of pharmaceuticals such as penicillin and dihydrostreptomycin

sulfate, separation of chlorosilanes, and purification of oils and fats (Kirk-Othmer, 1980).

Formamide has been used or has the potential to be used as an additive to lube oil and hydraulic fluid, a component of deicing fluids for airport runways, a curing agent for epoxy resins, a plasticizer, an affinity enhancer for dyes, and a component of liquid fertilizers (USEPA, 1986).

C. Occupational Exposure

The National Occupational Exposure Survey (NOES), conducted by the National Institute of Occupational Safety and Health (NIOSH) between 1981 and 1983, estimated that 2724 employees are potentially exposed to formamide in the United States (NIOSH, 1988). Of the total number of employees potentially exposed, 556 were estimated to be females. Sixty-six percent of exposure was estimated to result from exposure to the actual chemical and 34% of exposure was estimated to result from exposure to trade name products.

In a customer survey conducted by BASF Wyandotte Corp., about 400 workers were reported to be exposed to formamide under controlled use conditions (USEPA, 1986). Many of these workers may have been exposed during the manufacture of pens in which formamide-containing inks were used. The USEPA calculated a worst case scenario in which an adult male or female worker who

spilled formamide on both hands could be exposed to 1.45 mg/kg/contact, assuming 100% absorption, 0.13 m^2 hand surface area, and 70 kg body weight (USEPA, 1986).

The American Conference of Governmental Industrial Hygienists (ACGIH) has recommended for 1988-89 adoption a time-weighted average-threshold limit value (TWA-TLV) of 10 ppm (15 mg/m^3) (with a "skin" notation) (ACGIH, 1987, 1988). The "skin" notation refers to the potential contribution to overall exposure to formamide by the cutaneous route, including mucous membranes and eyes, particularly by direct contact or by contact with airborne formamide (ACGIH, 1988). The TLV is a recommendation, not a binding standard. No short-term exposure limit (STEL) has been suggested at this time (ACGIH, 1988). The previous ACGIH TWA-TLV (with no skin notation) was 20 ppm (30 mg/m^3) with a STEL of 30 ppm (45 mg/m^3) (ACGIH, 1988).

D. Consumer Exposure

Consumer exposure to formamide may result from its use in water-soluble ink formulations. It is used in about 4% of the pens used in the United States or about 130 million pens (USEPA, 1986). Formamide is generally used in finer point pens at a level of 5%. It is also utilized in high-performance industrial pens, such as high-speed computer plotter pens, which contain about 35% formamide. The use of such pens, however, should not result in significant consumer exposure. The USEPA calculated a

worst case scenario in which a child who painted the central surface of both hands with a broad-tip marker containing 20% formamide in the ink could be exposed to 0.3 mg/kg formamide, assuming 100% absorption (USEPA, 1986).

E. Environmental Data

Formamide is probably emitted to the environment as a result of its manufacture and use as an intermediate and solvent.

Data regarding the environmental occurrence of formamide were limited. Formamide has been detected at 2.0 mg/L in gas-condensate retort water in a modified in situ oil-shale retort, but was not detected in the processed retort water (Leenheer et al., 1982). Formamide has been detected in wastewater from a polyamide production plant (Pelezner and Melent'eva, 1975, as cited in USEPA, 1981). Also, formamide has been reported to be formed in the wastestreams from an acrylonitrile plant as a result of a detoxification process for cyanide-containing wastewaters (Anonymous, 1985).

If formamide is released to water, it will generally be subject to slow hydrolysis at room temperature. Acidic and basic conditions and elevated temperatures accelerate the hydrolysis (Kirk-Othmer, 1980). Based upon physical/chemical properties, it should not volatilize significantly (Hine and Mookerjee, 1975; Lyman et al., 1982); photolyze directly; adsorb to

sediment and suspended particulate matter (Hansch and Leo, 1985; Lyman et al., 1982); or bioconcentrate in aquatic organisms (Hansch and Leo, 1985; Lyman et al., 1982). However, it may be subject to biodegradation, based on its biodegradability in aqueous screening tests (Malaney and Gerhold, 1969; Sasaki, 1978). The following percentages of theoretical oxygen demand were observed in bench-scale activated sludge tests: 1.6% in 6 hours, 4.7% in 12 hours, 11.8% in 24 hours (Malaney and Gerhold, 1969), and greater than 30% in 2 weeks (Sasaki, 1978).

If released to soil, formamide may be subject to biodegradation, given its biodegradability in aqueous screening tests (Malaney and Gerhold, 1969; Sasaki, 1978). Based upon physical properties, it may leach to groundwater or volatilize from dry near-surface soils; however, volatilization from moist soils is not expected to be significant.

If released to the atmosphere, formamide is expected to exist primarily in the vapor phase (Eisenreich et al., 1981). It is not expected to photolyze directly, although the half-life for reaction with photochemically-produced hydroxyl radicals was estimated to be approximately 2.1 hours (Atkinson, 1987). Removal of formamide by rainout may be significant given its miscibility in water.

F. Regulatory Status

Although the Occupational Safety and Health Administration (OSHA) currently has no exposure limit for formamide, it has proposed a permissible exposure limit (PEL) of 20 ppm (30 mg/m^3) and a STEL of 30 ppm (45 mg/m^3) (OSHA, 1988). These proposed limits are derived from the 1987-1988 ACGIH TLV's (ACGIH, 1988), and are based on analogy to DMF and its acute toxicity (OSHA, 1988).

In its 10th report, the TSCA Interagency Testing Committee added formamide to its list of chemicals for priority consideration by the USEPA for development of a test rule (USEPA, 1982). The committee recommended testing for genotoxicity, carcinogenicity, and other health effects. Subsequently, BASF submitted results regarding dermal effects on rats from a subchronic study pursuant to a negotiated testing agreement between the EPA and BASF (USEPA, 1986). The EPA has determined that the data from this study are valid and, when considered with earlier data, are sufficient to reasonably predict the identified health effects of formamide. Also, the data do not suggest a potential for unreasonable risk at current exposures. The EPA also determined that current and anticipated releases of and exposure to formamide do not appear sufficient to warrant concern for any other health effects (USEPA, 1986).

Formamide is regulated by the USEPA under the Standards of Performance for New Stationary Sources of Pollutants (USEPA, 1987a). Formamide is subject to the provisions of 40 CFR Part 716, which stipulate health and safety data reporting requirements (USEPA, 1987b).

Formamide is not subject to reporting under Title III of the Superfund Amendments and Reauthorization Act (SARA) of 1986 according to the Title III List of Lists (USEPA, 1988b). The List of Lists covers SARA Section 302 Extremely Hazardous Substances, Reportable Quantity ("RQ") Hazardous Substances of the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA), SARA Section 313 Toxic Chemicals, and Hazardous Wastes of the Resource Conservation and Recovery Act of 1976 (RCRA).

The Food and Drug Administration (FDA) has approved the use of formamide as a component of adhesives in articles intended for use in packaging, transporting, or holding food in accordance with certain prescribed conditions (FDA, 1988).

III. Toxicological Effects

A. Human Data

1. Acute: No information was found.

2. Epidemiological Evidence/Case Reports: No information was found.

3. Absorption/Distribution/Metabolism/Elimination: No information was found.

4. Carcinogenicity/Chronic: No information was found.

5. Teratogenicity and Reproductive Effects: No information was found.

B. Animal Data

1. Acute: LD_{50} values and effects of acute exposure to formamide are summarized in Table 1. Formamide appears to be approximately equally toxic when administered by the oral, dermal, intraperitoneal, or intravenous routes. Lethal levels have not been reported for inhalation exposure. Haskell Laboratory (1976) reported that both undiluted formamide and a 50% aqueous formamide solution were strong temporary irritants to unabraded guinea pig skin. Additionally, a dose of 0.05 or 0.1 mL undiluted formamide caused various degrees of ocular injury, including mild corneal injury, mild iritis, and conjunctival irritation in the eyes of five male albino rabbits.

Table 1. Effects of Acute Administration of Formamide

Route	Species/Strain	Sex and Number	Dose	Results	Reference
Oral	Rat/NR	NR	NR	Approximate lethal dose (ALD) of 7.5 g/kg	Haskell Laboratory, 1976
Oral	Rat/NR	NR	NR	LD_{50} of 6 g/kg	Thiersch, 1971
Oral	Rat/NR	NR	NR	LD_{50} of 6.1 g/kg	Zaeva et al., 1967 as cited in ACGIH, 1986
Oral	Mouse/NR	NR	NR	LD_{50} of 3.15 g/kg	Zaeva et al., 1967 as cited in Kennedy, 1986
Dermal	Rat/ChR-CD	female (pregnant), 1/group	NR	ALD of 17 g/kg	Stula and Krauss, 1977
Dermal	Guinea pig/NR	NR	NR	LD_{50} of 2.539 g/kg	Sax, 1979 as cited in USEPA, 1981
Dermal	Guinea pig/NR	NR	NR	LD_{50} of less than 5.670 g/kg	Fassett, 1963 as cited in USEPA, 1981
Dermal	Rabbit/NR	NR	NR	LD_{50} of 6 g/kg	Czaikowska, 1981 as cited in ACGIH, 1986
Dermal	Rabbit/New Zealand white	female (pregnant), 1/group	NR	ALD of 3.4 mg/kg	Stula and Krauss, 1977
Inhalation	Rat/NR	NR	188, 2357, 3720, or 3921 ppm for 6 hours	All gained weight normally during a 2-week observation period.	Haskell Laboratory, 1976
Intraperitoneal	Rat/Wistar	NR	NR	LD_{50} of 5.7 to 5.9 g/kg	Chanh et al., 1971
Intraperitoneal	Mouse/NR	NR	NR	LD_{50} of 4.6 g/kg	Chanh et al., 1971
Intraperitoneal	Guinea pig/NR	NR	NR	LD_{50} of 1.25 g/kg	Zaeva et al., 1967 as cited in Kennedy, 1986
Intravenous	Rat/NR	NR	NR	LD_{50} of 5.6 g/kg	Zaeva et al., 1967 as cited in Kennedy, 1986
Intravenous	Mouse/NR	NR	NR	LD_{50} of 5.1 g/kg	Zaeva et al., 1967 as cited in Kennedy, 1986

Table 1. (continued)

Route	Species/Strain	Sex and Number	Dose	Results	Reference
Intravenous	Dog/NR	NR	3 g/kg	Increased respiratory output and cardiac activity; decreased hypertension induced by tyramine and ephedrine	Chanh et al., 1973 as cited in USEPA, 1981

NR = Not reported

2. Absorption/Distribution/Metabolism/Elimination: Data regarding the absorption and distribution of formamide were not located in the available literature. The only data regarding the metabolism of formamide are from early studies. Bray et al. (1949) studied the metabolism of formamide in rabbits by estimating the extra ether-soluble acid in the urine following administration of formamide by gavage at a level of 2, 3, or 4 g/animal. Approximately 60% of the administered formamide was estimated to be hydrolyzed and 40% excreted unchanged, although it was noted that the methods used could not exclude the contribution of other catabolic reactions to the results.

Extensive conversion of formamide to formate was reported previously in dogs (Halsey, 1898, as cited in Bray et al., 1949) and in sheep (Gonnermann, 1902, as cited in Bray et al., 1949). Metabolism studies using contemporary methodology were not located in the literature.

3. Prechronic: BASF (1986) reported the results of an unpublished study in which groups of 20 male and 20 female Sprague-Dawley rats were administered formamide in 20 oral (gavage) doses of 0, 30, 100, 300, and 1000 μL/kg over 4 weeks. A 2-week post-treatment observation period was allowed for 10 rats/sex/group. No effects were observed at

30 μL/kg. At 100 to 1000 μL/kg, decreased food consumption and statistically significant ($p \leq 0.05$) weight loss occurred. In the 300 μL/kg group, gross toxicity was apparent, as indicated by coat appearance, closed eyes, and posture; 50% of the rats in this group died. In the 1000 μL/kg group, 100% mortality occurred within 1 week of treatment. After administration of formamide was discontinued, rats in the 100 and 300 μL/kg groups recovered completely and partially, respectively. Macroscopic organ changes at necropsy in the rats in the 300 and 1000 μL/kg groups were attributed to general organ atrophy, poor nutritional status, and treatment-related ulceration (with bleeding) in the stomach. The macroscopic findings in the two lower dose groups were similar to those of the control. In the 300 and 1000 μL/kg groups, histological findings attributed to treatment included renal necrosis, testicular atrophy, fibrous lesions in the spleen and thymus, and flattened epithelial cells of the thyroid glands. Gastrointestinal lesions were observed only in the rats that died early and not in rats in the 300 μL/kg group that were killed at term.

A group of six rats (sex and strain not reported) were administered formamide by gavage at a dose of 1.5 g/kg, 5 days/week for 2 weeks (Haskell Laboratory, 1976). Mortality was observed between the 5th and 10th treatment,

and all rats were dead by the end of the 2-week period. Weight loss, malnutrition, and gastritis were observed in these rats.

A group of two male rats was exposed by inhalation to 1500 ppm formamide, 6 hours/day, 5 days/week for 2 weeks (Haskell Laboratory, 1976). No overt or histopathologic evidence of toxicity was observed.

Groups of 10 male and 10 female Wistar rats were given dermal applications of formamide at levels of 0, 300, 1000, and 3000 mg/kg for 90 days (BASF, 1984). Slightly decreased body weights occurred in males treated with 300 and 1000 mg/kg/day. At 3000 mg/kg/day, diminished food consumption, decreased weight gain (11% in males and 27% in females), erythema, apathy, dyspnea, and staggering gait occurred. Also, one female in the 3000 mg/kg/day group was moribund, and histopathology revealed gastric ulceration. All males and high dose females reportedly developed erythrocythemia. The histopathologic portion of this study has not been completed.

Groups of 10 male and 10 female Wistar rats received dermal applications of formamide at 0, 30, or 100 μL/kg for 3 months (BASF, 1985). An additional group of 20 male and 20 female rats received dermal applications of 3000 μL/kg.

No effects were observed in the groups treated at 30 or 100 μL/kg. In the males and females of the 3000 μL/kg group, food consumption was decreased and weight gain was decreased by more than 50%. Rats in this group also had a generally unhealthy appearance. Treatment-related deaths occurred in three male rats at 3000 μL/kg. Hematologic examination indicated compensatory polycythemia and increased carboxyhemoglobin. In males of the 3000 μL/kg group at necropsy, there was an increase in relative adrenal weight and testicular atrophy. The findings at necropsy in females of the 3000 μL/kg group were similar to those in control.

4. Carcinogenicity/Chronic: No information was found.

5. Teratogenicity and Reproductive Effects: Thiersch (1971) evaluated the teratogenic potential of formamide administered orally (by gavage) to groups of 2 to 12 pregnant Long-Evans rats at 2 g/kg (days 7, 11, 7 and 8, or 7, 8, and 9 post-coitus) or 1 g/kg (days 11 to 16 post-coitus). Effects on the dams were not described. The percentage of fetuses resorbed in the different treatment groups was the following: 51.2% (day 7), 14% (day 11), 79.7% (days 7 and 8), 100% (days 7, 8, and 9), and 35.8% (days 11 to 16). Increases in the number of stunted fetuses were observed with dams treated on days 7, 7 and 8, and 11 to 16. No

malformations were noted in fetuses from the five treatment groups. The authors reported that an additional dose level of 1 g/kg given on days 7 through 12 of gestation resulted in 90% resorption of fetuses and malformations of the palate and limbs in survivors (incidence not reported).

Von Merkle and Zeller (1980) administered formamide by gavage to groups of 11 to 25 pregnant rabbits at doses of 20, 70, or 200 μL/kg on days 6 to 18 post-insemination. At the low dose, no maternal or fetal effects were observed. The 70 μL/kg dose was considered non-toxic to the dams, but resulted in statistically significant decreases in live fetuses per litter and in fetal weight. At the high dose, 8 of the 10 pregnant dams died, and the other 2 experienced abortions.

Stula and Krauss (1977) investigated the fetotoxicity of undiluted formamide applied to the skin of pregnant ChR-CD rats (groups of six or seven) during organogenesis. Formamide was applied at a dose of 600 mg/kg on day 9, 10 or 11, or on days 11 and 12, or 12 and 13 of gestation. Maternal toxicity was not described. At termination on day 20 of gestation, embryomortality was observed at a rate of 2% (control), 5% (day 9 and days 10 to 11 groups), 13% (days 11 to 12 group) and 5% (days 12 to 13 group). Fetal abnormalities were observed in 1/53 fetuses from the group

of dams treated on days 10 to 11 (distorted face) and in 4/60 fetuses from the group treated on days 12 to 13 (subcutaneous hemorrhage).

Gleich (1974) evaluated the teratogenic potential of formamide in an unspecified number of pregnant NMRI mice administered 0.076 or 0.19 mL/kg formamide by intraperitoneal injection on gestation days 6 to 15. Fetal loss was 13 and 27% in the low and high dose groups, respectively, and malformations were observed in 4 and 25% of the fetuses, respectively. Gleich (1974) also applied 0.008 or 0.076 mL formamide to the skin of an unspecified number of pregnant NMRI mice on days 10 and 11 of gestation. The rate of fetal loss was 8% in the low dose group and in 61% in the high dose group, and the malformation rates were 0 and 36%, respectively.

As reviewed by USEPA (1981), Von Kreybig (1967) studied the teratogenic potential of formamide, and found no embryotoxic or fetotoxic effects when pregnant rats (strain and number not reported) received a subcutaneous injection of 1000, 2000, or 3000 mg/kg formamide on day 13 of gestation. A dose of 4200 mg/kg was reported to be embryotoxic and resulted in hypoplasia (not further described), internal bleeding, and edema in 60% of the surviving fetuses. Oettel and Frohberg (1964), as cited in USEPA (1981),

studied the effects of dermal application of 0.1 mL formamide on day 11 of gestation to pregnant NMRI mice. Effects reported included resorptions (50%), cleft palate (incidence not reported), and "isolated cases of unspecified exenteration and phocomelia in 50% of the remaining live fetuses." After two dermal applications of 0.1 mL, amelia and 80% resorptions occurred.

C. Genotoxicity: Mortelmans et al. (1986) tested formamide in a reverse mutagenicity assay with Salmonella typhimurium (strains TA100, TA1535, TA1537, TA98). The metabolic activation was provided by an S-9 fraction from Aroclor-induced rat livers. Formamide was not mutagenic in the absence or presence of metabolic activation.

BASF (1974) conducted a mouse dominant lethal assay in which a group of 20 male virgin albino SPF mice were given single intraperitoneal injections of formamide at 364 μL/kg (1/5 the LD_{50} for formamide). Groups of similar size were used as an untreated negative control and as a Trenimon-treated positive control. Each male was housed with three virgin females from the day after injection for 7 days; this mating schedule was continued through seven additional mating periods. Formamide produced no dominant lethal effects, as determined by the conception rate and the number of living or dead implants in the

mated females. The positive control elicited the expected response.

D. Other Relevant Information: No information was found.

E. Structure-Activity Relationships: Kennedy (1986) recently reviewed the *in vivo* and *in vitro* genotoxicity data on acetamide, dimethylacetamide, and dimethylformamide. The data were predominantly negative for these compounds. In an *E. coli* assay, monomethylacetamide induced a "small but consistent increase" in the reversion frequency per 10^6 surviving cells.

Kennedy (1986) also reviewed developmental toxicity studies of acetamide, dimethylacetamide, monomethylformamide, and dimethylformamide. When these compounds were administered as single or repeated doses during gestation at dose levels that resulted in maternal toxicity, a moderate to high degree of fetal resorption occurred. Some studies reported the occurrence of terata but these were observed at high doses. The rabbit appeared to be the most sensitive species.

The NTP testing status for compounds structurally related to formamide is summarized in Table 2.

Table 2. NTP Testing Status of Compounds Structurally Related to Formamide*

Chemical	CAS No.	Genotoxicity	Carcinogenicity	Other
Dimethyl-formamide	68-12-2	Negative in Salmonella	Selected for inhalation carcinogenesis studies	---
		Positive in mouse lymphoma in one study, negative in two other studies		
		Negative in Drosophila for sex-linked recessive lethal mutations		
		Negative for chromosomal aberrations and sister-chromatid exchanges in CHO cells in culture		
Acetamide	60-35-5	Negative in Salmonella	---	---
		Negative in Drosophila for sex-linked recessive lethal mutations		

*NTP CHEMTRACK, 1988

IV. Nomination Source

A. Source: 1) Environmental Defense Fund (Silbergeld, 1987)
2) National Cancer Institute (NCI, 1987b)

B. Recommendations: 1) - Genotoxicity
- Reproductive toxicity

2) - Carcinogenicity

C. Rationale/Remarks: 1) - Potential for exposure
- Lack of genotoxicity and reproductive toxicity data

2) - Extensive use
- Potential for exposure
- Structural relationship to acetamide, a liver carcinogen in rats
- Lack of carcinogenicity data

D. Priority: 1) None given
2) Moderate to high

E. Date of Nomination: 1) May 1987
2) July 1987

V. Chemical Evaluation Committee Review

A. Date of Review: December 1, 1988

B. Recommendations: - Carcinogenicity
- Reproductive effects

C. Priority: - Moderate for carcinogenicity
- High for reproductive effects

D. NTP Chemical Selection Principles: 3,4,8

E. Rationale/Remarks: - Widespread use
- Potential for exposure
- Lack of carcinogenicity data
- Adequate teratogenicity data available
- Structural interest — parent compound of formamides chemical class

VI. Board of Scientific Counselors Review

A. Date of Review:

B. Recommendations:

C. Priority:

D. Rationale/Remarks:

VII. Executive Committee Review

A. Date of Review:

B. Decision:

VIII. Information Sources

This report was prepared by a multidisciplinary team of scientists. The team consisted of Susan Coleman, Bill Jarvis, Joseph Ward, Philip Howard, and Michael Neal. The information resources used to prepare this review included the automated data bases listed below, journal articles, general reference materials, and agency reports.

ON-LINE DATA BASES SEARCHED

MEDLARS

CHEMLINE	
RTECS	
HSDB	
MEDLINE	1966-Present
TOXLINE	1965-Present
TOXLIT	1981-Present
TOXLIT-65	1965-1980
CANCERLIT	1963-Present

DIALOG

NTIS	1970-Present
Occupational Safety and Health (NIOSH)	1972-Present
Federal Register	1977-Present
Chemical Industry Notes	1975-Present
PTS Prompt	1972-Present

CIS

SANSS
TSCA Inventory

OTHER

NOES
NTP CHEMTRACK
CAS ONLINE 1967-Present

SRC

TSCATS
EFDB
CABE ARCHIVES
SRC DOCUMENTS

IX. References

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