NATIONAL TOXICOLOGY PROGRAM

EXECUTIVE SUMMARY OF SAFETY AND TOXICITY INFORMATION

N-(3-CHLOROALLYL)HEXAMINIUM CHLORIDE

CAS Number 4080-31-3

July 16, 1991

Submitted to:

NATIONAL TOXICOLOGY PROGRAM

Submitted by:

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Chemical Evaluation Committee Draft Report

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OVERVIEW[1]

Nomination History: *N-(3-Chloroallyl)hexaminium chloride was originally nominated for carcinogenicity testing by the National Cancer Institute (NCI) in 1980 with moderate priority. In March 1980, the Chemical Evaluation Committee (CEC) recommended carcinogenicity testing. Due to budgetary cutbacks in 1982, this compound was reevaluated and recommended for in vitro cytogenetics and chemical disposition testing by the CEC, and was selected for chemical disposition testing by the Executive Committee. The renomination of this chemical in 1984 by the NCI was based on potential for significant human exposure and concern that it may be carcinogenic due to structural considerations. This recent nomination was given a high priority for chemical disposition studies and a moderate priority for carcinogenicity testing. In 1987, the NCI recommended upgrading the priority for carcinogenicity testing.*

Chemical and Physical Properties: *N-(3-Chloroallyl)hexaminium chloride is a cream-colored powder with a pungent odor. The substance is soluble in water and has low to moderate solubility in organic solvents including ethanol, methanol, and acetone.*

Production/Uses/Exposures: *N-(3-Chloroallyl)hexaminium chloride is a broad spectrum biocide that is used as a preservative in many different consumer products including cosmetics, paints, metalworking fluids, adhesives, construction materials, petroleum and biodegradable surfactants. This compound is listed in the United States International Trade Commission publication Synthetic Organic Chemicals. However, no production data were available from this source or from the EPA Toxic Substances Control Act (TSCA) inventory or the Chemical Economics Handbook. The EPA has estimated that annual production may exceed 1 million pounds.*

Data from the National Occupational Exposure Survey (NOES), conducted by the National Institute for Occupational Safety and Health (NIOSH) during the years 1981 to

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[1]The information contained in this Executive Summary of Safety and Toxicity Information (ESSTI) is based on data from current published literature. The summary represents information provided in selected sources and is not claimed to be exhaustive.

1983, estimated that 137,008 workers, including 38,854 women, were potentially exposed to N-(3-chloroallyl)hexaminium chloride.

OSHA has not established a permissible exposure limit (PEL). Neither ACGIH nor NIOSH has recommended an exposure limit for this compound. The Food and Drug Administration (FDA) has approved N-(3-chloroallyl)hexaminium chloride for use as a preservative in the preparation of adhesives, as a preservative in latex, and as a preservative in the production of polyurethane resins. The Environmental Protection Agency has registered this chemical for use as a fungistat and for use in metal-working fluids.

Toxicological Effects:

Human: *N-(3-Chloroallyl)hexaminium chloride was found not to be a primary skin irritant in the majority of patch test studies conducted. However, in one study, this compound induced severe erythema upon dermal application. N-(3-Chloroallyl)hexaminium chloride was not found to cause sensitization reactions in the majority of studies found in the literature. However, this compound has been reported by one source to be the second most common human sensitizer, while other authors stated that this compound is the third most common human sensitizer in cosmetics. N-(3-Chloroallyl)hexaminium chloride may also cause cross sensitization reactions in formaldehyde-sensitive patients. No data were found on the chemical disposition, chronic, carcinogenic, reproductive, or teratogenic effects in humans.*

Animal: *In chemical disposition studies by oral and intravenous routes in rats, urinary excretion was more significant than fecal excretion. Forty to fifty percent of this compound was expired as carbon dioxide. N-(3-Chloroallyl)hexaminium chloride was observed to be primarily distributed to the liver and kidneys. Formic acid has been identified as a metabolite. Application to the skin of rabbits produced reactions ranging from mild-marked irritation to death. These results varied with concentration administered and depended on whether this compound was applied to intact or abraded skin. N-(3-Chloroallyl)hexaminium chloride was found to be mildly irritating when instilled into rabbits' eyes. The reported oral LD_{50} values range from 940.0 mg/kg to*

2,664.0 mg/kg in rats, and 68.0 to 78.5 mg/kg in rabbits. The oral LD_{50} in guinea pigs was 710.0 mg/kg. It was observed that this compound is a potential sensitizer in mice and guinea pigs, and is noncomedogenic in rabbits.

Application to abraded and intact skin of 3/5 and 4/5 sexually immature male rabbits, respectively, caused a decrease in spermatogenesis, testes weight, and testes to body and brain weight ratios. However, no treatment related testicular effects were observed when N-(3-chloroallyl)hexaminium chloride was applied to abraded skin of sexually mature male rabbits. Liver weights, however, were depressed in the test animals administered doses of 50 and 100 mg/kg per day. In a teratogenicity study, the fetuses of female rats given daily doses of 25 and 75 mg/kg during days 6-15 of gestation were observed to have major malformations, primarily of the eye (microphthalmia). In addition, dams receiving 75 mg/kg had decreased body weight and body weight gain, and increased liver weight. Fetal resorption was increased and the fetal weights were significantly decreased. In another teratogenicity study in which rats were administered dermal applications of N-(3-chloroallyl)hexaminium chloride during days 6-15 of gestation, no signs of maternal or fetal toxicity, or fetal malformations, were observed. However, fetal resorption was increased in dams given 250 mg/kg.
No data were found on the chronic/carcinogenic effects of N-(3-chloroallyl)hexaminium chloride in animals.

Genetic Toxicology: *N-(3-Chloroallyl)hexaminium chloride was non-mutagenic to Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, and TA1538 in the presence and absence of metabolic activation. However, another source reports that this compound was weakly mutagenic in TA100 and TA97 in the presence of metabolic activation and weakly mutagenic in TA98 in the absence of metabolic activation. N-(3-Chloroallyl)hexaminium chloride was mutagenic in mouse lymphoma strain L5178Y (TK+/TK-) in the presence and absence of metabolic activation. The chemical was not genotoxic in a rat hepatocyte unscheduled DNA synthesis assay.*

Structure Activity Relationships: *N-(3-Chloroallyl)hexaminium chloride has a vinyl chloride moiety and has been reported to be structurally related to vinyl chloride, a*

known carcinogen. As a quaternary amine, N-(3-chloroallyl)hexaminium chloride may act as an alkylating agent via the potential allylic carbonium ion. N-(3-Chloroallyl)hexaminium chloride has been reported to be structurally related to methenamine (hexamethylene-tetramine), a drug which is metabolized to formaldehyde and ammonia. The quaternary ammonium compound, (2-chloroethyl)-trimethlyammonium chloride was not carcinogenic to F344 rats or B6C3F1 mice following oral (dosed feed) administration.

I. NOMINATION HISTORY AND REVIEW

A. Nomination History

1. Source: National Cancer Institute (NCI) [NCI, 1984a,b]

2. Date: Nomination - October 1984 [NCI, 1984a,b]

3. Recommendations:
   - Chemical disposition
   - Carcinogenicity

4. Priority: High - Chemical disposition
   Moderate - Carcinogenicity (recommendation of upgrading priority [NCI, 1987])

5. Rationale/Remarks:

   - Previously nominated (1980) by NCI with moderate priority for carcinogenicity testing based on potential for human exposure and suspicion of carcinogenicity.
   - Reviewed by CEC in March 1980 and recommended for carcinogenicity testing.
   - Re-evaluated by CEC (1982), following budgetary cutbacks, and recommended for mouse lymphoma assay, *in vitro* cytogenetics, and dermal chemical disposition studies.
   - Executive Committee (1982) selected chemical for skin chemical disposition studies.
   - Renominated by NCI in 1984 based on the following considerations:
     - Potential for significant human exposure based on its use in approximately 1,210 consumer products.
     - Moderate suspicion of carcinogenicity due to the presence of a vinyl chloride moiety and quaternary ammonium functionality.
   - Disposition studies of radiolabelled material by oral and intervenous routes in rats indicated 30 to 40% of n-(3-chloroallyl)hexaminium chloride is converted to carbon dioxide; urinary excretion is more important than fecal excretion.

B. Chemical Evaluation Committee Review

1. Date of Review:

2. Recommendation:

3. Priority:

4. NTP Chemical Selection Principles:

5. Rationale/Remarks:

C. Board of Scientific Counselors Review

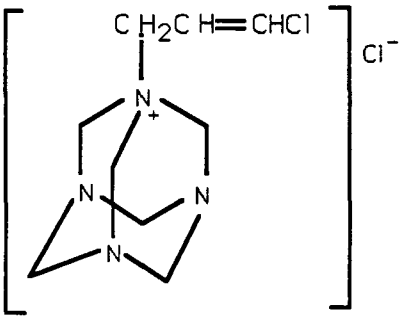
1. Date of Review:
2. Recommendations:
3. Priority:
4. Rationale/Remarks:

D. Executive Committee Review

1. Date of Review:
2. Decision:

II. CHEMICAL AND PHYSICAL DATA

A. Chemical Identifiers



N-(3-CHLOROALLYL)HEXAMINIUM CHLORIDE

Molecular Formula: $C_9H_{16}Cl_2N_4$ Molecular Weight: 251.17

CAS No. 4080-31-3
RTECS No. XX8450000

B. Synonyms and Tradenames

Synonyms: 3,-5,-7-triaza-1-azoniaadamantane, 1-(3-chloroallyl)-chloride (8Cl); 3,-5,-7-triaza-1-azoniatricyclo (3.3.1.13,7)) decane, 1-(3-chloro-2-propenyl)-, chloride (9Cl); 1-(3-chloroallyl)-3, 5, 7-triaza-1-azoniaadamantane chloride; 3, 5, 7-triaza-1-azoniatricyclo (3.3.1.1) decane, 1-(3-chloro-2-propenyl)-; 1-(3-chloro-2-propenyl)-3,5,7-triaza-1-azoniatricyclo (3.3.1.1) decane chloride; chloroallyl methenamine chloride

Trade names: Quaternium 15®; Dowicil 75®; Dowicil 100®; Dowicil 200®; Dowco 184®; Dowicide Q®

C. Chemical and Physical Properties

Description: Cream colored powder [Budavari, 1989] with a pungent odor [JACT, 1986].

Melting Point: No data were found.

Boiling Point: No data were found.

Specific Gravity/ Density: No data were found.

Refractive Index: No data were found.

Solubility in water: Up to 25% w/w [Budavari, 1989]
127.2 g/100 g @ 25°C [Marouchoc, 1977]
127 g/100 g [McConville, 1986]

Solubility in Other Solvents: Ethanol-2.4 g/100 g @ 25°C; methanol (anhydrous)-20.8 g/100 g @ 25°C; isopropanol (anhydrous)-<0.1 g/100 g @ 25°C; mineral oil-<0.1 g/100 g @ 25°C; glycerine (99.5%)-12.6 g/100 g @ 25°C [Marouchoc, 1977]; propylene glycol (USP)-18.0-18.7% @ 25°C [McConville, 1986; Marouchoc, 1977]. Also reported soluble in acetone and hexane [AAPCO, 1966].

Log Octanol/Water Partition Coefficient: No data were found.

Reactive Chemical Hazards:

- Reasonably stable in the presence of nonionic, anionic, cationic formulation ingredients [Stack and Davis, 1984; Marouchoc, 1977; JACT, 1986] and in highly concentrated proteinaceous substances [Marouchoc, 1977; JACT, 1986]. Stable over a wide pH range (pH 4.0 to pH 10.5) [Marouchoc, 1977; JACT, 1986; McConville, 1986].
- Decomposes when heated above 60°C. Decomposition may result in the release of pyrimidenes, formamides [JACT, 1986], and methylene glycol [McConville, 1986]. Hydrolysis at room temperature may result in the release of formaldehyde [Stack and Davis, 1984; Ford and Beck, 1986; Fisher, 1980]. However, another source reports that there is no rigorous chemical evidence to support the release of formaldehyde [JACT, 1986].

Flammability Hazards:

- At temperatures in excess of 100°C, it will decompose and may produce flammable vapors [McConville; 1986, JACT, 1986].

III. PRODUCTION/USE

A. Production

1. Manufacturing Process

The specific method for manufacturing N-(3-chloroallyl)hexaminium chloride is proprietary [JACT, 1986]. However, quaternary compounds are prepared by reacting hexamine with the appropriate halocarbon in a nonaqueous solvent at room temperature [Scott and Wolf, 1962].

2. Producers and Importers

U.S. Producers:

Producers	Reference
Dow Chemical U.S.A Midland, Michigan	SRI,1990 Chemical Week Buyers' Guide, 1991

European Producers:

No data were found on European producers.

Importers

Importers	Reference
CIBA-Geigy Corporation Ardsley, New York	USEPA, 1990

3. Volume

Production Volume

N-(3-Chloroallyl)hexaminium chloride is listed in the United States International Trade Commission's publication Synthetic Organic Chemicals. However, no production data were available on N-(3-chloroallyl)hexaminium chloride from this source for the years 1978 -1989 [USITC, 1979-1990][2]. N-(3-Chloroallyl)hexaminium chloride is listed in the public file of the EPA TSCA Inventory, but no information was provided on production volume [USEPA, 1990]. N-(3-Chloroallyl)hexaminium chloride was not listed in the Chemical Economics Handbook [SRI, 1991].

It was reported that an estimated 9.1×10^8 g/year of N-(3-chloroallyl)hexaminium chloride was produced for consumption as a biocide in paints in 1975 [Johnson, *et al.*, 1984]. It was reported by the National Cancer Institute (NCI) that the Office of Pesticide Programs of EPA indicated that the annual production of this compound is greater than 1 million pounds based on 1984 data [NCI, 1987b].

Import Volume

One company is listed as an importer of N-(3-chloroallyl)hexaminium chloride in the EPA TSCA Inventory. However, no import data were provided [USEPA, 1990].

4. Technical Product Composition

N-(3-Chloroallyl)hexaminium chloride is available in a technical grade typically containing 67.5% active ingredient and 25% sodium bicarbonate (as a stabilizer), with the remaining 9.5% comprising other inert ingredients [NCI, 1987b]. N-(3-Chloroallyl)hexaminium chloride used in cosmetics typically assays at 94% minimum 1-(3-chloroallyl)-3,5,7-triaza-1-azoniaadamantane

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2 Production statistics for an individual chemical are given only when there are three or more producers, no one or two of which may be predominant. Moreover, even when there are three or more producers, statistics are not given if there is any possibility that their publications would violate the statutory provisions relating to unlawful disclosure of information accepted in confidence by the Commission. Data are reported by producers for only those items where the volume of production or sales or value of sales exceeds certain minimums. Those minimums for all sections are 5,000 pounds of production or sales or $5,000 of value of sales with the following exceptions: plastics and resin materials--50,000 pounds or $50,000; pigments, medicinal chemicals, flavor and perfume materials, and rubber processing chemicals--1,000 pounds or $1,000.

with 13.9% minimum ionic chloride. Residual organics may be present at concentrations less than 500 ppm. 1,3-Dichloropropene has not been detected at the detection limit of 1 ppm [JACT, 1986]. N-(3-Chloroallyl)hexaminium chloride is available from Sigma Chemical Company at a purity of 95% [Sigma, 1990].

B. Use

N-(3-Chloroallyl)hexaminium chloride is used as a broad spectrum biocide for the preservation of many consumer products [Tosti, *et al.*, 1990; Stack and Davis, 1984] including cosmetics [Fisher, 1980; Stack and Davis, 1984], eyelid cleansing compositions [Adkins and Rooney, 1990]), paints [Johnson, *et al.*, 1984], metalworking fluids [Rossmoore, 1981], adhesives, and food packaging materials [JACT, 1986]. N-(3-Chloroallyl)hexaminium chloride is effective as a bactericide at low concentrations (0.1-0.2%) [Fisher, 1980; Marouchoc, 1977] and is effective over a wide pH range (pH 4.0-10.5) [Marouchoc, 1977; McConville, 1986; JACT, 1986].

Table 1 lists specific products containing N-(3-chloroallyl)hexaminium chloride, the total number of formulations in each product category, the number of these formulations containing N-(3-chloroallyl)hexaminium chloride, as well as the number of products within a given concentration range. This information reflects Food and Drug Administration (FDA) product formulation data from 1981.

Table 1. Products Containing N-(3-Chloroallyl)hexaminium Chloride as a Preservative.

Product category	Total no. of formulations in category	Total no. containing ingredient	No. of product formulations within each concentration range (%)	
			>0.1-1	<0.1
Baby shampoos	35	2	1	1
Baby lotions, oils, powders, and creams	56	1	1	-
Other baby products	15	2	-	2
Bath oils, tablets, and salts	237	4	-	4
Bubble baths	475	6	2	4
Bath capsules	3	2	-	2
Other bath preparations	132	10	2	8
Eyebrow pencil	145	1	-	1
Eyeliner	396	31	20	11
Eye shadow	2582	146	35	111
Eye lotion	13	3	--	3
Eye makeup remover	81	3	3	--
Mascara	397	88	55	33
Other eye makeup preparations	230	17	8	9
Fragrance powders (dusting and talcum, excluding aftershave talc)	483	32	2	30
Sachets	119	5	-	5
Other fragrance preparations	191	6	-	6
Hair conditioners	478	26	13	13
Hair sprays (aerosol fixatives)	265	3	1	2
Permanent waves	474	4	3	1
Hair rinses (noncoloring)	158	10	1	9
Hair shampoos (noncoloring)	909	81	33	48
Tonics, dressings, and other hair grooming aids	290	4	3	1
Waves sets	180	4	2	2
Other hair preparations (noncoloring)	177	6	1	5
Hair dyes and colors (all types requiring caution statement and patch test)	811	3	1	2
Blushers (all types)	819	18	11	7
Face powders	555	10	4	6
Makeup foundations	740	61	14	47
Makeup bases	831	102	11	91
Rouges	211	8	1	7
Other makeup preparations	530	13	4	9

Table 1. Products Containing N-(3-Chloroallyl)hexaminium Chloride as a Preservative. (cont'd)

Product category	Total no. of formulations in category	Total no. containing ingredient	No. of product formulations within each concentration range (%)	
			>0.1-1	<0.1
Cuticle softeners	32	1	-	1
Nail creams and lotions	25	2	-	2
Other manicuring preparations	50	5	2	3
Bath soaps and detergents	148	9	5	4
Deodorants (underarm)	239	2	1	1
Men's talcum	13	1	-	1
Other shaving preparation products	29	1	1	-
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	680	60	18	42
Face, body, and hand skin care preparations (excluding shaving preparations)	832	81	27	54
Hormone skin care preparations	10	2	2	-
Moisturizing skin care preparations	747	78	35	43
Night skin care preparations	219	10	3	7
Paste masks (mud packs)	171	6	1	5
Skin fresheners	260	6	4	2
Wrinkle smoothers (removers)	38	1	1	-
Other skin care preparations	349	18	10	8
Suntan gels, creams, and liquids	164	16	8	8
Indoor tanning preparations	15	1	1	-
Other suntan preparations	28	3	3	-
1981 Totals		1015	354	661

JACT, 1986

IV. EXPOSURE/REGULATORY STATUS

A. Consumer Exposure

Consumer exposure to N-(3-chloroallyl)hexaminium chloride results from the extensive use of this compound in consumer products ranging from paints and other home improvement materials to swimming pool chemicals and cosmetics [NCI, 1984b].

B. Occupational Exposure

Exposure to N-(3-chloroallyl)hexaminium chloride among workers handling cutting fluids has been reported [Grattan *et al*, 1989].

Data from the National Occupational Exposure Survey (NOES), conducted by the National Institute for Occupational Safety and Health (NIOSH) between 1981 and 1983, estimated that 137,008 workers including 38,854 female employees, were potentially exposed to N-(3-chloroallyl)hexaminium chloride in the workplace. The NOES database does not contain information on the frequency, level, or duration of exposure to workers of any chemicals listed therein [NIOSH, 1991].

C. Environmental Occurrence

As described in an abstract from an Italian study, N-(3-chloroallyl)hexaminium chloride at concentrations of 125 and 250 ppm was found to be degraded by activated sewer sludge. On the basis of this result, the investigators concluded that the chemical posed little hazard to the environment when released at low levels. However, at higher levels (not specified) N-(3-chloroallyl)hexaminium chloride was found to kill the microorganisms composing the sludge. No other data were found [Gambini, 1975].

D. Regulatory Status

- OSHA has not established a permissible exposure limit (PEL) for N-(3-chloroallyl)hexaminium chloride.
- The Food and Drug Administration (FDA) has approved N-(3-chloroallyl)hexaminium chloride for the following uses:
  - preservative in the preparation of adhesives to be used in components of packaging materials intended for use in packaging, transporting, or holding food within the limits of prescribed conditions {21 CFR 175.105}.
  - preservative at 0.3% in latex used as pigment binders in paper and paperboard in contact nonacidic and nonalcoholic foods. As a preservative at a level not to exceed 0.07% by weight in latexes and 0.05% by weight in pigment slurries used as components of coatings for paper and paperboard intended for use in contact with food{21 CFR 176.70}.
  - preservative in the production of polyurethane resins to be used as the food-contact surface of articles intended for use in contact with specified dry foods according to the prescribed conditions {21 CFR 177.1680}.

- The EPA has registered N-(3-chloroallyl)hexaminium chloride for the following uses:
  - As a fungistat for use in cosmetics Dowicil 200® [NCI, 1987b].
  - For use in metalworking fluids at a concentration of 0.015-0.2% [Rossmoore, 1981].

E. Exposure Recommendations

- ACGIH has not recommended an exposure limit for N-(3-chloroallyl)hexaminium chloride.
- NIOSH has not recommended an exposure limit (REL) for N-(3-chloroallyl)hexaminium chloride.
- The over-the-counter (OTC) drug ingredient advisory review panel on topical analgesics, antirheumatics, otic, burn, sunburn treatment, and preventative products classified N-(3-chloroallyl)hexaminium chloride as an inactive ingredient or pharmaceutical necessity. When used in concentrations at the level of, or above, the minimum effective dose, it is considered an active ingredient [JACT, 1986].

V. TOXICOLOGICAL EFFECTS

Of the studies reported throughout the Toxicological Effects Section (V. A-F) more than half come from unpublished data of studies performed by, or for, Dow Chemical Company from 1965-1984. Approximately one quarter of the studies summarized are from unpublished data submitted by the Cosmetic, Toiletry and Fragrance Association (CFTA). The summaries of the unpublished data that appear in this report are based on a toxicology review of N-(3-chloroallyl)hexaminium chloride that was published in the Journal of the American College of Toxicology (JACT).

A. Chemical Disposition

1. Human Data

No data were found on the chemical disposition of N-(3-chloroallyl)hexaminium chloride in humans.

2. Animal Data

oral, rats

- The chemical disposition of N-(3-chloroallyl)hexaminium chloride following oral administration was determined using a group of 9 male Fischer 344 rats. Disposition studies were also carried out after intravenous administration (see p.15). Each of the rats was given an oral dose, via gavage, of carbon-14 labelled ([^{14}C]) N-(3-chloroallyl)hexaminium chloride at doses of 1.86 mg/kg (0.101 mCi/Kg), 9.51 mg/kg (0.103 mCi/Kg), or 46.6 mg/kg (0.101 mCi/Kg). The solution of N-(3-chloroallyl)hexaminium chloride used was a mixture of *cis* and *trans* isomers with a specific activity of 13.3 mCi/mmol. This stock solution was diluted with an appropriate amount of unlabelled N-(3-chloroallyl)hexaminium chloride (*cis*) to prepare the doses for administration. The animals' urine and feces were collected daily for 3 days. Seventy-two hours after dosing, the following tissues were collected: liver, lungs, kidneys, fat, stomach, small intestine, large intestine, and gut contents. A portion of the blood collected was centrifuged to obtain plasma. The exhaled carbon dioxide (CO_2) was trapped with 1 N sodium hydroxide, and exhaled formaldehyde was trapped as it was bubbled through an absorption tower with a solution of 76% ethanol containing 2,4-dinitrophenylhydrazine. The materials were collected from the towers at 1, 2, 4, 8, 12, 24, 48, and 72 hours after dosing.

  Based on assays for radioactivity, results indicated that a large portion (41.1±0.9%, 32.6±1.1%, and 32.1±1.6%, for high, medium, and low dose groups, respectively) of the radioactive N-(3-chloroallyl)hexaminium chloride was recovered as [^{14}C] CO_2. For each of the 3 doses, the greatest amount was collected 2-4 hours after dosing. From 48-72 hours, the recovery of radioactive carbon dioxide was less than 0.6% of the administered dose. Total [^{14}C] formaldehyde collected was found to be 0.076±0.029%, 0.115±0.069%, and 0.076±0.007% of the administered dose for the high, medium, and low dose groups, respectively. For each dose, less than 0.12% of the administered dose was trapped as [^{14}C] formaldehyde. Urinary excretion of radioactivity for high, medium, and low dose groups, was observed to be 27.0±1.1%, 37.3±1.1%, and 32.9±9.8%, respectively. Fecal excretion accounted for 9.86±0.86%, 9.87±0.50%, and 16.9±9.5% of the administered doses, for the high, medium and low dose groups, respectively. The greatest amount of radioactivity was recovered in the urine within the first 24 hours of N-(3-chloroallyl)hexaminium chloride administration.

  Of the tissues examined, the kidneys had the greatest concentration of radioactivity (31.8±3.2-34.0±2.0 nCi/g), the liver had the greatest total amount of radioactivity (1.08±0.14-1.29±0.06% of the dose), and blood

(7.70±0.13-9.12±0.74 nCi/ml) had a higher concentration of radioactivity than plasma (5.71±0.59-6.81±1.21 nCi/ml). The total amount of [^{14}C] N-(3-chloroallyl)hexaminium chloride recovered was 85.6 ± 1.2%, 83.2 ± 0.5%, and 81.9 ± 0.6% for the animals dosed with 1.86, 9.51 and 46.6 mg/kg, respectively. The N-(3-chloroallyl)hexaminium chloride that was not accounted for was assumed to have been absorbed into tissue and organs not considered in this study.

The authors report that major conclusions from this study and the NIEHS study described on p.15 are that the rat converts large portions of [^{14}C] N-(3-chloroallyl)hexaminium chloride to [^{14}C] carbon dioxide, and that the urinary excretion route is more important than fecal excretion. Interpretations of the results of this study should be limited, however, by the following facts: (a) no purity check for [^{14}C] N-(3-chloroallyl)hexaminium chloride was performed (the compound is known to be unstable); (b) the radioactive compound was a mixture of the *cis* and *trans* isomers, whereas the unlabeled compound was cis isomer. Concerning the latter point, the authors reported that it is unlikely that the conformation of the side-chain would greatly affect the rate of degradation of the molecule [NIEHS, 1985].

oral, rats

- The absorption, distribution, metabolism, and excretion of N-(3-chloroallyl)hexaminium chloride was studied by Dow Chemical Company (unpublished data, 1984) using female Fischer 344 rats. For this study either the hexamethylenetetramine ring or the chloropropene side chain was labelled. The ring was uniformly labelled with carbon-14 ([^{14}C]); the side chain was labelled with [^{14}C] at the C-2 position. Two groups of 3 rats were given a single oral dose of labelled [^{14}C] (activity not reported) N-(3-chloroallyl)hexaminium chloride at a concentration of either 5.0 or 75.0 mg/kg. Both the ring and side-chain labelled compound were studied at each dose. Samples of blood, urine, and feces were collected (time of collection not specified). The N-(3-chloroallyl)hexaminium chloride was almost completely absorbed (84-88%) within 48 hours (absorption rate not determined). The excretion of [^{14}C] N-(3-chloroallyl)hexaminium chloride was initially rapid ($t_{1/2}$=1.3± 0.1 hour) then slow ($t_{1/2}$=22.7± 2.0 hour)[3]. The N-(3-chloroallyl)hexaminium chloride that reached the systemic circulation was metabolized extensively (for these results, no distinction between ring and side chain labelled compound was provided). Forty to fifty percent of the radioactive carbon derived from the ring was expired as carbon dioxide (results for the side chain labelled compound were not reported). Several metabolites were found in the urine, but only formic acid was identified by ion exclusion chromatography and high performance liquid chromatography [JACT, 1986].

intravenous, rats

- A group of 3 female Fischer 344 rats was given an intravenous dose of 5 mg/kg of carbon-14 labeled (activity not reported) N-(3-chloroallyl)hexaminium chloride to study its absorption, distribution, metabolism, and excretion in a study conducted by Dow Chemical Company (unpublished data, 1984). The authors did not specify whether ring or side-chain labelled compound was administered. Blood samples, urine, and feces were collected (time of collection not specified). Results concerning absorption were not reported. Excretion of radioactivity was initially rapid ($t_{1/2}$=1.3 ± 0.1 hour) and then slow ($t_{1/2}$=22.7 ± 2.0 hour)[3]. Several metabolites were found in the urine, but only formic acid could be identified by ion exclusion chromatography and high performance liquid chromatography; attempts to identify the other metabolites were unsuccessful [JACT, 1986].

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[3]In this study, the disposition of n-(3-chloroallyl) hexaminium chloride was studied by the oral, dermal, and intravenous routes of exposure. It was not specified for which route the half life values for excretion were reported, or if the half life values represent an average for the three routes of administration.

intravenous, rats

- In conjunction with NIEHS's oral chemical disposition study previously described, a group of 3 male Fischer 344 rats was used to determine the rate and route of excretion of carbon-14 labelled ([^{14}C]) N-(3-chloroallyl)hexaminium chloride following intravenous administration. Each of the rats was injected via the tail vein with a dose of [^{14}C] N-(3-chloroallyl)hexaminium chloride of 9.95 mg/kg (0.184 mCi/Kg) in water. The solution of N-(3-chloroallyl)hexaminium chloride was a mixture of *cis* and *trans* isomers with a specific activity of 13.3 mCi/mmol. This stock solution was diluted with an appropriate amount of unlabelled N-(3-chloroallyl)hexaminium chloride (*cis*) to prepare the doses for administration. Exhaled carbon dioxide (CO_2) was collected as it was bubbled through absorption towers with sodium hydroxide. The contents of the absorption towers was collected at 1, 2, 4, 8, 12, and 24 hours after dosing. All urine and feces output were collected daily for 3 days. Twenty-four hours after dosing, the animals were sacrificed and their organs (liver, lungs, kidneys, fat, stomach, small intestine, and gut contents) and blood were assayed for radioactivity. A portion of the collected blood was centrifuged to obtain plasma.

  A large percentage (30.3±1.9%) of the [^{14}C] N-(3-chloroallyl)hexaminium chloride was recovered as [^{14}C] CO_2, 24 hours after dosing. The initial half-life for elimination of radioactivity by this route was approximately 1 hour. During the last two collection periods (8-12 hrs. and 12-24 hrs.), only 0.765±0.057% and 0.860±0.241% of the dose was excreted, respectively. It was estimated that 50.4±1.8% of the dose was excreted in the urine and 1.22±0.88% was excreted in the feces. Of the tissues examined, the kidneys (127.0±15 nCi/g) and the liver (110.0±27 nCi/g) had the highest concentrations of radioactivity. The liver had the greatest total amount of radioactivity (2.13±0.18%). There was no statistical difference in the concentration of radioactivity in blood (17.8±1.2 nCi/ml) and plasma (20.8±2.0 nCi/ml). The total amount of radioactivity recovered was 89±2.7%. The authors report that the incomplete recovery can be attributed to the fact that not all tissues were assayed. The tail was observed to have 0.134±0.039% of the administered radioactivity, indicating that the animals were properly injected.

  The authors report the major conclusions from the NIEHS oral and intravenous studies are that the rat converts large portions of [^{14}C] N-(3-chloroallyl)hexaminium chloride to [^{14}C] carbon dioxide, and that the urinary excretion route is more important than fecal excretion. Interpretations of the results of this study should be limited, however, by the following facts: (a) no purity check for [^{14}C] N-(3-chloroallyl)hexaminium chloride was performed (the compound is known to be unstable); (b) the radioactive compound was a mixture of the *cis* and *trans* isomers, whereas the unlabeled compound was the *cis* isomer. Concerning the latter point, the authors report that it is unlikely that the conformation of the side-chain would greatly affect the rate of degradation of the molecule [NIEHS, 1985].

dermal, rats

- In conjunction with the oral and intravenous study described previously (see page 14), two groups of 3 Fischer 344 female rats were given a dermal application of carbon-14 labelled (activity not reported) N-(3-chloroallyl)hexaminium chloride to study absorption, distribution, metabolism, and excretion. Both the ring and side-chain labelled compounds were studied at a concentration of either 5.0 or 75.0 mg/kg. Blood, feces, and urine samples were collected (time of collection not specified). Only 1-2% of the radiolabeled N-(3-chloroallyl)hexaminium chloride was absorbed after 48 hours from both concentrations administered; the absorption rates were not determined. Excretion of radioactivity was initially rapid ($t_{1/2}$=1.3 ± 0.1 hour) and then slow ($t_{1/2}$=22.7 ± 2.0 hour) [see footnote number 3]. (For these results, no distinction between ring and side chain labelled compound was provided). Five percent of the dermally applied carbon-14 ring labelled N-(3-chloroallyl)hexaminium chloride was recovered as carbon dioxide. (Results for the side chain labelled compound were not reported). Several metabolites were found in the urine, but only formic acid was identified by ion exclusion chromatography and high performance liquid chromatography [JACT, 1986].

B. Acute

1. Human Data

The data presented in the acute dermal toxicity studies described below are summarized in Table 2.

dermal, human

- A group of 20 healthy volunteers (10 male, 10 female) was used in a study conducted for Dow Chemical Company (unpublished data, 1971) concerning the irritancy potential of 2% aqueous N-(3-chloroallyl)hexaminium chloride using a single-insult patch test. Each of the individuals was given a single, 24-hour application of N-(3-chloroallyl)hexaminium chloride via a closed patch to the shoulder. The irritancy potential of N-(3-chloroallyl)hexaminium chloride was scored at 20 minutes and 24 hours post-patch removal. Three of the test subjects exhibited slight erythema 20 minutes after the patch was removed. All of the observed reactions had cleared after 1 hour. No other signs of irritation were observed. The 2% aqueous solution of N-(3-chloroallyl)hexaminium chloride was determined not to be a primary irritant [JACT, 1986].

dermal, human

- The irritancy potential of N-(3-chloroallyl)hexaminium chloride was determined in a study conducted by Dow Chemical Company (unpublished data, 1971) involving 10 test subjects. Each individual received doses of 0.5, 1.0, or 2.5% N-(3-chloroallyl)hexaminium chloride in Eucerin via a single, 24-hour occlusive patch applied to their backs. The irritancy potential was then scored immediately upon removal of the patch, and again after 24 hours. Because no reactions were observed, it was determined that N-(3-chloroallyl)hexaminium chloride in Eucerin is not a skin irritant [JACT, 1986].

dermal, human

- In a study conducted by Dow Chemical Company (unpublished data, 1971) a cream shampoo containing 0 (control), 0.2, or 0.5% N-(3-chloroallyl)hexaminium chloride was tested for irritancy potential. A group of 16 test subjects was exposed to the shampoo for 3 hours. The shampoo containing N-(3-chloroallyl)hexaminium chloride was found to be non-irritating, as no reactions were observed [JACT, 1986].

dermal, human

- A cleanser containing 0.2% N-(3-chloroallyl)hexaminium chloride was evaluated in a single insult patch test in a study sponsored by the CTFA (unpublished data, 1978). A group of 20 test subjects were administered a single dose of the undiluted cleanser via an occlusive patch for an unspecified length of time. A reference control material was tested under the same conditions. A single, slight reaction was observed from the cleanser and from the control material. The cleanser was determined to be non-irritating under the conditions tested [JACT, 1986].

dermal, human

- A 2% aqueous solution of N-(3-chloroallyl)hexaminium chloride was tested for its irritancy potential in eczema patients in a study conducted for Dow Chemical Company (unpublished data, 1971). A group of 20 eczema patients, whose eczema was attributed to a variety of agents, was administered a 24-hour occlusive patch containing the 2% aqueous solution of N-(3-chloroallyl)hexaminium chloride to the shoulder. The irritation was scored 20 minutes and 24 hours after the patch was removed. There were no visible signs of reaction to N-(3- chloroallyl)hexaminium chloride, and this compound was determined not to be a primary irritant in eczema patients [JACT, 1986].

dermal, human

- A group of 10 eczema patients was used to evaluate the irritancy potential of N-(3-chloroallyl)hexaminium chloride in a study conducted by Dow Chemical Company (unpublished data, 1971). The individuals were administered single 24-hour occlusive patches containing 0.5, 1.0, or 2.5% N-(3-chloroallyl)hexaminium chloride in Eucerin to noneczematous sites. The irritancy was scored immediately upon removal of the patch and again at 24 hours post-patch removal. None of the test subjects had any visible reactions, and this compound was found not to be a primary skin irritant [JACT, 1986].

dermal, human

- Three preparations of hand cream formulated with N-(3-chloroallyl)hexaminium chloride were evaluated simultaneously for irritancy potential in a study conducted by Dow Chemical Company (unpublished data, 1971). The test material was administered to a group of 32 eczema patients as occlusive patches to noneczematous sites on the shoulder at doses of hand cream formulation containing 0 (control-formulation 1), 0.2 (formulation 2), or 0.5% (formulation 3) N-(3-chloroallyl)hexaminium chloride for an exposure period of 24 hours. The irritation reactions were scored immediately after the patches were removed and again after 24 hours. There were no visible reactions to cream containing 0.2% N-(3-chloroallyl)hexaminium chloride. One test subject and 3 controls were observed to have erythema from cream with 0.5% N-(3-chloroallyl)hexaminium chloride. The difference in the number of reactions between test and control groups was determined to be non-significant [JACT, 1986].

dermal, human

- Three individual studies were conducted by Dow Chemical Company (unpublished data, 1971) to examine the irritancy potential of 3 formulations of a cream shampoo, containing varying amounts of N-(3-chloroallyl)hexaminium chloride, compared to the irritancy of the same shampoo product diluted in Eucerin. Fifty-six eczema patients (group 1) were given undiluted doses of the shampoo, under occlusive patches, with N-(3- chloroallyl)hexaminium chloride at concentrations of 0.0 (control-formulation 1), 0.2 (formulation 2), or 0.5% (formulation 3) for 24 hours. The irritancy potential was scored at 24 and 48 hours after application. Severe erythema that resembled "hyperemia" was observed in 44 of the 56 patients tested.

  Forty-two eczema patients (group 2) were tested with the shampoo formulation as a 50% solution in Eucerin, and 38 eczema patients (group 3) were given the shampoo as a 25% solution in Eucerin. Severe erythema was observed in 6/42 patients and slight erythema was observed in 14/42 patients in group 2. Fifteen of the 38 patients in group 3 had erythema. The authors concluded that dilution of the shampoos with Eucerin reduced the severity of the erythematous reaction [JACT, 1986].

Table 2. Studies of Acute Dermal Exposure to N-(3-Chloroallyl)hexaminium Chloride in Humans

No. of Case Subjects Skin Condition	N-(3-Chloroallyl) hexaminium chloride Preparation	Symptoms/ conclusion	Concentration of Compound in Patch Test (Exp. Time)	No. of Positive Patch Test Results (Time after patch removal)
20, healthy	in water	slight erythema/ non-irritating	2% (24 hrs.)	3/20 (20 min.); no reaction observed (24 hrs.)
10, healthy	in Eucerin	no visible reaction / non-irritating	0.5, 1.0, or 2.5% (24 hrs.)	0/10 (imm., 24 hrs.)
16, healthy	0.2% and 0.5% in cream shampoo	none/ non-irritating	0.2, or 0.5% (3 hrs.)	0/16 (imm.)
20, healthy	0.2% in undiluted cleanser	slight irritation/ non-irritating	0.2% (unspecified)	1/20 (imm.)
20, eczema	in water	none/ non-irritating	2% (24 hrs.)	0/20 (20 min., 24 hrs.)
10, eczema	in Eucerin	none/ non-irritating	0.5%,1.0%, or 2.5% (24 hrs.)	0/20 (imm., 24 hrs.)
32, eczema	0.2% and 0.5% in hand cream	erythema/ non-irritating	0.2% or 0.5% (24 hrs.)	0.2%: 0/32 0.5%: 1/32 (imm., 24 hrs.)
56, eczema	0.2% and 0.5% in cream shampoo	severe erythema, "hyperemia"/ irritation induced	0.2% or 0.5% (24 hrs.)	44/56 (24 hrs., 48 hrs.)
38, eczema	0.2% and 0.5% in cream shampoo (25% in Eucerin)	erythema/ irritation induced	0.2 or 0.5% (24 hrs.)	15/38 (24 hrs., 48 hrs.)
42, eczema	0.2% and 0.5% in cream shampoo (50% in Eucerin)	slight-severe erythema/ irritation induced	0.2 or 0.5% (24 hrs.)	6/42 (24 hrs., 48 hrs.) 14/42 (24 hrs., 48 hrs.)

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exp-exposure
pet-petrolatum
imm-immediate

JACT, 1986

2. Animal Data

The acute toxicity data described below (LD_{50} studies) as well as additional LD_{50} studies found in the literature are presented in Table 3. Information concerning acute ocular and dermal irritancy is described below, but has not been included in Table 3.

oral, rats

- The LD_{50} of N-(3-chloroallyl)hexaminium chloride was determined using groups of 12 CDF (Fischer 344 derived) rats (6 males, 6 females per dose group) in a study conducted by Dow Chemical Company (unpublished data, 1983). The rats were given a single oral dose, by gavage, of N-(3-chloroallyl)hexaminium chloride at a concentration of 200.0, 400.0, 800.0, 1,600.0, 3,200.0, or 6,300.0 mg/kg (test vehicle not reported), and observed for two weeks for signs of toxicity. All of the rats receiving 6,300.0 mg/kg died within 24 hours, and 5 male and 5 female rats died after being dosed with 3,200.0 mg/kg. No toxic effects were observed in rats given 200.0 or 400.0 mg/kg of N-(3-chloroallyl)hexaminium chloride. However, the rats receiving doses of 800.0 and 1,600.0 mg/kg were lethargic, had diarrhea, and had eyelid closure and/or lacrimation. The rats given 3,200.0 mg/kg had staining exudates of the nares and body tremors. At the end of the 2 weeks, all of the survivors were sacrificed. Necropsy of the animals showed no treatment related changes. N-(3-Chloroallyl)hexaminium chloride was determined to be moderately toxic. The LD_{50} for both male and female rats was found to be 2,664.0 mg/kg with a 95% confidence interval of 1,836.0 - 3,512.0 mg/kg [JACT, 1986].

oral, rats

- The LD_{50} of N-(3-chloroallyl)hexaminium chloride was determined using groups of 5 male and 5 female Sprague-Dawley rats in a study conducted by Dow Chemical Company (unpublished data, 1983). The rats were administered a single oral dose of N-(3-chloroallyl)hexaminium chloride at a concentration of 126.0, 252.0, 1,000.0, or 2,000.0 mg/kg in a 10% aqueous solution. The number of deaths that occurred per group was found to be 2, 1, 0, 2, and 5 (females) and 0, 0, 1, 5 and 1 (males) for doses of 126.0, 252.0, 500.0, 1,000.0, and 2,000.0 mg/kg, respectively. The LD_{50} for females was determined to be 1,070.0 mg/kg (768.0 - 1,490.0 mg/kg); for males the LD_{50} was found to be 940.0 mg/kg (612.0 - 1440.0 mg/kg). No information regarding possible toxic effects was provided [JACT, 1986].

oral, rats

- The acute toxicity of N-(3-chloroallyl)hexaminium chloride was studied using 4 groups of 5 female Sprague-Dawley rats in a study conducted by Dow Chemical Company (unpublished data, 1983). The rats were administered a single oral dose by gavage of N-(3-chloroallyl)hexaminium chloride in a 50% aqueous solution at concentrations of 252.0, 500.0, 1,000.0, or 2,000.0 mg/kg. The rats were evaluated for signs of toxicity and gross lesions. The rats receiving a dose of 252.0 or 500.0 mg/kg showed no indication of toxic effects. Following the treatment with 1,000.0 mg/kg, rats were observed to have slight lethargy, piloerection, and wetness in the perineal region. Rats given 2,000.0 mg/kg were lethargic and had piloerection, dark deposits around the eyes, and diarrhea. Of the 5 rats receiving a dose of 2,000.0 mg/kg, only one survived the duration of the study. Pathological examination performed on the animals that were sacrificed did not indicate any gross lesions. The LD_{50} was determined to be 1,552.0 mg/kg (906.0 - 2,684.0 mg/kg) [JACT, 1986].

oral, rats

- An oral toxicity study of a cosmetic cleanser containing 0.2% N-(3-chloroallyl)hexaminium chloride was performed using 5 rats of an unspecified strain in a study sponsored by CTFA (unpublished data, 1978). Each rat was given a dose of 15 g/kg of the undiluted product by gavage and observed for 7 days. One rat died within 24 hours of dosing, and no toxic effects were observed in the remaining four rats. The cosmetic cleanser was classified as nontoxic via ingestion, with an LD_{50} greater than 15 g/kg [JACT, 1986].

oral, guinea pigs

- The oral toxicity of N-(3-chloroallyl)hexaminium chloride was studied in groups of 5 male Hartley guinea pigs in a study conducted by Dow Chemical Company (unpublished data, 1983). Animals were given single oral doses of N-(chloroallyl)hexaminium chloride as a 10% aqueous solution ranging from 126 to 3,980 mg/kg. The LD_{50} was determined to be 710 mg/kg, and N-(3-chloroallyl)hexaminium chloride was considered to be moderately toxic. Signs of toxicity were not reported [JACT, 1986].

oral, rabbits

- The toxic effects of N-(3-chloroallyl)hexaminium chloride were studied in 4 groups of 5 female New Zealand white rabbits in a study conducted by Dow Chemical Company (unpublished data, 1983). The rabbits were given a single oral dose of 31.6, 63.0, 126.0, or 252.0 mg/kg N-(3-chloroallyl)hexaminium chloride as a 50% aqueous solution. The test animals receiving a dosage of 31.6 mg/kg showed no signs of toxicity or death. However, slight lethargy was observed in the animals receiving doses of 63.0, 126.0 or 252.0 mg/kg. All of the rabbits given 126.0 or 252.0 mg/kg of N-(3-chloroallyl)hexaminium chloride died, and one rabbit died after receiving 63.0 mg/kg N-(3-chloroallyl)hexaminium chloride. The LD_{50} was determined to be 78.5 mg/kg. N-(3-chloroallyl)hexaminium chloride was found to be very toxic when administered to this strain of rabbit by the oral route [JACT, 1986].

oral, birds

- The acute oral LD_{50} and the repellency-toxicity index (R_{50}), which is analogous to an LD_{50}, was determined for red wing blackbirds, and the LD_{50} was also determined for starlings. N-(3-Chloroallyl)hexaminium chloride suspended in propylene glycol was administered to an unspecified number of birds (redwing blackbird and starling) via gavage. The dose(s) were not specified. The LD_{50} for N-(3-chloroallyl)hexaminium chloride in starlings and blackbirds was determined to be greater than 100 mg/kg. The R_{50} for redwing blackbirds was found to be greater than 1.00 percent [Schafer, *et al.*, 1983].

dermal, rats

- The dermal toxicity of N-(3-chloroallyl)hexaminium chloride was investigated in rats of an unspecified strain in a study conducted by Dow Chemical Company (unpublished data, 1983). Three groups of 2 rats of an unspecified sex were administered doses of 500.0, 1,000.0, or 2,000.0 mg/kg N-(3-chloroallyl)hexaminium chloride as a 50% aqueous solution. The exposure site was covered for 6.5 hours, after which the exposed area was washed. None of the test animals died, and no evidence of toxicity was noted at any concentration [JACT, 1986].

dermal, guinea pigs

- In a study conducted by Dow Chemical Company (unpublished data, 1973), two groups of 10 albino guinea pigs (male and female) were used to study the irritation potential of N-(3-chloroallyl)hexaminium chloride in aqueous solution and Eucerin anhydrous ointment. The animals' right flanks were shaved, and ten, 0.2-gram applications of 5 or 10% N-(3-chloroallyl)hexaminium chloride in aqueous solution, or 5 or 10% N-(3-chloroallyl)hexaminium chloride in Eucerin were administered. The 10 doses were applied over a two-week period. The test animals' flanks were not covered with occlusive patches and the test materials were not washed off between applications. None of the test animals exhibited any signs of irritation or toxic reaction to N-(3-chloroallyl)hexaminium chloride in Eucerin, or as an aqueous solution. No data were available on control groups [JACT, 1986].

dermal, guinea pigs

- In a study conducted by Dow Chemical Company (unpublished data, 1971) the irritancy potential of 5% N-(3-chloroallyl)hexaminium chloride in a Eucerin anhydrous preparation was tested using 10 male guinea pigs of an unspecified strain. The test animals were given a single unspecified amount of the test material as an open application. The test site was evaluated after 6 and 24 hours of exposure. No signs of irritation or toxic reaction were observed. No data were available on control groups [JACT, 1986].

dermal, rabbits

- The acute percutaneous toxicity of a 50% aqueous solution of N-(3-chloroallyl)hexaminium chloride was studied by Dow Chemical Company (unpublished data, 1983) using groups of 4 (2 male, 2 female) rabbits of an unspecified strain. The rabbits' trunks were shaved and a concentration of 250.0, 500.0, 1,000.0, or 2,000.0 mg/kg N-(3-chloroallyl)hexaminium chloride was applied for 24 hours via occlusive patches. The rabbits' trunks were then rinsed and made inaccessible by a collar for another 72 hours. The test animals were observed for 2 weeks for signs of toxicity. Twenty-four hours after application of the test materials, topical responses were observed in 13 rabbits, with no relationship between dosage given. The symptoms observed were erythema (moderate: {4/13}; marked: {8/13}), edema (slight: {5/13}; moderate: {7/13}), and necrosis (moderate: {5/13}; marked {7/13}). Indications of toxicity observed included lethargy, anorexia, and rapid, shallow breathing. The mortality of the groups was as follows: 250.0 mg/kg (1/4); 500.0 mg/kg (3/4); 1,000.0 mg/kg (1/4); and 2,000.0 mg/kg (4/4). Necropsy of the animals showed no treatment-related lesions. The LD_{50} was determined to be 605.0 mg/kg with a 95% confidence interval of 102.0 - 1,559.0 mg/kg [JACT, 1986].

dermal, rabbits

- In a study by Dow Chemical Company (unpublished data, 1983), the dermal toxicity of N-(3-chloroallyl)hexaminium chloride was studied on rabbits of an unspecified strain using the same procedure described in the previous bullet with several modifications. Groups of 5 rabbits (male and female) were given doses of the test material at concentrations of 252.0, 500.0, 1000.0, or 3980.0 mg/kg applied to intact skin. Groups of 3 rabbits (2 groups per concentration), were given doses of 2000.0 mg/kg of the aqueous test material or 3980.0 mg/kg of powdered N-(3-chloroallyl)hexaminium chloride on abraded or intact skin. All of the animals receiving N-(3-chloroallyl)hexaminium chloride on abraded skin died. The following mortality rate for animals of both sexes administered N-(3-chloroallyl)hexaminium chloride on intact skin was dose dependent: 252.0 mg/kg (2/5); 500.0 mg/kg (2/5); 1000.0 mg/kg (3/5); 2000.0 mg/kg (5/5 and 2/3 {sex assignment not specified}); 3980.0 mg/kg (4/5); 3980.0 mg/kg {powdered} (0/3). The combined LD_{50} for the groups was determined to be 565.0 mg/kg with a 95% confidence interval of 227.0 - 1400.0 mg/kg [JACT, 1986].

dermal, rabbits

- In a study submitted by CFTA (unpublished data, 1978) the irritancy potential of a cleanser (wipe-off) containing 0.2% N-(3-chloroallyl)hexaminium chloride was tested using 9 rabbits of an unspecified strain and sex in a single insult occlusive patch test. The rabbits received a single application of the undiluted cleanser under an occlusive patch for an unspecified exposure period. The irritancy potential was scored 2 and 24 hours after the patch was removed. The cleanser tested was found to be slightly irritating as slight erythema was observed in all of the animals after 2 hours, and in 8/9 animals 24 hours after patch removal. The group Draize Primary Irritation Index was 0.78 (maximum of 4.0). No information regarding control animals was provided [JACT, 1986].

dermal, rabbits

- The irritancy potential of N-(3-chloroallyl)hexaminium chloride was tested by Dow Chemical Company (unpublished data, 1983) using 6 female New Zealand rabbits. Occlusive patches containing a dose of 0.5 g of undiluted N-(3-chloroallyl)hexaminium chloride were applied to intact and abraded skin for 24 hours. The irritation potentials were scored immediately and 48 hours after the patches were removed. N-(3-Chloroallyl)hexaminium chloride was determined to be a mild skin irritant: as slight (2/6) to moderate (2/6) erythema and slight (5/6) to moderate (1/6) edema was observed in the rabbits. The Draize Primary Irritation Index was 1.2 with a maximum of 8.0 [JACT, 1989].

dermal, rabbits

- Five rabbits of an unspecified strain were used to study the dermal irritation potential of N-(3-chloroallyl)hexaminium chloride in a study conducted by Dow Chemical Company (unpublished data, 1983). The N-(3-chloroallyl)hexaminium chloride was tested as a powder or as a 1.0, 5.0, or 10% aqueous solution. Two rabbits received either a dry or wet occlusive patch of powdered N-(3-chloroallyl)hexaminium chloride or N-(3-chloroallyl)hexaminium chloride in aqueous solution applied to an intact (ten, 0.5-ml applications over 14 days) or abraded (three, 0.5-ml applications over 3 consecutive days) sites on the abdomen. The rabbits receiving N-(3-chloroallyl)hexaminium chloride in aqueous solution were also given ten, 0.1-ml applications over a 14-day period to an uncovered ear. No irritation was observed from the 1.0 and 5.0% aqueous solutions at any site. The 10% aqueous solution caused no irritation to the ear, slight erythema to both intact and abraded skin, and slight exfoliation, crusting, and scarring to abraded skin. Patches containing powdered N-(3-chloroallyl)hexaminium chloride were found to be nonirritating to the intact skin, but slightly irritating to the abraded skin which had erythema and edema. The wet occlusive patches with N-(3-chloroallyl)hexaminium chloride were moderately irritating to intact and abraded skin and caused erythema, edema, necrosis, crusting, and scarring of the site of administration [JACT, 1986].

ocular, rabbits

- In a study submitted by CFTA (unpublished data, 1978), a cleanser (wipe-off) containing 0.2% N-(3-chloroallyl)hexaminium chloride was tested for eye irritation in rabbits. A single dose of the undiluted product was instilled in the eyes of 6 rabbits of unspecified sex and strain. In 3 rabbits, slight conjunctival irritation was observed that cleared by the fourth day. N-(3-Chloroallyl)hexaminium chloride was determined to be a mild eye irritant [JACT, 1986].

ocular, rabbits

- In a study submitted by CFTA (unpublished data, 1981) the eye irritation potential of N-(3-chloroallyl)hexaminium chloride was tested in New Zealand rabbits. A mascara containing 0.2% N-(3-chloroallyl)hexaminium chloride was found to be mildly irritating in 6 rabbits that were treated once in one eye. The rabbits were observed to have slight conjunctivitis one hour after treatment which cleared within 24-48 hours. There was no irritation of the cornea or the iris [JACT, 1986].

ocular, rabbits

- Two lots of mascara containing 0.2% N-(3-chloroallyl)hexaminium chloride were tested for ocular irritation using groups of 6 rabbits of an unspecified strain in a study submitted by CFTA (unpublished data, 1981). The rabbits received 0.1 ml of undiluted mascara instilled in one eye. The other eye was used as a control. The rabbits' eyelids were kept closed for several seconds after treatment, and were not rinsed. One lot of mascara caused slight conjunctivitis after one hour of exposure which cleared within 48 hours. The other mascara also caused slight conjunctivitis after one hour exposure, but this effect took 72 hours to clear. This product was determined to be a mild eye irritant [JACT, 1986].

ocular, rabbits

- The ocular irritancy potential N-(3-chloroallyl)hexaminium chloride was tested using 6 rabbits of an unspecified strain in a study by Dow Chemical Company (unpublished data, 1983). The rabbits were given a single 0.1 gram instillation of pure N-(3-chloroallyl)hexaminium chloride into the conjunctival sac of the right eye. The left eye served as an untreated control. Slight irritation was observed in 3/6 rabbits, and moderate irritation with a slight discharge was seen in one of the animals. All of the reactions had cleared after 72 hours. The Draize Primary Irritation Index was determined to be 1.7. It was concluded that N-(3-chloroallyl)hexaminium chloride is practically nonirritating to the eye.

  An additional three rabbits of an unspecified stain were given a 0.1 gram instillation of pure N-(3-chloroallyl)hexaminium chloride into the right eye for 30 seconds before rinsing. The left eye served as the negative control. After a period of 24 hours, 2/3 rabbits had slight irritation which cleared by 48 hours. The Draize Primary Irritation Index was determined to be 1.3. N-(3-Chloroallyl)hexaminium chloride was determined to be practically nonirritating to the eye [JACT, 1986].

ocular, rabbits

- Four New Zealand rabbits were used to test the ocular irritancy of aqueous N-(3-chloroallyl)hexaminium chloride in a study conducted by Dow Chemical Company (unpublished data, 1983). A 1 ml dose of the test material at a concentration of 1.0, 3.0, 5.0, or 10% N-(3-chloroallyl)hexaminium chloride was instilled into the right eye, 3 times a day for 5 days of the first week. The left eye was used as a control. For the last 2 weeks, 0.1 ml of the respective solution was instilled 3 times/day, 5 days a week. An additional control rabbit was used for the last 2 weeks of the study and was given 0.1 ml of distilled water in both eyes 3 times/day, 5 days/week. The rabbits given N-(3- chloroallyl)hexaminium chloride rubbed their eyes after being dosed with the material, but no other signs of irritation or corneal injury were observed in any of the animals [JACT, 1986].

ocular, rabbits

- N-(3-Chloroallyl)hexaminium chloride caused slight corneal necrosis in one of six rabbits of unspecified strain and sex tested. No other information was provided [Rossmoore, 1981].

ocular, rabbits

- A group of New Zealand albino rabbits were used to test the ocular irritancy of an eyelid cleansing formula containing 0.10% N-(3-chloroallyl)hexaminium chloride. Other components of the formula were Miranol MS-2 (8.13%), sodium chloride (0.70%), and PEG tallow polyamine (0.16%). The cleansing material was instilled into the conjunctival sac of the rabbit's right eye and the left eye served as a control. The irritation was scored at 1, 24, 48, and 72 hours after instillation. The material was found to be minimally irritating with a maximum mean irritation score of 1.3 [Adkins and Rooney, 1990].

Table 3. Studies on Acute Toxicity of N-(3-Chloroallyl)hexaminium Chloride in Animals

Route of Exposure	Species (Sex)/Strain	Number of Animals per dose group	Dose/ Range (mg/kg)	Comment	Reference
Oral	Rat (NS)/NS	NS	LD_{50}=1,190.0	NA	Rossmoore, 1981
Oral	Rat (male/female)/ CDF (Fisher 344 derived)	6 males, 6 females	LD_{50} = 2,664.0/ 1,836.0-3,512.0	lethargy, diarrhea, eye closure and/or lacrimation, body tremors, and staining exudates of the nares	JACT, 1986
Oral	Rat (male)/Sprague Dawley	5	LD_{50} =940.0/ 612.0-1,440.0	NA	JACT, 1986
Oral	Rat (female)/Sprague Dawley	5	LD_{50}=1,070.0/ 768.0-1,490.0	NA	JACT, 1986
Oral	Rat (female)/Sprague Dawley	20	LD_{50}=1,552.0/ 906.0-2,684.0	lethargy, piloerection, wetness in the perineal region, dark deposits around eyes, and diarrhea	JACT, 1986
Oral	Guinea pig (male)/Hartley	5	LD_{50} = 710.0	NA	JACT, 1986
Oral	Rabbit (NS)/NS	NS	LD_{50} = 68.0	NA	Marouchoc, 1977
Oral	Rabbit (female)/New Zealand white	20	LD_{50} = 78.5	slight lethargy	JACT, 1986

Table 3. Studies on Acute Toxicity of N-(3-Chloroallyl)hexaminium Chloride in Animals (continued)

Route of Exposure	Species (Sex)/Strain	Number of Animals per Dose Group	Dose/Range (mg/kg)	Comment	Reference
Oral	Chicks (male)	5	LD_{50} = 2,800.0 Powder in capsule	NA	JACT, 1986
Oral	Bird (NS)/starling and blackbird	NS	LD_{50}> 100.0	NA	Schafer, *et al.*, 1983
Inhalation	Rat (NS)/NS	NS	NA dust/L air)	no effect (9.33 mg	Rossmoore, 1981
Dermal	Rabbit (male/female)/NS	4	LD_{50} = 605.0/ 102.0-1,559.0	lethargy, anorexia, rapid shallow breathing	JACT, 1980
Dermal	Rabbit (male/female)/NS	5	LD_{50} = 565.0/ 227.0-1,400.0	NA	JACT, 1980
Dermal	Rabbit (NS)/NS	4	LD_{50}=2,000.0 mg/kg	NA	Rossmoore, 1981

NS - Not Specified
NA- Not Applicable

C. Prechronic

1. Human Data

The importance of N-(3-chloroallyl)hexaminium chloride as a sensitizer is reported to vary by country and is presumably dependent upon local exposure in the community. Based on results of skin patch tests, using cosmetic ingredients, conducted between 1977 and 1980 on 149 dermatology patients, the incidence of sensitization to this compound is higher in the U.S. (20%) than in the Netherlands (2.8%) and France (2.8%). In the U.S., N-(3- chloroallyl)hexaminium chloride has been reported to be the second most frequent human sensitizer in cosmetics (a fragrance is the first) [Cronin, 1978]. Another source reports that this compound is the third most common human sensitizer [Maisey and Miller, 1986].

Data for N-(3-chloroallyl)hexaminium chloride induced contact allergy reported for the Netherlands, United Kingdom, Italy, France and the United States are included in Table 4.

Table 4. Cases of N-(3-Chloroallyl)hexaminium Chloride-Induced Contact Allergy By Country

Case Subjects	Country (year)	Concentration of compound in patch test	History	Nos. or % of positive patch test results (time)	Reference
3739	US (1977-1980)	2% aqueous	dermatology clinic patients	32/3739 (NS)	Eiermann *et al.*, 1982
3166	US (1980-1982)	2% aqueous 2% in pet	dermatology clinic patients	128/3166 (NS) 29/3166 (NS)	JACT, 1986
1348	US (1981-82)	2% aqueous	dermatology clinic patients	59/1348 (NS)	Ford and Beck, 1986
179	Netherlands (NS)	2% in pet	suspected contact dermatitis	5/179 (48 hrs., 72 hrs.)	De Groot, *et al.*, 1985
501	Netherlands (NS)	1% in pet	suspected contact dermatitis	0/501 (NS)	De Groot, *et al.*, 1986b
1128	Netherlands (NS)	NS	suspected contact dermatitis	3/1128 (NS)	De Groot and Bos, 1987
627	Netherlands (1985)	1% in pet	suspected contact dermatitis	3/627 (NS)	De Groot *et al.*, 1986a
2169	UK (NS)	NS	dermatology clinic patients	4.3% (NS)	De Groot and Bos, 1987
1575	UK (NS)	NS	dermatology clinic patients	1.9% (NS)	De Groot and Bos, 1987
1115	UK (1981)	1% in pet	female dermatology clinic patients	3% (NS)	Cronin, 1978
802	UK (1981)	1% in pet	male dermatology clinic patients	1% (NS)	Cronin, 1978
1117	UK (1982)	1% in pet	female dermatology clinic patients	3% (NS)	Cronin, 1978

Table 4. Cases of n-(3-Chloroallyl) Hexaminium Chloride-Induced Contact Allergy By Country (continued)

Case Subjects	Country (year)	Concentration of compound in patch test	History	Nos. or % of positive patch test results (time)	Reference
867	UK (1982)	1% in pet	male dermatology clinic patients	1% (NS)	Cronin, 1978
1004	UK (1983)	1% in pet	female dermatology clinic patients	4% (NS)	Cronin, 1978
820	UK (1983)	1% in pet	male dermatology clinic patients	1% (NS)	Cronin, 1978
1033	UK (1984)	1% in pet	female dermatology clinic patients	4% (NS)	Cronin, 1978
803	UK (1984)	1% in pet	male dermatology clinic patients	1% (NS)	Cronin, 1978
656	UK (1982)	1% in pet	suspected contact allergy dermatitis	0.6% (NS)	Ford and Beck, 1986
174	UK (1986-87)	NS	occupational eczema	10/174 (NS)	Grattan, *et al.*, 1989
2395	UK (1986-87)	NS	non-occupational eczema	45/2395 (NS)	Grattan, *et al.*, 1989
1008	UK (1981-82)	2% in pet	dermatology clinic patients	29/1006 (NS)	Ford and Beck, 1986
2298	UK (1983-84)	NS	dermatology clinic patients	59/2298 (NS)	Ford and Beck, 1986

Table 4. Cases of n-(3-Chloroallyl) Hexaminium Chloride-Induced Contact Allergy By Country (continued)

Case Subjects	Country (year)	Concentration of compound in patch test	History	Nos. or % of positive patch test results (time)	Reference
4470	Italy (1984-89)	NS	dermatology clinic patients	10/4470 or 0.22% (48 hrs., 72 hrs.)	Tosti, *et al.*, 1990
465	France (NS)	2% in pet 0.1% in pet	dermatitis patients	0.8% (NS) none	Meynadier, *et al.*, 1982

pet- petrolatum
NS- not specified

dermal,human

- The contact sensitivity of a cuticle cream containing 0.2% N-(3-chloroallyl)hexaminium chloride was determined using a maximization test in a study submitted by CFTA (unpublished data, 1976). A group of 25 volunteers was pretreated with a single 48-hour occlusive patch with the cuticle cream, then with 1.5% sodium lauryl sulfate (SLS) at the induction site. (It had previously been determined that SLS was needed to induce irritation at the test site.) Over an induction period of 14 days, five, 48-hour occlusive patches containing 0.3 grams undiluted product were administered to the same site. Following a 10-day nontreatment period, nontreated sites were pretreated with 5% SLS, and a single 48-hour occlusive challenge patch was applied. The sensitization reactions were scored immediately and 24 hours after the patch was removed. This product was found to be nonsensitizing under these conditions since no reactions were observed [JACT, 1986].

dermal, human

- A group of 25 individuals was used to evaluate the sensitization potential of a mascara formulation with 0.3% N-(3-chloroallyl)hexaminium chloride in a maximization test. Test procedures as described in the previous bullet were used. In addition, the induction sites were pretreated with a single dose of 2.5% sodium lauryl sulfate (SLS) and the challenge site was pretreated with 5-10% SLS. No symptoms of sensitization were observed from this product [JACT, 1986].

The data presented below concerning skin sensitization in humans are summarized in Table 5.

dermal, human

- In a study submitted by CTFA (unpublished data, 1979), a group of 10 individuals participated in a 21-day cumulative irritation test for a moisturizer containing 0.3% N-(3-chloroallyl)hexaminium chloride. The test subjects' backs were exposed to the product for 23 hours under an occlusive patch, rinsed, and scored after 1 hour. Another patch was applied to the test site immediately after scoring. This procedure was repeated for 21 consecutive days. One of the test subjects had barely perceptible erythema on the third day, but no other reactions were observed. The product tested was found to be nonirritating [JACT, 1986].

dermal, human

- The sensitization potential of N-(3-chloroallyl)hexaminium chloride was tested in 183 volunteers using a modified Draize method. Each individual was given a series of 10 induction patches with 5% N-(3-chloroallyl)hexaminium chloride (solvent not specified) for an exposure time of 24 hours, with a 24-hour rest period between applications. The individuals were challenged with patches containing 5% N-(3-chloroallyl)hexaminium chloride after a 10-14 day nontreatment period. Only one individual exhibited a sensitization reaction to N-(3-chloroallyl)hexaminium chloride following the challenge [JACT, 1986].

dermal, human

- In a study conducted for Dow Chemical Company (unpublished data, 1978) the sensitization potential of 1% aqueous N-(3-chloroallyl)hexaminium chloride was studied in 160 (male and female) volunteers in a modified Draize repeated insult patch test. Each of the individuals was given a total of nine, 24-hour occlusive patches with 1% aqueous N-(3-chloroallyl)hexaminium chloride over 3 weeks during the induction phase of the study. The individuals were challenged with concentrations of N-(3-chloroallyl)hexaminium chloride in distilled water at 0.1, 0.3, and 1% via patches applied to nontreated and induction sites after a 2-week nontreatment period. The challenge reactions were read 24 hours after application. No results were reported for volunteers from the 0.1 or 0.3% N-(3-chloroallyl)hexaminium chloride groups, but 11 reactions reportedly occurred from the 1% challenge dose, of which 3 were questionable.

  Because 3 of the reactions were questionable, 10 of the sensitized patients and a control group of 8 nonsensitized individuals were rechallenged with 1% aqueous N-(3-chloroallyl)hexaminium chloride. Seven of the 10 volunteers from the reactive group were confirmed to be sensitized, 2/10 had inconclusive reactions, and 1/10 had no reaction. No individuals in the control group had any reaction. These studies indicate that 1% aqueous N-(3-chloroallyl)hexaminium chloride caused a significant increase in contact sensitization in the original 160 member panel [JACT, 1986].

dermal, human

- In a study submitted by CFTA (unpublished data, 1972), a repeat insult patch test (RIPT) was performed on 97 individuals to determine the irritancy and sensitization of a cleanser (wipe-off) containing 0.2% N-(3-chloroallyl) hexaminium chloride. Each of the test subjects received 24-hour occlusive patches containing an unspecified amount of test material 9 times over the course of an unspecified duration. One test subject had slight erythema after removal of the ninth patch. No reactions were observed after a challenge patch was administered (time of challenge not specified). The cleanser was determined to be nonirritating and non-sensitizing [JACT, 1986].

dermal, human

- In a study conducted for Dow Chemical Company (unpublished data, 1965), a prototype underarm deodorant containing 2% N-(3-chloroallyl)hexaminium chloride was tested for its irritancy and sensitization in a repeat insult patch test (RIPT). A control formulation containing 2% ethanol instead of N-(3-chloroallyl)hexaminium chloride was run simultaneously. A group of 72 test subjects was given a total of 9 applications of 0.5 ml undiluted test material over a 3-week induction period, and the challenge patch was administered following a 3-week non-treatment period. The test materials were administered under occlusive patches for 24 hours. Slight irritation reactions were observed in one third of the subjects from both the N-(3-chloroallyl)hexaminium chloride and the control groups during the induction period. No sensitization reactions were observed in either group [JACT, 1986].

dermal, human

- In a study submitted by CFTA (unpublished data, 1972), the irritancy potential of a mascara containing 0.2% N-(3-chloroallyl)hexaminium chloride was studied in a modified Draize-Shelanski repeat insult patch test. A group of 206 healthy test subjects was given ten, 24-hour occlusive patches with 0.1 g of undiluted product, 3 times a week, for a 6-week induction period. Irritation reactions were scored immediately upon removal of the patches. During the induction phase, irritation reactions consisting of erythema (8/206), erythema and edema, or induration (3/206) were observed. A final challenge patch was administered after 12 days of nontreatment. Erythema was observed in 1 subject, erythma, edema or induration were observed in 2 panelists, and erythema, edema/induration and vesiculation were noted in 1 subject during the challenge phase [JACT, 1986].

dermal, human

- In a study submitted by CFTA (unpublished data, 1982), a moisturizer containing 0.3% N-(3-chloroallyl)hexaminium chloride was tested for irritancy and sensitization using a modified Draize-Shelanski repeat insult patch test. A group of 108 test subjects was given 10 applications of 24-hour occlusive patches containing an unspecified amount of test material. A challenge patch containing an unspecified amount of test material was given at an unspecified time to induction and untreated sites. No irritation or sensitization reactions were observed [JACT, 1986].

dermal, human

- In a study submitted by CFTA (unpublished data, 1982), the irritancy and sensitization potential of a moisturizer containing 0.3% N-(3-chloroallyl)hexaminium chloride was evaluated in 101 volunteers in a modified Draize-Shelanski repeat insult patch test. Each of the test subjects was given 10 applications of a 24-hour occlusive patch containing an unspecified amount of material. Challenge patches containing an unspecified amount of test material were given at an unspecified time to induction and untreated sites. This product did not elicit any irritation or sensitization reactions [JACT, 1986].

dermal, human

- In a study submitted by CFTA (unpublished data, 1982), a group of 205 individuals was tested using a modified Draize-Shelanski repeat insult patch test for irritancy and sensitization from a moisturizer containing 0.3% N-(3-chloroallyl)hexaminium chloride. Each of the individuals was given 10 applications of a 24-hour occlusive patch containing an unspecified amount of test material during an induction period of an unspecified duration, followed by a challenge at the induction site and a naive site. Erythema, or erythema with edema, or induration was observed in 2 of the test subjects during the induction period. Ten individuals developed erythema from the challenge. None of these reactions was considered significant or indicative of irritation or sensitization [JACT, 1986].

dermal, human

- The irritancy and sensitization of mascara containing 0.2% N-(3-chloroallyl)hexaminium chloride was studied in a prophetic patch and use test submitted by CFTA (unpublished data, 1982). A group of 102 females was given two 48-hour occlusive patches containing an unspecified amount of the mascara. A pre-induction patch was applied to the right arm of each subject, and a post-induction patch was applied to the same area of the subject's left arm 4 weeks later. Both of these exposures were scored for irritation one hour and 24 hours after the patch was removed. The women were asked to use the product daily for a 4-week induction period. None of the test subjects reported any irritation from the product during the induction period. One woman had a marked reaction when given the challenge exposure. This panelist was rechallenged and again had a severe reaction indicative of sensitization. The individual was then exposed to the components of the product and found to be sensitized to parabens and chloroxylenol, and possibly to the water and oil phases [JACT, 1986].

dermal, human

- In a study submitted by CFTA (unpublished data, 1981), three different shades of mascara containing 0.2% N-(3-chloroallyl)hexaminium chloride were tested for irritancy and sensitization in 221 subjects using a modified Schwartz-Peck procedure. Each of the test subjects received a preinduction 48-hour occlusive patch with an unspecified dose of each mascara. A second set of patches was applied following a four week induction period of daily use of one of the three products. The challenge patch was scored for irritation and sensitization at removal of the 48-hour occlusive patch and 24 hours later. One subject had erythema and edema or induration at the second scoring of two of the three shades of mascara. Subsequent retesting elicited no reactions to either formulation and the reaction in the subject was attributed to the test patches being in close proximity to three strong irritants tested simultaneously. The authors reported that these products were non-irritants and non-sensitizers [JACT, 1986].

dermal, human

- In a study submitted by CFTA (unpublished data, 1981), a mascara containing 0.2% N-(3-chloroallyl)hexaminium chloride was tested for its irritancy and sensitization potential using the modified Schwartz-Peck procedure described above. A group of 213 test subjects was used in this study. Two of the test subjects reported periorbital edema and mild conjunctivitis after one or four weeks of mascara use, although no reactions were observed during the preinduction phase or after the challenge patch was applied. The authors report that the observed reactions indicate a low degree of sensitization. However, the negative patch tests indicate that the product was probably not a potent sensitizer. A second mascara also containing 0.2% N-(3-chloroallyl)hexaminium chloride was tested under the same conditions using 114 test subjects. No irritation or sensitization to this product were reported [JACT, 1986].

dermal, human

- The ability of N-(3-chloroallyl)hexaminium chloride to cause a sensitization reaction in individuals sensitized to formaldehyde was tested. It is believed that the sensitization reaction elicited by N-(3-chloroallyl)hexaminium chloride is due to its formaldehyde releasing properties. Two commercial creams containing 0.1% N-(3-chloroallyl)hexaminium chloride were tested on 9 formaldehyde-sensitive individuals. The test subjects were given 4 patches, at time zero, and the reactions were scored. Patches were reapplied at 72 and 120 hours. A final scoring was done at 168 hours. The first cream caused 6/9 individuals to exhibit an allergic reaction consisting of an infiltrated, confluent, papulovesicular response. Three of the reactions were observed at 72 hours, one was noted at 120 hours, and 2 at 168 hours. The second cream elicited 5 allergic reactions, 2 were recorded at 72 hours and 120 hours, and one at 168 hours. The observed responses were very similar to responses to aqueous formaldehyde solutions containing 60-100 ppm formaldehyde. It was determined that N-(3-chloroallyl)hexaminium chloride is able to elicit dermatitis in formaldehyde-sensitive patients because of its formaldehyde-releasing properties [Jordan *et al*, 1979 as cited in JACT, 1986].

dermal, human

- The ability of N-(3-chloroallyl)hexaminium chloride to produce cross-sensitization in 6 formaldehyde-sensitive patients was tested using a variety of N-(3-chloroallyl)hexaminium chloride containing preparations in a study conducted by Dow Chemical Company (unpublished data, 1983). The preparations studied were hand cream (0, 0.2, and 0.5% N-(3- chloroallyl)hexaminium chloride), cream shampoo (0, 0.2, and 0.5% N-(3-chloroallyl)hexaminium chloride), 5% N-(3-chloroallyl)hexaminium chloride in Eucerin, 5% N-(3-chloroallyl)hexaminium chloride, 20% N-(3-chloroallyl)hexaminium chloride, and 2% formaldehyde (control). All 6 individuals received patches with each test material. The test sites were scored for sensitization 24 and 48 hours after application.

  Each of the test subjects reacted positively to the formaldehyde control. One of the individuals developed slight erythema from each of the hand cream formulations and 4 individuals had erythema with or without edema and induration after contact with all 3 of the cream shampoos indicating that N-(3-chloroallyl)hexaminium chloride was not the irritating component. No reactions were observed from the 5% aqueous solution of N-(3-chloroallyl)hexaminium chloride. However, 1 erythematous reaction to 5% N-(3-chloroallyl)hexaminium chloride in Eucerin, and 4 reactions consisting of slight erythema to the 20% aqueous solution of N-(3-chloroallyl)hexaminium chloride were observed. The sensitization reactions observed in test materials using Eucerin as the vehicle were reported by the authors to be invalid because Eucerin contains 2-bromo-2 nitropropane-1,3-diol, a known formaldehyde releaser. The authors concluded that N-(3-chloroallyl)hexaminium chloride did not cause cross-sensitization reactions in formaldehyde-sensitive patients [JACT, 1986].

dermal, human

- In a study conducted by Dow Chemical Company (unpublished data, 1973), the ability of N-(3-chloroallyl)hexaminium chloride to elicit a sensitization reaction in formaldehyde-sensitive individuals was tested using 0.1, 0.5, 1.0, and 5.0% N-(3-chloroallyl)hexaminium chloride in an aqueous solution and 0.1 and 1.0% N-(3-chloroallyl)hexaminium chloride in aqueous and anhydrous Eucerin. A group of 12 formaldehyde-sensitive individuals with no previous contact with N-(3-chloroallyl)hexaminium chloride was chosen to participate in this study. The individuals were exposed to 8 patches, one at each concentration and vehicle tested. Three of the test subjects reacted to 0.5, 1.0, and 5.0% N-(3-chloroallyl)hexaminium chloride in aqueous solution. The observed reactions were dose-dependent varying from slight erythema (0.5%) to pronounced erythema with papulovesicles (5%). The positive reactions to N-(3-chloroallyl)hexaminium chloride in Eucerin were disregarded because Eucerin contains 2-bromo-2-nitropropane-1, 3-diol, a known formaldehyde releaser. The results of this study indicate that N-(3- chloroallyl)hexaminium chloride can cause cross-sensitization reactions in formaldehyde-sensitive patients [JACT, 1986].

dermal, human

- A series of 13 test and control materials was evaluated for photo-sensitization using 50 volunteers in a study conducted for Dow Chemical Company (unpublished data, 1970). During the induction period, test subjects were exposed to 0.1 ml of product containing N-(3-chloroallyl)hexaminium chloride (1.0% in water, 0.25% in facial gel cleanser, 0.75% in freshly prepared hand lotion, or 0.1% aged hand lotion) and control product with no N-(3-chloroallyl)hexaminium chloride (facial gel cleanser, fresh hand lotion, aged hand lotion, petrolatum or a methanol control). 3, 3', 4' 5-Tetrachlorosalicylanilide (TCSA) was applied as a 2% solution in methanol or petrolatum to 20 positive control subjects. The test materials were applied to the test area for 60 seconds. The test sites were subsequently exposed to ultraviolet radiation for 30 seconds at a distance of 12 inches from the source. The induction period lasted for 5 weeks and the individuals received exposures 5 days per week. After a 3-week nontreatment period, the subjects received a challenge exposure of the test materials specified above.

  No reactions were observed during the induction or challenge to 1.0% N-(3-chloroallyl)hexaminium chloride in water, 0.25% N-(3-chloroallyl)hexaminium chloride in a facial gel cleanser, 0.75% N-(3-chloroallyl)hexaminium chloride in newly prepared hand lotion, 0.1% N-(3-chloroallyl)hexaminium chloride in aged hand lotion, or any of the controls specified above. Nine of 10 and 8/10 individuals were photosensitized to TCSA in methanol or petrolatum, respectively. A reaction to 2% N-(3-chloroallyl)hexaminium chloride in methanol was observed in 3/20 individuals concurrently in a state of hypersensitivity to TCSA. These reactions were irritant in nature, and were not produced again at subsequent challenge applications. It was determined that concentrations of 1% N-(3-chloroallyl)hexaminium chloride or less in

aqueous-based formulations are not photosensitizers under these test conditions [JACT, 1986].

dermal, human

- A study submitted by CFTA (unpublished data, 1979) using 25 volunteers was performed to determine the photosensitizing ability of a cleansing product containing 2% N-(3-chloroallyl)hexaminium chloride. Each of the test subjects was administered a 24-hour occlusive patch of undiluted test material on a site on his back. After the patch was removed, the exposure site was evaluated and irradiated with 3 times the individual's minimal erythema dose, which was previously determined. This procedure was repeated twice a week for a total of 6 exposures. After a 10-day nontreatment period, the test subjects were given a 24-hour challenge patch which was irradiated for 3 minutes after the patch was removed. The test sites were evaluated for photosensitivity reactions 15 minutes and 24, 48, and 72 hours after exposure to radiation. The cleanser was determined not to be a photosensitizer because none of the test subjects exhibited any reactions [JACT, 1986].

Table 5. Studies of Skin Sensitization to N-(3-Chloroallyl)hexaminium Chloride in Humans

No. Case Subjects	N-(3-Chloroallyl) hexaminium chloride Preparation	Induction Period (#patches)/exposure time/conc. of N-(3-Chloroallyl) hexaminium chloride in patch	Challenge (exposure)/conc. of N-(3-Chloroallyl) hexaminium chloride in patch	No. Positive Sens. Reaction
183	5% (solvent not specified)	20 days (10)/24 hrs/ 5%	Post 10-14 days nontreatment (24 hrs)/5%	1
160	1% in water	3 weeks (9)/24 hrs/ 1%	Post 2 week nontreatment (24 hrs)/0.1,0.3,and 1%	0.1%-NR 0.3%-NR 1%-7 confirmed sens. reactions, 2 possible sens. reactions
97	cleanser (wipe-off)	N.S. (9)/24 hrs/ 0.2%	N.S. nontreatment period/0.2%	1-slight erythema after removal of patch
72	Prototype deodorant	3 weeks (9)/24 hrs/ 2%	3 week nontreatment period (24 hrs)/2%	0
206	Mascara	6 weeks (10)/24 hrs/ 0.2%	12 days nontreatment (24 hrs)/0.2%	4
108	Moisturizer	N.S.(10)/24 hrs/ 0.3%	N.S. nontreatment period (24 hrs)/ 0.3%	0

Table 5. Studies of Skin Sensitization to N-(3-Chloroallyl)hexaminium Chloride in Humans (continued)

No. Case Subjects	N-(3-Chloroallyl) hexaminium chloride Preparation	Induction Period (#patches)/exposure time/ conc.N-(3-Chloroallyl) hexaminium chloride in patch	Challenge (exposure)/conc. of N-(3-Chloroallyl) hexaminium chloride in patch	No. Positive Sens. Reaction
101	Moisturizer	N.S.(10)/24 hrs/ 0.3%	N.S. nontreatment period (24 hrs)/ 0.3%	0
205	Moisturizer	N.S.(10)/24 hrs/ 0.3%	N.S. nontreatment period (24 hrs)/ 0.3%	0
102	Mascara	4 weeks (1 patch, 4 weeks use)/24 hrs (patch)/0.2%	Imm. after induction period (24 hrs)/ 0.2%	0
221	Mascara (3 shades)	4 weeks (1 patch, 4 weeks use)/48 hrs (patch)/0.2%	Imm. after 4 weeks induction period (patch/masc.)(48 hrs)/0.2%	0
213	Mascara	4 weeks of use/N.S. 0.2%	Imm. after 4 weeks use/0.2%	2-periorbital edema and mild conjunctivitis during induction. 0-sens. reaction from challenge patch
114	Mascara	NS/NS/0.2%	NS/0.2%	0 sens. reaction

NS- not specified
sen-sensitization
imm- immediately
NR- not reported

JACT, 1986

2. Animal Studies

dermal, rats

- In a 13-week study submitted by CFTA (unpublished data, 1980), the dermal toxicity of a cleanser (wipe-off) containing 0.2% N-(3-chloroallyl)hexaminium chloride was evaluated using 15 female rats of unspecified strain. The rats were given a daily dose of 3.0 ml/kg of the product 5 days per week, which resulted in a dose of 3,000.0 mg/kg N-(3-chloroallyl)hexaminium chloride per day. This dose is reportedly approximately 60 times the normal dose received by consumers during cleanser use. A control group consisting of 15 untreated female rats was used. Body weight gain, blood and urine values, and organ weight values were comparable with those of the control groups. At the conclusion of the study, 3 of the treated rats were observed to have skin hyperkeratosis, as confirmed by microscopic observation. No cumulative systemic toxic effects were noted [JACT, 1986].

dermal, mice

- In an investigation designed to evaluate the usefulness of feeding mice diets supplemented with vitamin A acetate (VAA) to enhance sensitization reactions, the contact sensitizing potential of N-(3-chloroallyl)hexaminium chloride was studied by measuring the ear thickness of animals induced and challenged with N-(3-chloroallyl)hexaminium chloride. During a 2- week induction period, a group of 10 female Balb/c mice fed a diet supplemented with VAA was administered six, 100 µl-topical applications of 15% N-(3-chloroallyl)hexaminium chloride in acetone:water:tween (A:W:T) to the shaved abdomen and thorax, on days 0, 2, 4, 7, 9, and 11. The negative control group, consisting of ten animals, was treated with A:W:T only. A separate group of mice was included as the positive control and was sensitized to 25-µl of 0.3% oxazolone in acetone:oil:tween. A 25-µl challenge dose with 15% N-(3-chloroallyl)hexaminium chloride in A:W was applied to all of the test animals' ears after one week without treatment. The positive control group was challenged with 25 µl of 0.3% oxazolone in acetone:oil. The ear thickness of the animals was measured prior to the application of the challenge then again 24 hours and 48 hours post-challenge. N-(3-Chloroallyl)hexaminium chloride was found to cause a significant increase in ear thickness at 24 hours ($P<0.001$) and 48 hours ($P<0.01$) compared to the control group. This compound was therefore determined to be a sensitizer when ear swelling is used as the basis for assessment [Maisey and Miller, 1986].

dermal, guinea pigs

- The sensitization potential of a 10% solution of N-(3-chloroallyl)hexaminium chloride in PPG-2 methyl ether/polysorbate 80 (9:1) was tested using guinea pigs of an unspecified strain in a study conducted by Dow Chemical Company (unpublished data, 1983). Ten test animals were administered four 48-hour induction occlusive patches containing 0.1 ml of test material. When the third induction patch was applied, the animals were also given a 0.2 ml intradermal injection of Freund's adjuvant at the induction site. Another group of 10 guinea pigs used as positive controls was given 4 doses of 10% epoxy resin in PPG-2 methyl ether/polysorbate on the same schedule. Two weeks after the induction period, the animals were challenged with N-(3-chloroallyl)hexaminium chloride in PPG-2 methyl ether/polysorbate 80 (uncovered) and with the control vehicle. Sensitization responses were observed in 7/10 guinea pigs in the epoxy resin control group. No reactions were observed in the negative control. Four of the test animals exhibited slight erythema and edema induced by N-(3-chloroallyl)hexaminium chloride 24 hours after challenge; 2/4 of these reactions cleared after 48 hours. The authors reported that one of these reactions was possibly a weak sensitization response [JACT, 1986].

dermal, guinea pigs

- In a study conducted by Dow Chemical Company (unpublished data, 1983), two groups of 10 guinea pigs of an unspecified strain were used to determine the sensitization potential of 1% aqueous N-(3-chloroallyl)hexaminium chloride and 10% N-(3-chloroallyl)hexaminium chloride in PPG-2 methyl ether and polysorbate 80 (9:1). A positive control group of 10 guinea pigs induced with 15% epoxy resin in PPG-2 methyl ether and polysorbate 80 was also used. The test animals were administered 4 doses of the 1% or 10% N-(3-chloroallyl)hexaminium chloride solution or control material via occlusive patches for a 48-hour induction period. The animals were given a 0.2 ml intradermal injection of Freund's adjuvant at the induction site when the third induction patch was administered. A second test was performed in which a total of six, 0.1-ml occlusive 24-hour induction patches were applied twice a week for 3 weeks. After a 2-week nontreatment period, all of the test animals were challenged with a single open application of N-(3-chloroallyl)hexaminium chloride along with a solvent control application. The responses to sensitization were read 24 and 48 hours after the challenge. Eighteen of the 20 test guinea pigs were sensitized to the positive control; no animals were sensitized to 1% N-(3-chloroallyl)hexaminium chloride; and 7/10 animals were sensitized to 10% N-(3-chloroallyl)hexaminium chloride. The authors concluded that N-(3-chloroallyl)hexaminium chloride appeared to be a skin sensitizer in situations where gross contact is likely, or in the presence of a penetrating solvent [JACT, 1986].

dermal, guinea pigs

- The sensitization potential of N-(3-chloroallyl)hexaminium chloride was tested in 40 albino guinea pigs (male and female) in a study conducted by Dow Chemical Company (unpublished data, 1971). Each of the animals was given four, intracutaneous injections per day of 0.5-ml isotonic 0.5% N-(3-chloroallyl)hexaminium chloride (totalling 1 mg N-(3-chloroallyl)hexaminium chloride daily) for a 4-day consecutive induction period. A 0.03 ml dose of Freund's adjuvant was administered with the first and third induction injections.

  A second group of 10 animals were given 0.5 ml intracutaneous injections of N-(3-chloroallyl)hexaminium chloride, daily, during a 10-day induction period. (No injections were given on Sunday.) After an 18-day nontreatment period, all of the animals were challenged with 6 weekly applications of 1% and 5% N-(3-chloroallyl)hexaminium chloride in Eucerin. The challenge materials were applied to intact, untreated skin on the animals' flanks. Of the first 30 animals tested, only one animal reacted to 1% N-(3-chloroallyl)hexaminium chloride, and 1 reacted to 0.5% N-(3-chloroallyl)hexaminium chloride. In these 2 guinea pigs, weakly visible erythema was observed 24 hours after the challenge. No other indication of contact sensitization was observed. No evidence of contact reactions to N-(3-chloroallyl)hexaminium chloride was found in any of the animals from the second group. Skin samples were evaluated microscopically from 6 animals from the second group, and no microscopic indications of contact sensitization were noted[JACt, 1986].

dermal, guinea pigs

- In a sensitization study conducted by Dow Chemical Company (unpublished data, 1973), ten guinea pigs of an unspecified strain were given four daily intracutaneous injections of 0.5% N-(3-chloroallyl)hexaminium chloride in 0.9% NaCl (total of 4 mg of N-(3-chloroallyl)hexaminium chloride). The animals were also given injections of Freund's adjuvant on days 1 and 3. After 14 days of nontreatment, the animals were challenged with 0.1, 0.5, 1.0, and 5.0% N-(3-chloroallyl)hexaminium chloride in aqueous solution and Eucerin ointment. Five additional challenges were applied at weekly intervals. No evidence of sensitization reactions was observed in any of the animals. No data were available on control groups [JACT, 1986].

dermal, guinea pigs

- The sensitization potential of N-(3-chloroallyl)hexaminium chloride in guinea pigs was determined by Dow Chemical Company (unpublished data, 1973). A group of 10 guinea pigs (of unspecified strain), previously sensitized to 2,4-dinitro-1-chlorobenzene, were given 4 intracutaneous injections of 0.03 ml Freund's adjuvant. After a 3-day nontreatment period, the animals were given 10 intracutaneous injections of 0.5 ml 5% N-(3-chloroallyl)hexaminium chloride in saline. The injections were given daily, 5 days per week, for 2 weeks. After an 18-day nontreatment period, the animals were challenged with 1 and 5% N-(3-chloroallyl)hexaminium chloride in aqueous solution and Eucerin ointment. Subsequent challenge tests with 0.1, 0.5, 1.0, and 5.0% N-(3-chloroallyl)hexaminium chloride were given weekly. None of the animals showed any sign of sensitization. No data were available on control groups [JACT, 1986].

dermal, guinea pigs

- A group of 10 guinea pigs was used to determine the sensitization potential of N-(3-chloroallyl)hexaminium chloride in a study conducted by Dow Chemical Company (unpublished data, 1973). Each of the animals was given 15 cutaneous applications of 5% aqueous N-(3-chloroallyl)hexaminium chloride over a 3-week induction period. After one week of nontreatment, the animals were challenged with applications of 0.1, 0.5, 1.0, and 5.0% aqueous N-(3-chloroallyl)hexaminium chloride to untreated sites. The challenge applications were repeated once a week for 6 weeks. No sensitization reactions were observed [JACT, 1986].

dermal, guinea pigs

- The sensitization potential of N-(3-chloroallyl)hexaminium chloride was tested using groups of 10 male Hartley albino guinea pigs in a study conducted by Dow Chemical Company (unpublished data, 1973). Four of the groups were induced with N-(3-chloroallyl)hexaminium chloride as a 2% aqueous solution (40 animals) and 2 groups were induced with N-(3-chloroallyl)hexaminium chloride as a 2% suspension in petrolatum (20 animals). Two positive control groups received either 10% epoxy resin in a 9:1 mixture of PPG-2 methyl ether and polysorbate 80 (10 animals) or 37% formaldehyde (10 animals). All animals received 4 induction applications followed by a 2-week nontreatment period. The animals were then challenged with their respective test material. The test animals receiving N-(3-chloroallyl)hexaminium chloride during the induction period were also challenged with formaldehyde to detect possible cross-sensitivity. No sensitizition to N-(3-chloroallyl)hexaminium chloride was observed, and no cross-sensitizition to formaldehyde was detected. All of the animals in the control groups were observed to exhibit sensitization to PPG-2 methyl ether and polysorbate 80 and formaldehyde. The authors concluded that 2% N-(3-chloroallyl)hexaminium chloride was not a skin sensitizer [JACT, 1986].

dermal, guinea pigs

- In a study conducted by Dow Chemical Company (unpublished data, 1973) sensitization potential of N-(3-chloroallyl)hexaminium chloride was studied in 20 guinea pigs, of an unspecified strain, previously used in a 2-week primary irritancy study using 5 and 10% N-(3-chloroallyl)hexaminium chloride. Following a 16-day nontreatment period, the animals were challenged with single, simultaneous applications of N-(3-chloroallyl)hexaminium chloride in aqueous solutions and Eucerin ointment. Challenge doses of 0.1 and 0.5% N-(3-chloroallyl)hexaminium chloride applied to the induction sites, and 1 and 5% N-(3- chloroallyl)hexaminium chloride applied to previously nontreated sites were employed. The animals were observed 24 and 48 hours after the challenge. None of the test animals exhibited any signs of sensitization [JACT, 1986].

dermal, rabbits

- A study of the subchronic dermal toxicity of prototype cosmetic formulations containing 0.1, 1.0, or 3.0% N-(3-chloroallyl)hexaminium chloride was performed by Dow Chemical Company (unpublished data, 1969). Five groups of 10 rabbits (5 male, 5 female) of unspecified strain were given daily applications, 5 days a week (total of 62 applications over a 91-day period), of 1.0 mL/kg tap water (control), 1.0 mg/kg base cosmetic formulation (base control), or 1 ml/kg of the prototype cosmetic formulations, which resulted in a daily dose of 1.04, 10.5, or 31.3 mg/kg N-(3-chloroallyl)hexaminium chloride. The test materials were applied in the morning, and any remaining residual material was removed at the end of the day with a damp sponge. There were no treatment-related differences between test and control animals concerning mortality, indications of toxicity, local skin reactions, body weights, food consumption, clinical chemistry values, or pathological changes. The authors concluded that under these test conditions, dermal application did not present a hazard due to absorption of test material through the skin [JACT, 1986].

dermal, rabbits

- The comedogenic potential of N-(3-chloroallyl)hexaminium chloride was studied in a rabbit ear assay using groups of 6 male New Zealand albino rabbits. Each animal was administered 0.2 ml of 0.2% or 0.5% N-(3-chloroallyl)hexaminium chloride in water to the inner surface of the basal portion of the right ear using a syringe. Half of the animals' left ears were used as a positive control and were treated with Acetulan. The left ears of the remaining animals were left as untreated controls. Three of the 6 test rabbits were dosed 5 days a week for 2 weeks, and the remaining 3 rabbits received doses 5 days a week for 4 weeks. The rabbits' ears were scored for evidence of comedone formation on days 5, 12, 15, 19, 26, and 29 after dosing. The animals were sacrificed after the treatment period (day 29), their ears removed, and fixed. The epidermis was evaluated for evidence of follicular hyperkeratinization. It was determined that N-(3-chloroallyl)hexaminium chloride is noncomedogenic as neither of the 2 dose levels caused a significant increase in the number of comedones observed compared to the sham treatment [Silber, *et al.*, 1989].

dermal, rabbits

- In a study conducted for Dow Chemical Company (unpublished data, 1966), ten groups of 10 sexually immature rabbits (5 male, 5 female) of an unspecified strain were used to determine dermal toxicity of N-(3-chloroallyl)hexaminium chloride. Doses of 0.0, 10.0, 25.0, 50.0, or 100.0 mg/kg of N-(3-chloroallyl)hexaminium chloride in a 20% aqueous solution were applied to intact or abraded skin 5 days a week for 3 weeks and left in contact with the skin for 7 hours per application. No deaths were observed. There was almost no difference in the parameters studied (mortality, behavior, local skin reactions, body weights, hematological values, blood chemistry values, urine analysis, gross and microscopic lesions, or organ weight and ratio data) between the control groups and the groups given 10.0 and 25.0 mg/kg. In the groups administered 50.0 mg/kg, slight skin irritation and slightly decreased spermatogenesis were observed. All other parameters were comparable to the control group. The groups administered 100.0 mg/kg exhibited significant decreases in

absolute testes weight and in the testes to body and brain weight ratios, as well as decreased spermatogenesis (intact 4/5, abraded 3/5) and irritation at the site where N-(3-chloroallyl)hexaminium chloride was applied (See section V.E., Reproductive Effects and Teratogenicity). All of the other parameters studied were similar to the control groups [JACT, 1986].

D. Chronic/Carcinogenicity

1. Human Data

No data were found in the literature on the chronic or carcinogenic effects of N-(3-chloroallyl)hexaminium chloride in humans.

2. Animal Data

No data were found in the literature on the chronic or carcinogenic effects of N-(3-chloroallyl)hexaminium chloride in animals.

E. Reproductive Effects and Teratogenicity

1. Human Data

No data were found in the literature on the reproductive and teratogenic effects of N-(3-chloroallyl)hexaminium chloride in humans.

2. Animal Data

dermal, rabbits

- In a prechronic dermal toxicity study described in section V.C. 2, 20% aqueous solutions of various doses up to 100.0 mg/kg of N-(3-chloroallyl)hexaminium chloride were applied to the intact or abraded skin of groups of 10 sexually immature rabbits 5 days per week for 3 weeks. Animals in the 50.0 mg/kg group had slightly decreased spermatogenesis. The animals administered 100.0 mg/kg exhibited significant decreases in absolute testes weight and in the testes to body weight ratios, as well as decreased spermatogenesis (intact 4/5, abraded 3/5). No other reproductive effects were noted [JACT, 1986].

dermal, rabbits

- A follow-up of the above study was conducted by Dow Chemical Company (unpublished data, 1978) in an attempt to confirm the testicular atrophy and decreased spermatogenesis observed. The effect of N-(3-chloroallyl)hexaminium chloride was studied using groups of 7 sexually mature, male rabbits of an unspecified species. N-(3-Chloroallyl)hexaminium chloride in 20% aqueous solution was applied to abraded skin for 7 hours, 5 days a week for 30 days at a concentration of 0.0, 25.0, 50.0, or 100.0 mg/kg. Dose related chronic inflammation, degeneration, and necrosis of the epidermis and dermis with thickening and keratinization at the application site were observed. The animals were sacrificed 30 days after the start of the treatment. Incidental lesions including disseminated lymphosarcoma and focal hypoplasia of the seminiferous tubules of the testes were observed in both control and test animals and were not considered to be significant. Liver weights were significantly (P value not specified) depressed in the rabbits (number not specified) given 50.0 or 100.0 mg/kg N-(3-chloroallyl)hexaminium chloride per day. No signs of systemic toxicity were apparent in any animals and no testicular or other reproductive effects were determined to be attributed to N-(3-chloroallyl)hexaminium chloride [JACT, 1986].

oral, rats

- The teratogenic effects of N-(3-chloroallyl)hexaminium chloride were investigated using Fischer 344 rats in a study conducted by Dow Chemical Company (unpublished data, 1982). In a preliminary study to determine the maximum tolerated dose in pregnant rats, maternal toxicity (decreases in body weight, body weight gain and water consumption; increased liver weight relative to body weight) and embryolethality were observed among rats orally administered 100.0, 200.0, or 400.0 mg/kg/day N-(3-chloroallyl)hexaminium chloride.

  Based on these results, groups of 33 or 34 bred rats were administered daily doses of aqueous N-(3-chloroallyl)hexaminium chloride at a concentration of 0.0, 5.0, 25.0, or 75.0 mg/kg by gavage on days 6-15 of gestation. Control groups were given an equivalent volume of distilled water. The food and water consumption were monitored for all of the rats. The rats fed 25.0 or 75.0 mg/kg consumed less food than controls. The 75.0 mg/kg group drank less water between days 9-11 and drank significantly more on days 18-20 of gestation. On the 21st day of gestation, the test animals were sacrificed and their fetuses examined.

  Significant maternal and fetal toxicity and fetal malformations were observed in the group administered 75.0 mg/kg of N-(3-chloroallyl)hexaminium chloride. The dams had decreased body weights and body weight gain and significantly (P value not specified) increased liver weights in comparison to the control group. Fetal resorption was increased compared to the control groups and the fetal weights were significantly decreased (P value not specified). In the 7 litters, 11 fetuses had major malformations, primarily of the eye (microphthalmia). The authors stated that the significant increase (P value not specified) in unspecified minor malformations was indicative of delayed development.

  The group administered a dose of 25.0 mg/kg did not exhibit any signs of

maternal toxicity although it had a transient decrease in food consumption. This dose resulted in significant (P value not specified) malformations. Major malformations, primarily of the eye, were observed in 10 fetuses from nine litters.

In the 5.0 mg/kg N-(3-chloroallyl)hexaminium chloride dosed group, no maternal toxicity or fetal abnormalities were observed. The investigators concluded that N-(3-chloroallyl)hexaminium chloride is teratogenic at doses of 25.0 and 75.0 mg/kg in Fischer 344 rats following oral administration on days 6-15 of gestation [JACT, 1986].

dermal, rats

- In a study conducted for Dow Chemical Company (unpublished data, 1984), the teratogenicity of N-(3-chloroallyl) hexaminium chloride when applied dermally was tested using groups of 25 bred female Fischer 344 rats. The test animals were given a daily dose of 250.0 or 500.0 mg/kg N-(3-chloroallyl)hexaminium chloride as a 50% aqueous solution during days 6-15 of gestation. The N-(3-chloroallyl)hexaminium chloride was kept in continuous contact under an occlusive patch. There was no significant (P value not specified) maternal toxicity, fetal toxicity, or fetal malformations associated with the dermal applications. However, the incidence of fetal resorption was increased in the groups given 250.0 mg/kg compared to the control group. There was no significant differences (P value not specified) between the control groups and the group administered 500.0 mg/kg with respect to fetal resorption. It was determined that N-(3-chloroallyl)hexaminium chloride is nonteratogenic to rats when applied dermally at doses up to 500.0 mg/kg. The authors report that these results are consistent with the low rate of dermal absorption for this compound [JACT, 1986].

F. Genetic Toxicity

1. Prokaryotic Data

Salmonella typhimurium

- In a standard Ames test conducted for Dow Chemical Company (unpublished data, 1979), N-(3-chloroallyl)hexaminium chloride was found to be nonmutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538. The mutagenicity tests were performed in the presence and absence of metabolic activation with concentrations of N-(3-chloroallyl)hexaminium chloride at 25.0-500.0 µg/plate [JACT, 1986].

Salmonella typhimurium

- The mutagenic effects of N-(3-chloroallyl)hexaminium chloride were studied in *Salmonella typhimurium* strains TA97, TA98, TA100, TA1535, and TA1537 in the absence of exogenous metabolic activation and in the presence of liver S-9 from Aroclor-induced male Sprague Dawley rats and Syrian hamsters. The studies were conducted with concentrations of N-(3-chloroallyl)hexaminium chloride in water of 0.0, 3.3, 10.0, 33.0, 100.0, 250.0, 256.0, 333.0, and 666.0 µg/plate. N-(3-Chloroallyl)hexaminium chloride was found to be weakly mutagenic in TA100 and TA97 in the presence of metabolic activation, and in TA98 in the absence of metabolic activation, but was non-mutagenic to TA1537 and TA1535 with and without metabolic activation [Zeiger *et al.*, 1988].

Salmonella typhimurium

- In the standard Ames test, N-(3-chloroallyl)hexaminium chloride was nonmutagenic to *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 in the presence of Aroclor 1254-induced S-9 rat and hamster liver metabolic activation. The chemical was tested at doses of 6.4-800 µg/plate [CCRIS, 1990].

Salmonella typhimurium

- In the standard Ames test, N-(3-chloroallyl)hexaminium chloride at concentrations of 6-600 µg/plate was nonmutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538, in the absence of metabolic activation [CCRIS, 1990].

2. Eukaryotic Data

rat hepatocyte

- The genotoxic activity of N-(3-chloroallyl)hexaminium chloride was studied by Dow Chemical Company (unpublished data, 1983) in a rat hepatocyte unscheduled DNA synthesis assay. N-(3-Chloroallyl)hexaminium chloride at concentrations of 4×10^{-8} to 2×10^{-1}M and tritiated thymidine were added to primary cultures of hepatocytes isolated from CDF Fischer 344 rats. N-(3-Chloroallyl)hexaminium chloride was toxic to the hepatocyte cultures at concentrations of 4×10^{-4} M and greater. No significant DNA synthesis was observed, indicating a lack of genotoxicity under the test conditions [JACT, 1986].

mouse lymphoma

- The genotoxic effects of N-(3-chloroallyl)hexaminium chloride were determined in a study using mouse lymphoma cell strain L5178Y (TK+/TK-), in the absence of metabolic activation. This compound was tested at concentrations of 3.6-8.7 µg/ml and found to be genotoxic under the test conditions [CCRIS, 1990].

mouse lymphoma

- The genotoxicity of N-(3-chloroallyl)hexaminium chloride was tested in mouse lymphoma cells, strain L5178Y (TK+/TK-), in the presence of metabolic activation. This compound was found to be genotoxic at concentrations of 23.0-87.0 µg/ml [CCRIS, 1990].

G. Other Toxicological Effects

1. Immunotoxicity

No data were found in the literature on the immunotoxicological effects of N-(3-chloroallyl)hexaminium chloride in humans or animals.

2. Neurotoxicity

No data were found in the literature on the neurotoxic effects of N-(3-chloroallyl)hexaminium chloride in humans or animals.

3. Biochemical Toxicology

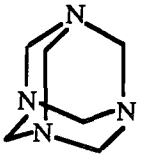
No data were found in the literature on the biochemical toxicity of N-(3-chloroallyl)hexaminium chloride in humans or animals.

VI. STRUCTURE ACTIVITY RELATIONSHIPS

N-(3-Chloroallyl)hexaminium chloride possesses a vinyl chloride moiety and is thereby structurally related to known vinyl halide carcinogens, including vinyl chloride. As a quaternary amine, there is also interest in the possibility that N-(3-chloroallyl)hexaminium chloride may act as an alkylating agent via the potential allylic carbonium ion [NCI, 1984b]. N-(3-Chloroallyl)hexaminium chloride has been reported to be structurally related to methenamine (hexamethylenetetramine), a drug which is metabolized to formaldehyde and ammonia in the gastrointestinal tract [NCI, 1984b; Gilman *et al*, 1985].

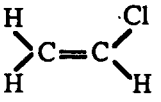
The NCI/NTP tested the quaternary ammonium compound, (2-cloroethyl)trimethylammonium chloride for possible carcinogenicity by administering the chemical in feed to male and female F344 rats and male and female B6C3F1 mice for 108 and 102 weeks, respectively. No tumors occurred in the rats and mice of either sex at incidences that could be associated with (2-cloroethyl)trimethylammonium chloride administration. It was concluded that under the conditions of this bioassay, (2-chloroethyl)-trimethlyammonium chloride was not carcinogenic to F344 rats or B6C3F1 mice [NCI, 1979].

Figure 1. Stucturally Related Compounds.



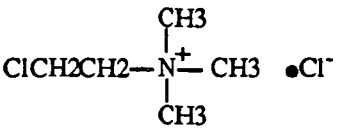
Hexamethylenetetramine

100-97-0



Vinyl Chloride

75-014



(2-Chloroethyl)trimethylammonium chloride

999-81-5

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APPENDIX I. ON-LINE DATABASES SEARCHED

	DATE OF SEARCH	TIME PERIOD
BRS:		
HZDB	November, 1990	
DIALOG:		
Agricola	December, 1990	1970-1990
Agris International	December, 1990	1974-1990
Aquatic Sciences Abstracts	December, 1990	1974-1990
Biosis Previews	December, 1990	1969-1990
CAB Abstracts	December, 1990	1972-1990
Cancerlit	December, 1990	1963-1990
Chem Bus Newsbase	December, 1990	1984-1990
Chemical Exposure	December, 1990	1974-1990
Compendex Plus	December, 1990	1970-1990
CRIS USDA	December, 1990	
Embase	December, 1990	1974-1990
Enviroline	December, 1990	1970-1990
Environmental Bibliography	December, 1990	1974-1990
Federal Register	December, 1990	1977-1990
Foods Adlibra	December, 1990	1974-1990
FSTA	December, 1990	1969-1990
Life Sciences Collection	December, 1990	1978-1990
Medline	December, 1990	1966-1990
NTIS	December, 1990	1964-1990
Occupational Safety and Health	December, 1990	1973-1990
PTS Newsletter	December, 1990	1987-1990
PTS Prompt	December, 1990	1972-1990
Pollution Abstracts	December, 1990	1970-1990
Trade and Industry ASAP	December, 1990	1983-1990
MEAD:		
Nexis/Lexis-BNA ENV	December, 1990	
NLM:		
Chemline	December, 1990	
HSDB	December, 1990	
RTECS	December, 1990	
Toxline 65	December, 1990	1965-1980
Toxline	December, 1990	1981-1990
Toxlit	December, 1990	1981-1990
Toxlit 65	December, 1990	1965-1980
STN:		
CA	December, 1990	1967-1990
Chemlist	December, 1990	

APPENDIX II. SAFETY INFORMATION

- **HANDLING AND STORAGE**

N-(3-Chloroallyl) hexaminium chloride is stable under normal laboratory conditions. This compound shall be stored in a cool, well ventilated area. Decomposition can occur at temperatures above 60°C, resulting in the possible release of methylene glycol [McConville, 1986], pyrimidenes and formamides [JACT, 1986]. This compound may also hydrolize at room temperature to release formaldehyde [Stack and Davis, 1984; Ford and Beck, 1986; Fisher, 1980].

- **EMERGENCY FIRST AID PROCEDURES**

Eye: First check the victim for contact lenses and remove if present. Flush victim's eyes with water or normal saline solution for 20 to 30 minutes while simultaneously calling a hospital or poison control center. Do not put any ointments, oils, or medication in the victim's eyes without specific instructions from a physician. IMMEDIATELY transport the victim, after flushing eyes, to a hospital if symptoms (such as redness or irritation) develop.

Skin: IMMEDIATELY flood affected skin with water while removing and isolating all contaminated clothing. Gently wash affected skin areas thoroughly with soap and water. If symptoms such as inflammation or irritation develop, IMMEDIATELY call a physician or go to a hospital for treatment.

Inhalation: IMMEDIATELY leave the contaminated area and take deep breaths of fresh air. If symptoms (such as wheezing, coughing, shortness of breath, or burning in the mouth, throat, or chest) develop, call a physician and be prepared to transport the victim to a hospital.

Provide proper respiratory protection to rescuers entering an unknown atmosphere. Whenever possible, Self-Contained Breathing Apparatus (SCBA) should be used.

Ingestion: If the victim is conscious and not convulsing, give 1 or 2 glasses of water to dilute the chemical and IMMEDIATELY call a hospital or poison control center. Be prepared to transport the victim to a hospital if advised by a physician.

If the victim is convulsing or unconscious, do not give anything by mouth, ensure that the victim's airway is open, and lay the victim on his/her side with the head lower than the body. DO NOT INDUCE VOMITING. IMMEDIATELY TRANSPORT THE VICTIM TO A HOSPITAL.

- **PROTECTIVE EQUIPMENT**

  Eye: Safety glasses

  Gloves: Two pairs of dissimilar protective gloves shall be worn when handling the neat chemical, otherwise one pair. When contact with this chemical has been known to occur, change gloves immediately.

  Clothing: Minimally, a disposable laboratory suit (e.g. Tyvek ®) shall be worn, as specified in the most current NTP Statement of Work or NTP Health and Safety Minimum Requirements.

  Respiratory Protection: A NIOSH-approved chemical cartridge respirator with an organic vapor and high-efficiency particulate filter cartridge.

- **EXTINGUISHANT**

  Dry chemical, carbon dioxide or halon extinguisher

- **MONITORING PROCEDURES**

  There is no NIOSH analytical method reported in the NIOSH Manual of Analytical Methods for N-(3-chloroallyl) hexaminium chloride.

- **SPILLS AND LEAKAGE**

  Persons not wearing the appropriate protective equipment and clothing shall be restricted from areas of spills until cleanup has been completed. When exposure to unknown concentrations may occur, air-purifying respirators may not be used. Chemical cartridge respirators with organic vapor cartridges may not be used when airborne concentrations exceed 1000 ppm.

  If N-(3-chloroallyl) hexaminium chloride is spilled the following steps shall be taken:

  1. In order to prevent dust formation, use moistened paper towels to clean up a solid spill. Avoid dry sweeping.

  2. If a liquid solution is spilled, use vermiculite, sodium bicarbonate, sand, or paper towels to contain and absorb the spill.

  3. Clean the spill area with dilute alcohol (approximately 60-70%) followed by a strong soap and warm water washing.

  4. Dispose of all absorbed material as hazardous waste.

- **DECONTAMINATION OF LABORATORY EQUIPMENT**

  TDMS Terminal: Whenever feasible, a protective covering (e.g., plastic wrap) shall be placed over the keyboard when in use.

  General Equipment: Before removing general laboratory equipment (i.e., lab carts, portable hoods and balances) from animal dosing rooms and/or chemical preparation areas, a decontamination process shall be conducted in addition to routine housekeeping procedures.

- **WASTE MANAGEMENT AND DISPOSAL PROCEDURES**

  Waste Management: If an inhalation study is to be conducted, all exhaust air from the inhalation chamber must be cleaned with appropriate air cleaning devices unless the laboratory has informed local and state air pollution regulatory agencies of both the laboratory's operating practices and the potential hazards of the chemicals in use. Compliance with all federal, state, and local air pollution laws and regulations is required. A specific air cleaning system design must consider the specific conditions of the laboratory (eg., air flow rates and volumes, mixing of exhaust streams, size of inhalation chamber) and the dosing regimen selected. Air cleaning systems designs must be described by the laboratory and approved by the NTP Office of Laboratory Health and Safety.

  Waste Disposal: Securely package and label, in double bags, all waste material. All potentially contaminated material (i.e., carcasses, bedding, disposable cages, labware) shall be disposed of by incineration in a manner consistent with federal (EPA), state, and local regulations or disposed of in a licensed hazardous waste landfill.