Methylolurea
[1000-82-4]

Review of Toxicological Literature

March 2002

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Prepared for

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Executive Summary

Basis for Nomination

Methylolurea was nominated by the National Institute of Environmental Health Sciences (NIEHS) for toxicological characterization including biological disposition studies. Four structurally related methylolurea compounds were nominated as a class in 1997 by the NIEHS for toxicity and carcinogenesis studies. The nomination is based on high production volumes (including urea-formaldehyde [UF] resins which contain methylolurea or dimethylolurea as residual starting materials or breakdown products), widespread use and potential for human exposure, and the lack of data on carcinogenicity. In the formal review of the 1997 nomination, a testing recommendation was deferred pending further review of information from previously conducted studies on one member of this class (1,2-dimethylol-4,5-dihydroxyethyleneurea [DMDHEU]) by the National Toxicology Program (NTP). The NTP conducted biological disposition, 14-day, and 13-week oral toxicity studies of DMDHEU in rats and mice. DMDHEU was not selected for carcinogenicity testing due to the limited oral bioavailability and lack of significant toxicity observed in these studies.

Nontoxicological Information

Methylolurea, as a solution, is a mixture of formaldehyde gas in water with urea. In the production of UF resins, it exists as an unisolated intermediate. Methylolurea monomers are dispersed as soft pastes containing 55-65% active ingredient. The products Asulgan® K and Kaurit® S contain about 82% dimethylolurea and 15% methylolurea. Both methylolurea and dimethylolurea are derived from the combination of urea and formaldehyde in a 1:1 and 1:2 molar ratio, respectively. This reaction requires the presence of salts or alkaline catalysts, heat, and control of pH. Methylolurea can be obtained as a hydrolysis product of methylenediurea. Additionally, oxidative damage to DNA causes base degradation, which produces numerous products including methylolurea. The last reported figures show that production of methylolurea for commerce was between 31 and 161 million pounds [14,000 and 73,000 Mg] in the United States in 1977. Several sources list production volumes of UF resins, some of which contain at least 10% of methylolurea or dimethylolurea as impurities. In 1994 and 1995, 1.91 and 1.84 billion pounds (866,185 and 834,440 metric tons [Mg]), respectively, of UF resins were produced in the United States. About 95% of particleboard products are based on UF resins, while approximately 80% of the slow-release fertilizer market is based on UF-containing products.

Methylolurea is used to treat textiles and wood, and is mixed with fillers for use in molding adhesives. It is also used in disinfectants and other biocidal products, as an in-can preservative, as a preservative for liquid-cooling and processing systems, and as a slimicide. Dimethylolurea is currently used as a preservative in metal-working fluids (cutting fluids), as a developer of photographic film, and as a cleaning agent and disinfectant.

Methylolurea is not expected to persist in the environment. However, the presence of methylolurea class compounds in cutting fluids and cleaning agents, in permanent-press fabrics, and as an impurity in UF resins suggests that environmental exposures are likely. Methylolurea readily hydrolyzes to release formaldehyde. Under ambient conditions and during curing, uncured UF resins can release free formaldehyde, at rates gradually decreasing over time.

As a liquid, an exposure limit of 0.75 ppm as an eight-hour time weighted average (TWA) has been established for methylolurea. The potential exists for occupational exposure to methylolurea or dimethylolurea during the production of UF resins and from the use of any products containing such resins (e.g., pressed wood products, dinnerware, foundry core binder, flexible foams, insulation materials, slow-release fertilizers). Between 1972 and 1974, NIOSH estimated that 391,074 workers were potentially exposed to UF resins; the fraction exposed to methylolurea, however, was not known.

In May 1983, methylolurea was added to the Environmental Protection Agency (EPA) *Priority List* by the Toxic Substances Control Act (TSCA) Interagency Testing Committee (ITC) (48 FR 24443-24452). A year later, it was removed from the list (49 FR 21371-21375). In 2000, methylolurea was listed in the TSCA Inventory. Under the 1990, 1994, and 1998 Inventory Update Rule (IUR), methylolurea was available for sponsorship in the U.S. EPA's High Production Volume (HPV) Challenge Program, but has not yet been sponsored.

Toxicological Information

Human Data: Numerous studies suggest that the toxicity of uncured UF resins (containing methylolurea) may be attributed to the presence of formaldehyde.

Chemical Disposition, Metabolism, and Toxicokinetics: In rats exposed to *N*-methyl-*N'*-(hydroxymethyl)thiourea, a bactericide used in humans for the treatment of peritonitis and infections of the bladder and uterus, both methylolurea and dimethylolurea were identified in the urine.

Acute Toxicity: A spray dried UF powdered glue containing as much as 10% methylolurea caused no deaths in rats exposed via inhalation for one hour (200 mg/L [2.22 mol/m^3]) or via oral gavage (single dose; 5.2 g/kg [57.7 mmol/kg]). In rabbits, dermal application of the substance (2.2 g/kg [24.4 mmol/kg]) also resulted in no death, while application to the eye (0.1 g [1.1 mmol]) produced no irritation, injury, or ocular damage in the animals.

Synergistic/Antagonistic Effects: In mice, pretreatment with methylolurea reduced the LD_{50} for formaldehyde from 330 to 293 mg/kg.

Genotoxicity: In outbred male rats, intragastric intubation of methylolurea in a UF condensate (dose reported to be 1/10 LD_{50}; neither were provided) induced chromosomal aberrations of the bone marrow cells at 24 and 48 hours following dose administration. It also changed the apparent molecular weight of isolated DNA and increased the rate at which DNA attached to bacterial and animal cells; this property was correlated with the ability of the precondensate to produce cancer *in vivo*.

Other Data: Dimethylolurea and DMDHEU were found to be causal agents in textile-related dermatitis. Studies of UF resins show that "dermal exposure poses little or no significant risk to human health." In rats and rabbits, however, UF resins (tested as Aerotex® products) were irritating.

No studies on human exposure, shorter-term, subchronic, or chronic exposure, reproductive toxicity, teratology, or carcinogenicity were located.

Structure-Activity Relationships

Dimethylolurea

Short-term or Subchronic Toxicity: Male and female rats administered 1.0, 10.0, or 100.0 mg/kg dimethylolurea via an intragastric cannula for 14 consecutive days showed no significant exposure-related effects.

Genotoxicity: Consistent with DNA crosslinking activity, treatment of human lymphocytes with dimethylolurea alone or in combination with methyl methanesulphonate (MMS) resulted in reduced DNA migration compared to untreated cells and MMS-treated cells, respectively, in the alkaline single cell electrophoresis (comet) assay. Additionally, dimethylolurea was positive in the *Salmonella* mutagenicity test.

Polyoxymethylene Urea

In 1995, the Cosmetic Ingredient Review (CIR) Expert Panel reported on the safety assessment of polyoxymethylene urea, a synthetic polymer used in the cosmetic industry as a bulking agent and to form the outer shell of microcapsules. (Noncosmetic uses include application in resinous and polymeric coatings coming in contact with food; in polysulfide polymer-polyepoxy resins for contact with dry foods; as a bonding agent in the production of particleboard, chip board, and interior plywood; in coatings for paper products and fiberglass insulation; in the formulation of foam insulations; and in the manufacture of textiles, primarily wrinkle-resistant clothing fabrics.) Based on the studies, the panel concluded the compound was "safe as used." The low-molecular weight ureas are quickly degraded in the environment, releasing free formaldehyde. Before curing, polyoxymethylene urea contains 0 to 14% monomethylolurea (per high-performance liquid chromatography [HPLC]) and 0 to 8% dimethylolurea (per HPLC).

Human Data: Exposure to polyoxymethylene urea results in toxicity that seems to be mostly associated with formaldehyde gas. In two patch tests, polyoxymethylene urea (undiluted form and microcapsule form) was not irritating or sensitizing. Exposure from the use of polyoxymethylene urea in the wood industry has resulted in respiratory tract irritation.

Acute Toxicity: In rats, oral LD_{50} values of >5.8 g/kg for polyoxymethylene urea, >5.2 mL/kg for liquid polyoxymethylene urea, 5.2 g/kg for spray-dried UF powdered glue, and 10,000 and 15,800 mg/kg for undiluted polyoxymethylene urea were reported. For microcapsule shell walls made of the urea, an oral LD_{50} of >20 g/kg was reported. The dermal LD_{50} and LC_{50} of polyoxymethylene urea were >2.1 g/kg and >167 mg/m^3 air (four-hour exposure), respectively.

Rats and mice administered polyoxymethylene urea, as well as in its liquid form and as UF powdered glue, all survived and showed no signs of toxicity and no lesions at necropsy. In dermal irritation studies, patches of liquid polyoxymethylene urea on the intact and abraded skin of the animals produced a very low primary irritation index. The same could be said of polyoxymethylene urea glue, undiluted polyoxymethylene urea, powdered polyoxymethylene urea in polyethylene glycol 400, and polyoxymethylene urea in microcapsule form. In rabbits, dermal applications of polyoxymethylene urea, its liquid form, and UF powdered glue produced neither death nor lesions.

Instillation of polyoxymethylene urea as a liquid (0.1 mL), including in a diluted form (0.1 mL), as a glue (0.1 g), and as a microcapsule (dose not provided) into the eyes of rabbits produced signs of irritation (e.g., minimal conjunctivitis, edema, and a small ulcer), which disappeared by 72 hours.

Short-term/Subchronic Toxicity: In male rats, inhalation of a formulation containing 66-71% polyoxymethylene urea and cellulose for 28 days caused no clinical signs of toxicity and no deaths. Body weight gain was slightly but not statistically significantly reduced. Absolute kidney and kidney/brain weights were also decreased, but there were no gross lesions. Over half the number of rats had interstitial pneumonia, while 30% had minimal, multifocal interstitial fibrosis.

Genotoxicity: In *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538, polyoxymethylene urea (1, 10, 100, 500, and 1000 µL/plate) was not mutagenic in the absence and presence of metabolic activation. A 50/50 polyester/cotton fabric treated with polyoxymethylene urea was also negative in the Ames test using the five strains with and without S9. A combination of polyoxymethylene urea (0.3-6%) and mouse liver extract significantly increased binding between the DNA and bacterial cells of *Escherichia coli*.

DMDHEU

Human Data: Exposure to DMDHEU occurs primarily as a result of the preparation of or the wearing of DMDHEU-treated permanent-press fabrics. No adverse effects have been reported.

Chemical Disposition, Metabolism, and Toxicokinetics: When male $B6C3F_1$ mice were given [^{14}C]-DMDHEU (5, 50, or 500 mg/kg), 60 to 70% of the administered dose was eliminated in the feces and 7 to 12% in the urine after 24 hours. In male Fischer 344 rats, intravenous administration of radiolabeled DMDHEU (50 mg/kg) resulted in >95% of the dose excreted unchanged in urine at 24 hours. Oral absorption of [^{14}C]-DMDHEU, based on urinary excretion, was dose-dependent in the animals. With both routes, muscle and skin contained the highest proportion of ^{14}C; dermal application (3.5 or 13 mg/cm^2 for six days), however, resulted in the largest amounts of ^{14}C in adipose tissue and lesser amounts in muscle.

In rabbits receiving occlusive or semi-occlusive dermal applications of cotton or polyester-cotton fabrics treated with [^{14}C]-DMDHEU, up to 2.6% of the radioactivity was detected in the skin after 48 hours, with smaller amounts found in the kidneys, liver, blood, urine, and exhaled CO_2. Uptake from the cloth into the skin was increased when [^{14}C]-DMDHEU was prepared from isolated DHEU (two-step preparative method) rather than the three-step commercial process, or was commercially prepared and incorporated into cotton polyester rather than cotton. The addition of synthetic perspiration tended to increase the amount of radioactivity in the skin, 80 to 90% of the radioactive material released from the cloth was found in the skin under the patch. In rabbits receiving dermal applications of fabrics treated with DMDHEU prepared from [^{14}C]-formaldehyde, DMDHEU had absorption, distribution, and excretion characteristics similar to those of topically applied formaldehyde.

Acute Toxicity: The oral LD_{50} for DMDHEU in rats was reported to be >7500 mg/kg. In rats exposed via inhalation to an enriched atmosphere of DMDHEU for 8 hours at room temperature, difficulty in breathing and irritation of the mucous membranes were observed. Severe skin irritation was observed in rabbits topically treated with 500 mg DMDHEU for 24 hours, and mild irritation was observed in the eyes of rabbits similarly treated. Another study, however, reported that an aqueous solution of DMDHEU was not irritating to the skin or eyes of rabbits.

Short-term or Subchronic Toxicity: No treatment-related effects were found in mice and rats administered DMDHEU by oral gavage for 13 weeks at doses ranging from 1000 to 6000 mg/kg/day. The no observed adverse effect level (NOAEL) was 6000 mg/kg/day in male and female mice and in female rats, and 1000 to 3000 mg/kg/day in male rats.

Reproductive Toxicity and Teratology: A 90-day gavage study produced no toxic effects on reproductive function or morphological abnormalities in sex organs (e.g., testes, prostate, and ovaries) in male rats treated with up to 3000 mg/kg/day and in female rats, female mice, and male mice treated with up to 6000 mg/kg/day. In pregnant Wistar rats, DMDHEU (250, 500, and 1000 mg/kg day on days 7-16 of pregnancy) produced no compound-related teratogenic effects. An NOAEL of 640 mg/kg was established for both maternal toxicity and teratogenicity.

Genotoxicity: When dissolved in dimethyl sulfoxide and tested using the pre-incubation assay at doses up to 10,000 mg/plate in either the presence or absence of rat or hamster S9, DMDHEU was not mutagenic in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537. However, when dissolved in water, it was mutagenic in strains TA98 (without metabolic activation and with hamster S9) and TA100 (with either rat or hamster S9). In *Drosophila melanogaster,* DMDHEU administered in food at 60,000 ppm caused a significant increase in sex-linked recessive lethal mutations but not reciprocal translocations.

Table of Contents

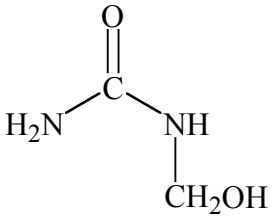
1.0 Basis for Nomination

Methylolurea was nominated by the National Institute of Environmental Health Sciences (NIEHS) for toxicological characterization including biological disposition studies. Four structurally related methylolurea compounds were nominated as a class in 1997 by the NIEHS for toxicity and carcinogenesis studies. The nomination is based on high production volumes (including urea-formaldehyde [UF] resins which contain methylolurea or dimethylolurea as residual starting materials or breakdown products), widespread use and potential for human exposure, and the lack of data on carcinogenicity. In the formal review of the 1997 nomination, a testing recommendation was deferred pending further review of information from previously conducted studies on one member of this class (1,2-dimethylol-4,5-dihydroxyethyleneurea [DMDHEU]) by the National Toxicology Program (NTP). The NTP conducted biological disposition, 14-day, and 13-week oral toxicity studies of DMDHEU in rats and mice. DMDHEU was not selected for carcinogenicity testing due to the limited oral bioavailability and lack of significant toxicity observed in these studies.

2.0 Introduction

Because dimethylolurea is usually found in combination with monomethylolurea in products (e.g., UF resins), the majority of nontoxicological information in this report discusses both chemicals. In addition, toxicological data regarding UF resins are contained in Section 9.6 and that for dimethylolurea and selected other related compounds is in Section 10.

Methylolurea
[1000-82-4]



2.1 Chemical Identification

Methylolurea ($C_2H_6N_2O_2$, mol. wt. = 90.08) is also called:

1-(Hydroxymethyl)urea	*N*-Methylolurea
N-(Hydroxymethyl)urea	Mono(hydroxymethyl)urea
(Hydroxymethyl)urea	Monomethylolurea
Formaldehyde-urea mixture	Urea, 1-hydroxymethyl
GP 5326	Urea, (hydroxymethyl)- (6CI, 7CI, 8CI, 9CI)

Sources: Ascension Parish CAER (undated); HSDB (2001); Registry (2001)

2.2 Physical-Chemical Properties

Property	Information	Reference(s)
Color	Colorless	Lewis (1993a)
Physical State	Crystals	Lewis (1993a)
	Prisms (from alcohol)	HSDB (2001)
Melting Point (°C)	111	Weast and Astle (1980)
Boiling Point (°C)	100 (liquid form)	Ascension Parish CAER (undated)
	Decomposes (solid form)	U.S. EPA (1983)
Soluble in:	Water (limited; ~30%), alcohol, and acetic acid	Updegraff et al. (1979);Weast and Astle (1980)

Methylolurea, as a solution, is a mixture of formaldehyde gas in water with urea (Ascension Parish CAER, undated). In the production of UF resins, it exists as an unisolated intermediate (American Cyanamid Co., 1984).

2.3 Commercial Availability

Methylolurea monomers are dispersed as soft pastes containing 55-65% active ingredient (Updegraff et al., 1979). The products Asulgan® K and Kaurit® S contain about 82% dimethylolurea together with 15% methylolurea and 3% water (DFG, 1993).

3.0 Production Processes

Methylolurea and dimethylolurea are derived from the combination of urea and formaldehyde in a 1:1 and 1:2 molar ratio, respectively. This reaction requires the presence of salts or alkaline catalysts, heat, and control of pH (DFG, 1993; Lewis, 1993a,b). Urea and formaldehyde are combined in a two-stage process to produce an amino resin. The first step (hydroxymethylation) is carried out in alkaline conditions to form stable resin intermediates such as methylolurea and dimethylolurea. Methylolurea is stable under neutral or alkaline conditions, but polymerizes under acidic conditions. By increasing the temperature and maintaining the acidic conditions of the reaction, dimethylolureas can be made as a series of short, water-soluble polymers. In the second step (resinification), acidic catalysts and heat are added along with monomeric urea units which condense with methylolurea and dimethylolurea to form UF resins. To overcome stability and water solubility problems, methylolurea and dimethylolurea resins are often alkylated with methanol to block the reactive hydroxyl group(s). Methylation of one methylol group is enough to ensure adequate shelf life and water solubility (Updegraff et al., 1979; Dunky, 2001).

Additionally, methylolurea can be obtained as a hydrolysis product of methylenediurea (Jahns et al., 1997; cited by Enzyme Commission, 1999). Oxidative damage to DNA causes base degradation, which produces numerous products including methylolurea (Imlay and Linn, 1986; cited by McKersie, 1996).

4.0 Production Volumes

From 1975 to 1977, the Resin Division of Georgia-Pacific Corporation produced between 10 and 50 million pounds (4500 to 23,000 metric tons [Mg]) of methylolurea at three sites: Russellville, SC; Columbus, OH; and Coos Bay, OR. Other production facilities reported between 10,000 and 100,000 pounds [45,360 to 45.36 Mg] (Louisville, MS), between 100,000 and 1 million

pounds [45.36 to 453.6 Mg] (Vienna, GA), and between 1 and 10 million pounds [453.6 to 4536 Mg] (Port Wentworth, GA). Auralux Corporation (Hope Valley, RI) reported production volumes between 10,000 and 10,000 pounds [45,360 to 45.36 Mg] (TSCAPP, 2001). In 1977, production of methylolurea for commerce was between 31 and 161 million pounds [14,000 and 73,000 Mg] in the United States (EPA, 1982; cited by U.S. EPA, 1983).

Several sources listed production volumes of UF resins, some of which contain at least 10% of methylolurea or dimethylolurea as impurities (Ludlam, 1973). In 1996, 28 domestic manufacturers produced UF resins, up from 22 producers in 1992 and 20 producers in 1994 (USITC, 1992, 1994; SRI Int., 1996). In 1994 and 1995, 1.91 and 1.84 billion pounds (866,000 and 835,000 Mg), respectively, of UF resins were produced. The 3.8% drop in the average annual growth of UF resins in these two years was the first decline in production volumes in over ten years (Kirschner, 1996). The *Farm Chemicals Handbook* listed two companies producing UF reaction products as fertilizers (W.A. Cleary Chemical Corp. produces Fluf and NOR-AM Chemical Corp. produces Nitroform); no production volumes were reported (Sine, 1991).

5.0 Uses

Methylolurea is used to treat textiles and wood, and is mixed with fillers for use in molding adhesives (Lewis, 1993a). In disinfectants and other biocidal products (e.g., algaecides), methylolurea is used for the disinfection of air, surfaces, materials, equipment, and furniture not used for direct food or feed contact in areas such as swimming pools, aquariums, hospital waste, air-conditioning systems, etc. As an in-can preservative, the compound is used to control the microbial deterioration of containers of manufactured products, other than foodstuffs and feedingstuffs, thereby ensuring shelf life. Additionally, methylolurea is used as a preservative for liquid-cooling and processing systems (not including products for the preservation of drinking water). It also finds use as a slimicide, controlling and preventing slime growth on materials, equipment, and structures used in industrial processes (e.g., on wood and paper pulp) (ECB, 1998, undated).

Dimethylolurea is used as a preservative in metal-working fluids (cutting fluids), as a developer of photographic film, and as a cleaning agent and disinfectant (DFG, 1993; Budavari, 1996). Wood is treated with dimethylolurea to increase its hardness and fire resistance, and to form self-binding laminations for plywood manufacture. Until 1980, the main use of dimethylolurea was in the textile industry, where it was used on permanent-press fabrics to increase their stiffness, on cotton fabrics to make them crease- and shrink-proof, and for finishing, drying, sizing, and tanning (Lewis, 1993b; Budavari, 1996). Since this compound has been found to release a high amount of formaldehyde compared to other durable-press resins (i.e., over 1000 ppm per gram of fabric), the percentage of durable-press fabrics finished with dimethylolurea in the United States has dropped from 30% in 1980 to 6% in 1990 (Hatch and Maibach, 1995). Dimethylurea has been used successfully as a reagent for modifying tyrosine residues in feed proteins and it has the potential to increase nutritional quality of feed proteins by decreasing their microbial degradation in the rumen (largest compartment in the cow stomach) (Friedman et al., 1982).

Both methylolurea and dimethylolurea are found as impurities in UF resins. These resins can be converted to thermosetting resins by controlled heating and pressing in the presence of catalysts. Urea-formaldehyde reaction products are used as controlled release nitrogen fertilizers (Sine, 1991). Approximately 80% of the slow-release fertilizer market is based on UF-containing products (Gerberich et al., 1979). A UF concentrate known as UF-71 (mixture of 50.5% formaldehyde, 20.5% urea, and 29% water) has been used to promote anticaking of urea prill products (Wycon Chemical Co., 1984). Furthermore, methylolurea moieties are used in melamine resins (Erickson and Golden, undated).

6.0 Environmental Occurrence

Methylolurea is not expected to persist in the environment (Landquist, 1955; cited by U.S. EPA, 1983). However, the presence of methylolurea class compounds in cutting fluids and cleaning agents, in permanent-press fabrics, and as an impurity in UF resins suggests that environmental exposures are likely. Methylolurea readily hydrolyzes to release formaldehyde (Hsiao and Villaume, 1978; cited by U.S. EPA, 1983). Dimethylolurea too releases formaldehyde to the environment (Robbins et al., 1984).

UF resins cannot be made free of residual formaldehyde. Under ambient conditions and during curing, uncured resins can release free formaldehyde, at rates gradually decreasing over time (Formaldehyde Institute, 1984). In pressed wood products, under high load conditions, even traces of residual, unreacted formaldehyde from the UF resin can result in measurable offgassing, causing discernible formaldehyde levels in indoor air. High temperatures and humidity, which hydrolyze formaldehyde, promote the release; they can triple or quadruple the rate of release. Urea also strongly affects the release rate because of an equilibrium reaction in which hydrolyzed formaldehyde is consumed, yielding methylolurea. Building materials, such as composition boards (e.g., particleboard), which consist of UF resins, can emit formaldehyde for several years after manufacture. During the last two decades, the molar ratio (formaldehyde:urea [F/U]) has been significantly decreased to limit the emission of formaldehyde. However, depending on the type of board and process, sometimes a UF resin with a low F/U is used, while sometimes the use of a resin with a higher F/U and the addition of a formaldehyde catcher will give better results (Meyer and Hermanns, 1985; Godish, 1989; Nuess and Price, 1997; McCann and Babin, 1998; Dunky, 2001).

7.0 Human Exposure

As a liquid, an exposure limit of 0.75 ppm as an eight-hour time weighted average (TWA) has been established for methylolurea (Ascension Parish CAER, undated).

Occupational exposure to the methylolurea class compounds may occur in industries producing these compounds commercially, treating textiles and wood, mixing and handling methylolurea compound-containing fillers used in molding adhesives, mixing and handling methylolurea compound-containing preservatives in metal-working fluids, developing photographic film, and producing or using methylolurea compound-containing cleaning agents or disinfectants.

Because methylolurea and dimethylolurea are impurities formed during the production of UF resins, the potential for occupational exposure to the compounds exists at any stage in the commercial manufacturing of UF resins or from the use of products containing these resins (e.g., pressed wood products, dinnerware, foundry core binder, flexible foams, insulation materials, and slow-release fertilizers) (Ludlan, 1973; Kumlin and Simonson, 1978; U.S. EPA, 1983). Prior to polymerization through heat and pH adjustment, UF prepolymers or precondensates are composed of methylolurea (29 to 40%) and its oligomers in various concentrations depending on the application and the precondensate stage. Therefore, exposure to the precondensate could result in exposure to methylolurea (Tomita and Hirose, 1976; Meyer, 1979; Kumlin and Simonson, 1981; all cited by U.S. EPA, 1983). Between 1972 and 1974, NIOSH estimated that 391,074 workers were potentially exposed to UF resins; the fraction exposed to methylolurea, however, was not known (U.S. EPA, 1983). [Noted: Contact with uncured UF resins is very low (Formaldehyde Institute, 1984).]

8.0 Regulatory Status

Federal regulations pertaining to methylolurea are in the table below. In May 1983, methylolurea was added to the Environmental Protection Agency (EPA) *Priority List* by the Toxic Substances Control Act (TSCA) Interagency Testing Committee (ITC). Recommended studies included health effects, short-term genotoxicity, toxicokinetics, and long-term bioassay, if indicated by results of the latter tests (48 FR 24443-24452) (U.S. EPA, 1983). A year later, methylolurea was removed from the list (49 FR 21371-21375) (U.S. EPA, 1984). EPA's decision was based on the responses received to the Advance Notice of Proposed Rulemaking (ANPR) (49 FR 21371-21375) regarding methylolurea and UF resins. Several companies reported that occupational exposure to uncured UF resins in the workplace was very low due to changes in UF resin manufacturing technology (e.g., the use of closed systems) and presented the results of exposure studies (e.g., many patch tests have proven negative) (American Cyanamid Co., 1984; Formaldehyde Institute, 1984; Wycon Chemical Co., 1984). Methylolurea is listed in the TSCA Inventory (TSCAINV, 2001).

The National Industrial Chemicals Notification and Assessment Scheme (NICNAS [Australia]), in consultation with the chemical industry and other governmental agencies, proposed that the criteria for Synthetic Polymers of Low Concern (PLCs) be revised. The proposal included the reclassification of methylolureas, currently in the Moderate Concern category under U.S. EPA, as reactive functional groups of high concern, until information by industry and/or other parties had been received (NICNAS, 1998).

Under the 1990, 1994, and 1998 Inventory Update Rule (IUR), methylolurea was available for sponsorship in the High Production Volume (HPV) Challenge Program though it has yet to be sponsored. In 1990, four companies reported manufacture or importation of the chemical: Auralux Corporation, BASF Corporation, DYNO Polymers, Inc., and Georgia-Pacific Corporation. In 1994, only Auralux Corporation and Georgia Pacific Resins, Inc. reported the data, and in 1998, BASF Corporation and Sybron Chemicals, Inc. reported such information (U.S. EPA, 1998, 1999, 2000).

	Regulatory Action	Effect of Regulation/Other Comments
E P A	40 CFR 716 PART 716 HEALTH AND SAFETY DATA REPORTING. Promulgated: 51 FR 32726, 09/15/86. U.S. Code: 15 U.S.C. 2607(d)	The provisions of this part require the submission of lists and copies of health and safety studies on chemical substances and mixtures selected for priority consideration for testing rules under section 4(a) of TSCA and on other chemicals for which EPA requires health and safety information in fulfilling the purposes of TSCA.
	40 CFR 716.120—Sec. 716.120 Substances and listed mixtures to which this subpart applies.	Methylolurea was listed on 07/01/83 and thus subject to all of the provisions of part 716.

9.0 Toxicological Data

9.1 General Toxicology

9.1.1 Human Data

No studies were located.

Numerous studies suggest that the toxicity of uncured UF resins may be attributed to formaldehyde (Formaldehyde Institute, 1984).

9.1.2 Chemical Disposition, Metabolism, and Toxicokinetics

Both methylolurea and dimethylolurea have been identified in rats as metabolic products of *N*-methyl-*N′*-(hydroxymethyl)thiourea, a bactericide used in humans for the treatment of peritonitis and infections of the bladder and uterus (Jones and Mashford, 1983). In male Sprague-Dawley rats (age not provided) administered *N*-methyl-*N′*-(hydroxy[^{14}C]-methyl)thiourea by intraperitoneal injection, methylolurea and dimethylolurea were identified in the urine. Their presence was attributed to the hydrolysis of *N*-methyl-*N′*-(hydroxymethyl)thiourea to formaldehyde within the bladder; formaldehyde then reacts with urea to form methylolurea and dimethylolurea (Mashford and Jones, 1982).

9.1.3 Acute Exposure

No data were found for methylolurea alone. However, studies using Elmer's Plastic Resin Cascamite Glue #DO 8 HL, a spray dried UF powdered glue containing as much as 10% methylolurea, were available. In rats, inhalation of the glue (200 mg/L [2.22 mol/m^3]) for one hour caused no deaths (Borden, 1973a). Oral administration of the glue (5.2 g/kg [57.7 mmol/kg]) also caused no deaths in the animals (Borden, 1973b). In rabbits, dermal application of the substance (2.2 g/kg [24.4 mmol/kg]) resulted in no mortality, and application to the eye (0.1 g [1.1 mmol]) caused no irritation, injury, or damage in the cornea, iris, or conjunctivae (Borden, 1973c,d).

9.1.4 Short-Term and Subchronic Exposure
No data were available.

9.1.5 Chronic Exposure
No data were available.

9.1.6 Synergistic/Antagonistic Effects
In mice, pretreatment with methylolurea reduced the LD_{50} for formaldehyde from 330 to 293 mg/kg (Horiguchi et al., 1973; cited by HSDB, 2001).

9.2 Reproductive and Teratological Effects
No data were available.

9.3 Carcinogenicity
No data were available.

9.4 Genotoxicity
In 48 outbred male rats, intragastric intubation of methylolurea in a UF condensate (dose reported to be 1/10 LD_{50}; neither were provided) induced a statistically significant difference in the number of chromosomal aberrations of the bone marrow cells between treated and control animals at 24 and 48 hours following dose administration (Erkis and Ratpan, 1973; cited by U.S. EPA, 1983). In a separate study, the chemical changed the apparent molecular weight of isolated DNA and increased the rate at which DNA attached to bacterial and animal cells. This property was correlated with the ability of the precondensate to produce cancer *in vivo* (Morin and Kubinski, 1978; cited by U.S. EPA, 1983).

9.5 Immunotoxicity
No data were available. (See the following section regarding studies with UF resins.)

9.6 Other Data
In humans suspected of having dermatitis, 63 of 462 patients tested positive in a patch test (American Academy screening series) to formaldehyde or formaldehyde-releasing products. Of these, 13 patients were originally referred because they had suspected clothing dermatitis. Ten of the 13 (90.9%) patients patch tested positive for dimethylolurea, and one of the 13 (9.1%) patch tested positive for DMDHEU (Sherertz, 1992; cited by Hatch and Maibach, 1995). In a retrospective study on 678 patients referred due to dermatitis of an unknown origin, 16 tested positive in a patch test (Chemotechnique Diagnostics patch test series or the Hermal textile series) to textile formaldehyde resins. Ten of the 16 (62.5%) and 5 of the 16 (31.3%) patients tested positive in the patch test to dimethylolurea and DMDHEU, respectively (Fowler et al., 1992; cited by Hatch and Maibach, 1995). Based on the results, the authors suggested that the causal agent for the observed dermatitis is the resin itself, and not the formaldehyde that it may release. Other reports of contact dermatitis from textiles treated with formaldehyde resins have

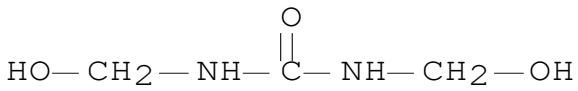
been attributed to the resins themselves (Malten, 1964; Hatch and Maibach, 1986; both cited by CIR Expert Panel, 1995).

Studies of UF resins show that "dermal exposure poses little or no significant risk to human health." Employees (average number of 50) who worked in molding compound manufacturing operations—i.e., tasks involving significant exposure to UF resins—for five years and were exposed to dust concentrations approximating the OSHA limit of nuisance dusts (15 mg/m^3) reported no adverse health effects. Human patch tests (n=200) showed that UF resins (Aerotex® resins 105, 140, and 218; Aerotex® cream 450; Aerotex resins or creams or Aerotex® Syrup 250 concentrate [solution of polymerized mono and dimethylolurea containing a significant quantity of the latter] on rayon gabardine; or cotton treated with Aerotex® products) were not irritating nor sensitizing (American Cyanamid Co., 1984).

Animal studies, however, showed an Aerotex® product to be irritating. Oral and dermal LD_{50} values of >10 g/kg (mL/kg) were reported for Aerotex® Syrup 581 (78% mixture of methylated methylolurea resins) in the male albino rat and rabbit. Hilltop-Wistar male albino rats orally dosed with 5.0 or 10.0 mL/kg Aerotex® Syrup 581 showed no signs of toxicity. In New Zealand male albino rabbits, a 24-hour occluded dermal application of 10.0 mL/kg of the solution produced edema in two animals and erythema and ecchymosis in all other animals. A much lower dose (0.5 mL) produced erythema and edema on the abraded skin of two rabbits. When applied to the eyes, Aerotex® Syrup 581 (0.1 mL) produced effects on the cornea (distinct opacity or ulceration and a slight dulling of the normal luster), iris (inflammation and a slight deepening of the folds or slight circumcorneal injection), and conjunctivae at 24 and 48 hours. With time, the effects were greatly reduced; at 72 hours, those on the iris had disappeared (American Cyanamid Co., 1984).

10.0 Structure-Activity Relationships

10.1 Dimethylolurea (CAS No. 140-95-4)

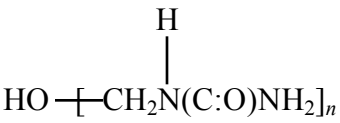


Short-term or Subchronic Toxicity: Male and female Sprague-Dawley rats administered dimethylolurea (1.0, 10.0, or 100.0 mg/kg) in 1% methyl cellulose via an intragastric cannula for 14 consecutive days and killed one day after the last treatment showed no significant exposure-related effects (Komsta et al., 1989).

Genotoxicity: Dimethylolurea in a concentration-dependent manner reduced the ability of the DNA in methyl methanesulphonate (MMS)-treated cells to migrate in the single cell gel electrophoresis (comet) assay. Two protocols were used: leukocytes in human whole blood were (1) simultaneously treated for two hours with 70 □M MMS and 1000, 3300, 10,000, or

20,000 µM dimethylolurea; and (2) treated for two hours with 70 µM MMS and then with 20,000 µM dimethylolurea at 0, 30, or 60 minutes after the start of treatment. Dimethylolurea alone decreased the extent of DNA migration compared to that for the solvent controls. The reduced ability for the DNA of dimethylolurea-treated cells (control or MMS-treated) to migrate was attributed to the ability of dimethylolurea to induce DNA crosslinks via its release of free formaldehyde (Pfuhler and Wolf, 1996). Additionally, dimethylolurea was positive in the *Salmonella* mutagenicity test (NTP, 2002).

10.2 Polyoxymethylene Urea (CAS No. 9011-05-6)



In 1995, the Cosmetic Ingredient Review (CIR) Expert Panel reported on the safety assessment of polyoxymethylene urea. This section contains data from this review. References cited in the report are provided. Based on the studies, the panel concluded the compound was "safe as used."

Polyoxymethylene urea, a synthetic polymer produced in stages by the condensation reaction of urea with formaldehyde, is used in the cosmetic industry as a bulking agent and to form the outer shell of microcapsules (Nikitakis, 1988; Nikitakis et al., 1991). Noncosmetic uses include application in resinous and polymeric coatings coming in contact with food; in polysulfide polymer-polyepoxy resins for contact with dry foods; as a bonding agent in the production of particleboard, chip board, and interior plywood; in coatings for paper products and fiberglass insulation; in the formulation of foam insulations; and in the manufacture of textiles, primarily wrinkle-resistant clothing fabrics (Marcussen, 1962; Breysse, 1985; Hatch and Maibach, 1986; Rothschild, 1988). The low-molecular weight ureas are quickly degraded in the environment, releasing free formaldehyde (Franklin Institute Research Laboratories, 1978). Before curing, polyoxymethylene urea contains 0 to 14% monomethylolurea (per high-performance liquid chromatography [HPLC]) and 0 to 8% dimethylolurea (per HPLC) (Formaldehyde Institute, 1984).

Human Data: Exposure to polyoxymethylene urea results in toxicity that seems to be mostly associated with formaldehyde gas (Harris et al., 1981). In two patch tests, polyoxymethylene urea (undiluted form and microcapsule form) was not irritating or sensitizing (Industrial Bio-Test Laboratories, 1975; 3M, 1991). Exposure from the use of polyoxymethylene urea in the wood industry has resulted in respiratory tract irritation (Cockcroft et al., 1982; Vale and Rycroft, 1988).

Acute Toxicity: In rats, oral LD_{50} values of >5.8 g/kg for polyoxymethylene urea, >5.2 mL/kg for liquid polyoxymethylene urea, 5.2 g/kg for spray-dried UF powdered glue, and 10,000 and 15,800 mg/kg for undiluted polyoxymethylene urea were reported (Ciba-Geigy Corp., 1973a; Wells Laboratories, 1973a; Younger Laboratories, 1974, 1979; Anonymous, 1986a). For microcapsule shell walls made of the urea, an oral LD_{50} of >20 g/kg was reported (3M, 1991). The dermal LD_{50} and LC_{50} of polyoxymethylene urea were >2.1 g/kg and >167 mg/m^3 air (four-hour exposure), respectively (Ciba-Geigy Corp., 1973b).

Rats given liquid polyoxymethylene urea (gavage; 10 g/kg) all survived until the end of the two-week observation period (Litton Bionetics, 1977a). A 24-hour application of polyoxymethylene urea (5000 mg/kg) to the occluded intact or abraded skin of the abdomens of rabbits produced neither death nor lesions; slight erythema, however, occurred on days 1 and 2 of treatment (Litton Bionetics, 1977b). In another study, application of the liquid form (2.2 g/kg for 24 hours) resulted in no deaths (Anonymous, 1986b); the same occurred with 2.2 g/kg of UF powdered glue and 7940 mg/kg polyoxymethylene urea (Well Laboratories, 1973b; Younger Laboratories, 1974, 1979). In other dermal irritation studies (durations not specified), patches of liquid polyoxymethylene urea (0.5 mL) on the intact and abraded skin of rats produced a very low primary irritation index (Anonymous, 1986d). The same could be said of polyoxymethylene urea glue, undiluted polyoxymethylene urea, powdered polyoxymethylene urea in polyethylene glycol 400, and polyoxymethylene urea in microcapsule form (Wells Laboratories, 1971a; Ciba-Geigy Corp., 1973d; Younger Laboratories, 1974, 1979; 3M, 1991).

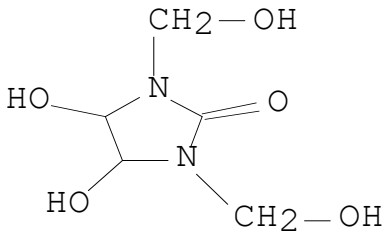
Rats exposed to a test atmosphere of 2 mg/kg of polyoxymethylene urea for one hour showed no signs of toxicity as well as no lesions at necropsy; all rats survived (Litton Bionetics, 1977c). In other studies, no signs of toxicity were seen in rats tested with 5.0 mg/L polyoxymethylene urea or mice exposed to 200 mg/L liquid polyoxymethylene urea or 200 mg/kg UF powdered glue (Well Laboratories, 1973c).

Instillation of polyoxymethylene urea as a liquid (0.1 mL), including in a diluted form (0.1 mL), as a glue (0.1 g), and as a microcapsule (dose not provided) into the eyes of rabbits produced signs of irritation (e.g., minimal conjunctivitis, edema, and a small ulcer), which disappeared by 72 hours (Wells Laboratories, 1971b; Ciba-Geigy Corp., 1973e; Younger Laboratories, 1974, 1979; Anonymous, 1986e; 3M, 1991).

Short-term/Subchronic Toxicity: In male rats, inhalation of a formulation containing 66-71% polyoxymethylene urea and cellulose (99.9 mg/m^3 for six hours per day for five days during weeks 1-3 and then four days on the last week) for 28 days caused no clinical signs of toxicity and no deaths. Body weight gain was slightly but not statistically significantly reduced. Absolute kidney and kidney/brain weights were also decreased, but there were no gross lesions. The lung/body weight value was also increased. Over half the number of rats (specifically, 70%) had interstitial pneumonia, while 30% had minimal, multifocal interstitial fibrosis (Bushy Run Research Center, 1987).

Genotoxicity: In *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538, polyoxymethylene urea (1, 10, 100, 500, and 1000 µL/plate) was not mutagenic in the absence and presence of metabolic activation (Hill Top Research, 1980). A 50/50 polyester/cotton fabric treated with polyoxymethylene urea was also negative in the Ames test using the five strains with and without S9 (Litton Bionetics, 1977d). A combination of polyoxymethylene urea (0.3-6%) and mouse liver extract (one-hour incubation) significantly increased binding between the DNA and bacterial cells of *Escherichia coli*. Additionally, the finding that sedimentation rate of DNA was faster with the combination than with control DNA implied that "metabolically activated polyoxymethylene urea produces DNA damage… [suggesting] the possibility that this ingredient could be mutagenic or carcinogenic" (Morin and Kubinski, 1978).

10.3 DMDHEU (CAS No. 1854-26-8)



The relative release of formaldehyde by DMDHEU is low compared to that by dimethylolurea; DMDHEU releases <100 ppm formaldehyde per gram of fabric, while dimethylolurea releases >1000 ppm formaldehyde per gram of fabric (Hatch and Maibach, 1995). It is classified as "inherently biodegradable" (logarithmic octanol/water partition coefficient [log K_{OW}] of -2.2 indicates no potential for bio- or geoaccumulation) (OECD/UNEP, undated).

Human Data: DMDHEU is not a primary irritant. However, products containing ≥0.21 (units not specified) formaldehyde may induce skin sensitization (OECD/UNEP, undated).

Chemical Disposition, Metabolism, and Toxicokinetics: DMDHEU is well absorbed by the skin and from the gastrointestinal tract. More than 90% of absorbed DMDHEU is excreted unchanged in urine within 24 hours after exposure (Anonymous, 1995).

When male B6C3F_1 mice were given [^{14}C]-DMDHEU (5, 50, or 500 mg/kg body weight), 60-74% of the administered dose was eliminated in the feces and 7-12% in the urine after 24 hours. At 48 hours, the recoveries were 88-93% in feces and 8-14% in the urine. Analysis of fecal extracts suggested that radiolabeled DMDHEU was excreted unchanged (IRDC, 1982).

In male Fischer 344 rats, intravenous administration of [^{14}C]-DMDHEU (~50 mg/kg) resulted in 85% of the dose excreted unchanged in the urine at six hours and >95% at 24 hours. Minor

amounts were in feces (<3%) and breath (<0.2%). Oral absorption of [^{14}C]-DMDHEU, based on urinary excretion, was dose-dependent: 17% of ~500 mg/kg dose was absorbed, 28% of ~1000 mg/kg dose, and 38% of ~ 2000 mg/kg. Muscle and skin contained the highest proportion of ^{14}C with both routes; after 72 hours, <0.5% of the dose was in the tissues. Dermal application of 3.5 and 13 mg/cm^2 [^{14}C]-DMDHEU for six days resulted in absorption of ~5% of the applied dose, while a dose of 0.3 mg/cm^2 resulted in ~1% of the applied dose. Partial occlusion of the site caused a >4-fold increase in dermal absorption. Compared to the intravenous and oral routes, the largest amounts of ^{14}C were observed in adipose tissue, while lesser amounts were found in muscle (RTI, 1985).

In New Zealand White rabbits receiving occlusive or semi-occlusive dermal applications of cotton or polyester-cotton fabrics treated with [^{14}C]-DMDHEU, up to 2.6% of the radioactivity was detected in the skin after 48 hours, with smaller amounts found in the kidneys, liver, blood, urine, and exhaled CO_2. The total radioactivity in the blood and exhaled CO_2 increased with time and reached a peak value at 24 hours, after which it declined. Uptake from the cloth into the skin was increased when [^{14}C]-DMDHEU was prepared from isolated DHEU (two-step preparative method) rather than the three-step commercial process, or was commercially prepared and incorporated into cotton polyester rather than cotton. The addition of synthetic perspiration tended to increase the amount of radioactivity in the skin. Eighty to 90% of the radioactive material released from the cloth was found in the skin under the patch, with very little radioactivity being found in the directly underlying muscle tissue. The authors concluded that the radioactive material released from the [^{14}C]-DMDHEU-containing cloth binds to the skin but penetrates the epidermis poorly (Robbins et al., 1984). In another rabbit study, radiolabeled DMDHEU (in cloth treated with DMDHEU prepared from [^{14}C]-formaldehyde) was absorbed through the skin of the animals and had absorption, distribution, and excretion characteristics similar to those of topically applied formaldehyde. It was determined that no more than 2 to 3% of the penetrating radiolabel could be free formaldehyde (Georgia-Pacific Corp., 1984).

Acute Toxicity: In rats, an oral LD_{50} of >7500 mg/kg was reported for DMDHEU (Anonymous, 1995). In another study, the LD_{50} was calculated to be >10,000 mg/kg body weight (IRDC, 1983a,b).

Rats exposed to an enriched atmosphere of DMDHEU (level not specified) for eight hours at room temperature exhibited difficulty in breathing and irritation of the mucous membranes (Anonymous, 1995). In rabbits, dermal application with DMDHEU (500 mg) for 24 hours produced severe irritation; when applied to the eyes, mild irritation was observed (Marhold, 1972; cited by RTECS, 1996). A 45% aqueous solution of DMDHEU, however, was not irritating to the skin or eyes of the animals (Anonymous, 1995).

Short-term or Subchronic Toxicity: Mice and rats orally given DMDHEU (256-11,680 mg/kg body weight) daily for 12 days all survived and showed no compound-related changes in general appearance, mean body and organ weights, and micro- and macroscopic findings. At 4000 mg/kg, the heart relative weight mean of males was significantly increased compared to controls;

however, the biological importance of this was unknown (IRDC, 1981a, 1983a). Under the same conditions, rats also showed no treatment-related changes, except for those receiving 11,680 mg/kg. All high-dose animals had an increased bilateral inflammation of the nasal passages with an increased severity of reaction compared to controls (IRDC, 1981b,c).

No treatment-related effects were found in mice administered DMDHEU (1000, 3000, and 6000 mg/kg/day) by oral intubation for five days per week for 13 weeks. The chronic interstitial pneumonia observed in the animals (and controls) was consistent with the Sendai virus. A maximum tolerated dose (MTD) of ≥6000 mg/kg/day was therefore reported (IRDC, 1983a). The Pathology Working Group (PWG) confirmed the occurrence of vascular lesions in the hearts of females (Hall et al., 1984 lett.).

When rats were put through the same experimental conditions, three males were found dead on day 3 of week (one from aspiration pneumonia; the other two of unknown causes). Additionally, male rats showed a consistently lower mean body weight gain compared to controls beginning on week 3; statistically significantly lower mean body weights were seen at weeks 8-13. At termination, group mean body weight was 12.3% lower than that of the controls. For the mid-dose males, statistically significantly lower mean body weights were seen at weeks 9 and 12, and at termination, the group mean body weight was 7.5% lower than controls. Female rats showed no significant body weight differences compared to controls. No compound-related organ weight differences were observed in either sex (IRDC, 1983b; Hall et al., 1984 lett.).

Pharmacotoxic signs included yellow discoloration of fur in the anogenital region (mid and high dose, males and females), yellow discoloration in the abdominal region (high dose, males), soft stool (high dose, males), flesh from or the distal tail itself missing, clear or red ocular discharges, and ptosis (high dose, females). On day 3 of week 1, one male exhibited hypoactivity, decreased grasping reflex, extremities hypothermic to touch, and ataxia. In the high-dose group, one male had multiple yellowish linear lesions in the testis unilaterally. Mild mineralization of the myocardium or valvular endocardium was seen in two males of the same group; one of these rats also had a moderate bilateral mineralization of the testes (corresponding to the lesion found macroscopically). Mild mineralization in the lungs was observed in two additional rats of this group. The MTD is 3000 mg/kg for male rats and ≥6000 mg/mg for female rats. The observed perivascular lymphoid infiltration in the lung, interstitial pneumonia, and lymphoid infiltrations in the nasal passage were consistent with the elevated Sendai titer (IRDC, 1983b; Hall et al., 1984 lett.).

Reproductive and Teratological Effects: In rats and mice, DMDHEU (41.4% in water) given five days per week for 90 days, produced no toxic effects in reproductive function or morphological abnormalities in sex organs (e.g., testes, epididymis, prostate, preputial gland, uterus, ovaries, and clitoral gland) in male rats treated with up to 3000 mg/kg/day and in female rats, female mice, and male mice treated with up to 6000 mg/kg/day (IRDC, 1983a,b [also cited by SURG SOCMA, 2001]). In pregnant Wistar rats, DMDHEU (64% in water; 250, 500, and 1000 mg/kg day on days 7-16 of pregnancy) produced no compound-related teratogenic effects. A no observed

adverse effect level (NOAEL) of 640 mg/kg was established for both maternal toxicity and teratogenicity (HMR, 1998 [cited by SURG SOCMA, 2001]; OECD/UNEP, undated).

Genotoxicity: DMDHEU (33-10,000 µg/plate) dissolved in dimethyl sulfoxide (DMSO) did not induce a significant increase in *his* gene mutations in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 using the pre-incubation method in the presence and absence of 10% rat or 10% hamster liver S9 mix. Using the same experimental conditions except for the substitution of distilled water for DMSO as the solvent, DMDHEU was mutagenic in *S. typhimurium* strain TA100 in the presence of rat and hamster liver S9 mix, and was weakly mutagenic in strain TA98 in both the presence and absence of hamster liver S9 mix. It was postulated that the conflicting results could be attributed to the use of different solvents in the two laboratory trials (Zeiger et al., 1987).

In *Drosophila melanogaster*, DMDHEU (60,000 ppm) induced a significant (four-fold) increase in sex-linked recessive lethal mutations but not reciprocal translocations (Foureman et al., 1994; OECD/UNEP, undated). In an *in vivo* micronucleus assay, the substance (dose not provided) failed to show clastogenicity (OECD/UNEP, undated).

11.0 Online Databases and Secondary References

11.1 Online Databases

Chemical Information System Files
TSCATS (Toxic Substances Control Act Test Submissions)
SANSS (Structure and Nomenclature Search System)

DIALOG Files
359 Chemical Economics Handbook
161 NIOSHTIC (Occupational Safety and Health)
302 Kirk-Othmer Encyclopedia of Chemical Technology

National Library of Medicine Databases
EMIC and EMICBACK (Environmental Mutagen Information Center)

STN International Files

BIOSIS	CIS	MEDLINE
CA File	CSNB	PROMT
CANCERLIT	EMBASE	Registry
CEN	HODOC	RTECS
CHEMSAFE	HSDB	TOXLINE

TOXLINE includes the following subfiles:

Toxicity Bibliography	TOXBIB
International Labor Office	CIS
Hazardous Materials Technical Center	HMTC
Environmental Mutagen Information Center File	EMIC
Environmental Teratology Information Center File (continued after 1989 by DART)	ETIC
Toxicology Document and Data Depository	NTIS
Toxicology Research Projects	CRISP
NIOSHTIC®	NIOSH
Pesticides Abstracts	PESTAB
Poisonous Plants Bibliography	PPBIB
Aneuploidy	ANEUPL
Epidemiology Information System	EPIDEM
Toxic Substances Control Act Test Submissions	TSCATS
Toxicological Aspects of Environmental Health	BIOSIS
International Pharmaceutical Abstracts	IPA
Federal Research in Progress	FEDRIP
Developmental and Reproductive Toxicology	DART

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