1,6-HEXANEDIAMINE

Document History
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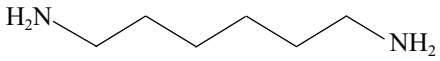
I. IDENTIFICATION

Chemical Name: 1,6-Hexanediamine
Synonyms: Hexamethylenediamine; 1,6-diaminohexane; HMDA; HMD
CAS Number: 124–09–4
Molecular Formula: $C_6H_{16}N_2$
Structural Formula:



II. CHEMICAL AND PHYSICAL PROPERTIES[1, 2]

Physical State: white crystalline solid.
Molecular Weight: 116.2
Conversion Factors: 1 ppm = 4.74 mg/m^3;
1 mg/m^3 = 0.21 ppm(v/v)
Boiling Point: 205°C (401°F) at 760 mmHg (100% concentration)
Melting Point: 23°–41°C (73°–106°F) (85–100% concentrations)
Vapor Pressure: 0.4 mmHg at 25°C (77°F) (estimated)[3] 3 mmHg at 60°C (140°F);
Saturated Vapor Concentration: 526 ppm (2493 mg/m^3) at 25°C (77°F) (estimated)
Odor Description and Threshold: fishy, ammoniacal; 0.0041 mg/m^3 (0.6 ppm) (threshold type not specified)
Vapor Density: 3.8
Flash Point: 85°C (185°F) (100% concentration)
Specific Gravity: 0.854 at 25°C (77°F)
Solubility: highly water soluble; slightly soluble in alcohol, benzene
Log K_{ow}: 0.02[3]
pH (5% aqueous): 12.4
Stability: hygroscopic[4]
Reactivity and Incompatibilities: behaves as a strong base. Reacts with oxidizing agents.

III. USES

Approximately 99% of production is used as an isolated intermediate in polyamide manufacture. The major use is in nylon fiber production; smaller amounts are used in plastics, coatings and adhesives manufacture.

IV. ANIMAL TOXICITY DATA

A. Acute Toxicity and Irritancy

1. Oral Toxicity

Rat LD_{50} = 980 mg/kg administered as a 10% aqueous solution[5]
Rat LD_{50} = 750–800 mg/kg[6]
Rat LD_{50} = 792 mg/kg (fasted) 1127 mg/kg (non-fasted)[7]
Rat LD_{50} >500 mg/kg[8]
Rat ALD (acute lethal dose) = 1500 mg/kg[9]
Rat ALD = 1000 mg/kg[10]
Mouse LD_{50} = 380 mg/kg[11]

2. Eye Irritation

Powdered hexamethylenediamine, because of its alkalinity, is strongly irritating or corrosive to the eye.[6]

A dose of 0.5 mL of a 1% solution in either water or propylene glycol produced a severe ocular burns in rabbits.[12]
A 25% aqueous solution (no volume given) caused irreversible damage to rabbit eyes.[13]

The application of 85% HMDA to rabbit eyes initially caused extensive lacrimation; severe conjunctivitis was noted 6 hours post-exposure.[14] Treated eyes were normal within 5–10 days post exposure.

3. Skin Absorption

Rabbit LD_{50} = 1100 mg/kg[6]

4. Skin Irritation

Rabbit: 8/10 Draize score[12]
Rabbit: severe[10]
Rabbit: extreme erythema with numerous small vesicles/blisters after 15 minute contact with 85% aqueous solution[14]
Rabbit: corrosive as a 50% ethanol solution; significant weight loss and paralysis of the hind legs were observed in one animal[15]

Rabbit: corrosive after 24-hr. contact with the powdered solid or a 25% aqueous solution[13]

Guinea Pig: severe[10]

Guinea Pig: irritation at 1% in petroleum jelly[16]

Guinea Pig: severe irritation at 6 and 10% aqueous solutions; washing within one minute of application resulted in no irritation[10]

5. *Sensitization*

Dermal sensitization testing in guinea pigs is negative.[10,17] The DuPont study was conducted according to a standard Draize procedure that utilized 10 intradermal injections of a 0.1% solution in 0.85% NaCl, paraffin oil or polyethylene glycol over a 21-day induction period. An intradermal injection was also used for the challenge.[18] This method is regarded as ineffective for the detection of weak allergens in particular, and is not included in current OECD Test Guidelines.

6. *Inhalation Toxicity*

4-hr LC_{50} in rats as a heated aerosol >950 mg/m^3 (4-hr exposure; test material heated to 42–48°C; analytical measurement)[13]

Following a 10-minute exposure to an estimated concentration of 750 mg/m^3, one in ten animals died.[19]

7. *Other*

a. Intraperitoneal Toxicity

Mouse LD_{50} = 320 mg/kg[20]

b. Intravenous Toxicity

Mouse LD_{50} = 180 mg/kg[21]

c. Subcutaneous Toxicity

Rat: a single injection of 10% HMDA in water at doses ranging from 96 to 465 mg/kg did not cause death; however, all animals developed necrosis at the injection site and variable changes in weight. Pathological examination indicated local ulceration of the skin that was still present after 8 weeks.[16]

d. *In vitro*

HMDA suppressed the lymphocyte proliferative response to B and T cell antigens *in vitro*, in part, by alteration of ornithine decarboxylase and polyamine activity.[22]

B. Genotoxicity

No mutagenic effects were observed in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, or TA 1538 with and without mammalian microsmal enzyme activation.[10,23] When tested for co-mutagenic activity with nitrite, negative results were also obtained in *Salmonella typhimurium* strains TA1950, TA1952, G46, and GW19.[24]

A chromosomal aberration assay conducted using rat bone marrow was negative.[25] In this study, groups of rats were administered 0, 74, 250, or 750 mg/kg by gavage and 6 animals of each sex were sacrificed at 6, 24, and 48 hours post dosing. Negative results were also obtained in an unscheduled DNA synthesis test conducted in rat hepatocytes.[26]

C. Metabolism and Pharmacokinetics

Urinary HMDA and 6-aminohexanoic acid were determined in a group of six human volunteers following oral administration of 8.2 mg (~0.1 mg/kg bodyweight) HMDA on two separate occasions, three months apart.[27] In hydrolyzed urine, a mean of 0.28 mg of the dose (range 1–6%) was recovered as HMDA and a mean of 0.8 mg (range <1–27% of the dose) was recovered as 6-aminohexanoic acid. In all subjects, >90% of the excreted amounts of HMDA and 6-aminohexanoic acid were detected in urine within 10 hours of exposure. Excretion of 6-aminohexanoic acid varied between subjects based on N-acetylation phenotype. Slow acetylators excreted a mean of 2% of the given dose, while rapid acetylators excreted 5%.

After a single oral dose of 7–8 mg/kg of ^{14}C-HMDA, 85–95% of radioactivity was recovered from rats during a 3-day period.[28] The major routes of elimination were the feces and urine (no percent given). In a second study, following oral administration of 0.4 mg/kg ^{14}C-HMDA, >98.5% was recovered after 72 hrs.[29] Again, the major routes of elimination were feces and urine (47% and 27% of administered radioactivity, respectively). Approximately 20% of the dose was recovered as carbon dioxide. Of several tissues examined for residual radioactivity at 24 and 72 hours post-dose, the prostate contained the highest concentration.

D. Developmental and Reproductive Toxicity

Groups of 22 pregnant Sprague-Dawley rats were dosed by gavage with 0, 112, 184, or 300 mg/kg HMDA on days 7 through 16 of gestation.[5] The high dose level was maternally toxic as demonstrated by reduced body weight, decreased food consumption, and a 10% mortality rate. No effects on maternal toxicity were observed at or below 184 mg/kg. The number of implantation sites per dam,

mean litter size, incidence of resorptions, sex ratio and fetal length were similar among treated and control groups. Fetal toxicity was evidenced by significantly ($p \leq 0.05$) reduced weight gain at the 300 mg/kg dose level. Delayed ossification of cervical centra or sacral/caudal vertebra was noted at the 184 and 300 mg/kg dose levels. No treatment related effects were observed at the 112 mg/kg dose level. No evidence of a teratogenic response was observed at any dose level. This study established NOAELs of 184 mg/kg/day for maternal toxicity and 112 mg/kg/day for embryofetal toxicity.

Groups of 26 Sprague-Dawley rats of each sex were administered HMDA in the diet at 0, 50, 150, or 500 mg/kg/day for two consecutive generations.[30] Body weights were significantly reduced ($p \leq 0.05$) in high dose males of both generations as compared to the controls. Body weights were also reduced approximately 10% in high-dose females during gestation. High dose groups of both generations incurred reductions in the litter size at birth and decreased pup weights during the lactation period. Copulatory interval, gestation length, nesting and nursing behavior and appearance of pups was similar among treated and control groups. No treatment-related effects occurred in testes weights or in gross or histopathological examination of tissues. No adverse effects on the viability of offspring occurred at any dose level. This study establishes a NOEL of 150 mg/kg/day.

Pregnant rats were administered 0, 10, 100, or 200 mg/kg/day of HMDA by gavage on Days 0 to 14 of gestation.[29] HMDA was not embryotoxic at any dose but did induce maternal toxicity at the high dose.

Groups of pregnant CD-1 mice were administered 103 mg/kg HMDA in 0.9% saline by intraperitoneal injection, 4 times a day on Days 10 through 14 of gestation.[31] Maternal food consumption was reduced on treatment days and several days thereafter. Treatment resulted in retarded fetal skeletal development and depressed weight gain in CD-1 mice.

Groups of 20 male and 40 female $B6C3F_1$ mice and Fisher 344 rats were exposed via whole-body inhalation exposure to aqueous aerosols of HMDA dihydrochloride at 16, 50, or 160 mg/m^3 for 13 weeks and mated to produce F1 offspring.[32] The pH of the test material was 4.5 to 5.5. The only adverse effect on body weight noted in the parental generation of either species was a lower female body weight in rats on gestation day 0 as compared to the control. No abnormal clinical signs were observed in the parental generation of mice or rats and all mating, gestation, and lactation parameters were similar between treated and control groups. No adverse effects were reported in offspring of either species. The NOEL for both the mouse parental and F1 generations was 160 mg/m^3 HMDA dihydrochloride.

E. Subacute Toxicity

Groups of 4 male and female rats were exposed via whole-body inhalation to 10 mg/L (~10,000 mg/m^3) of HMDA as heated vapor for 6 hours per day for 2 days.[33] Clinical signs included nose irritation, respiratory difficulty, and lethargy. One male and one female died; autopsy and histopathology findings included lung congestion, peribronchiolar inflammation, areas of hemorrhage and edema in lungs, and vacuolation of kidney tubules.

One of eight rats (four males and females) died following eleven 6-hr exposures to 5 mg/L (~5000 mg/m^3) HMDA as heated vapor by whole body inhalation.[33] Nose and lung irritation, reduced weight gain, and lethargy were observed. Necropsy revealed petechial hemorrhage and inflammation in the lung. In a similar study, all rats survived following 15, 6-hr exposures to 1 mg/L HMDA. No abnormal clinical signs were noted and organ histopathology was normal.

A group of ten guinea pigs was exposed by inhalation to 50 ppm (237 mg/m^3) (method of test atmosphere generation is not described) for two hours/day.[14] All animals died after 3–4 days of exposure. Clinical signs included general weakness, decreased appetite, reduced alertness and reaction to stimuli, and dyspnea. The severity of dyspnea increased with successive exposures. No pathological changes were observed.[14]

Groups of 10 male and female rats were exposed via whole-body inhalation to 0, 49, or 262 mg/m^3 (analytical concentrations) of HMDA dust for 6 hr/day, 5 days/week for four weeks.[25] Ruffled fur, ptosis, and hypoactivity were noted at the low dose, however there was no evidence of target organ toxicity. Sneezing, rhinitis, rattled breathing, discolored hair and depressed body weight gains were reported at the high concentration level; ear and tail lesions indicative of burns were also observed.

Losses in body weight were reported in rabbits following daily dermal application of a 50% solution of HMDA in ethanol for 12 to 15 days; the dose administered was not given.[17] One animal exhibited paralysis of posterior extremities. No other effects were reported. In a second dermal study, a mixture of 1% HMDA in petroleum jelly was applied to the intact shaved skin of six rats,

5 days/week for a total of 16 applications.[10] An additional group of six rats were treated with a 2% mixture for a total of 7 applications. Application doses were not reported and the application sites were not occluded, which may have allowed for oral exposure. Initially, erythema and scaly skin were noted at the 1% level, but these effects subsided by the end of the treatment period. Histopathological examination of tissues revealed mild degenerative changes in the liver cells of 3/6 rats and mild to moderate regressive lesions of the renal tubules in 2/6 rats. Gross examination of the tissues from rats treated at the 2% concentration revealed mildly hyperemic livers and kidneys. Histopathological findings consisted of mild degenerative changes of the cortical tubules associated with a few invaginations into Bowman's capsule space; the remaining organs were normal. Scaling and cracking of the skin persisted in this group over the exposure period. The authors of this report speculated that the systemic effects seen in this study were related to oral exposure, rather than dermal absorption.

One of six rats fed 300 mg/kg/day of HMDA for two weeks died within 10 days of the last exposure.[10] The surviving animals showed reduced weight gain, which the author attributed to the corrosive nature of the test material.

Groups of five male and female $B6C3F_1$ mice and Fischer 344 rats were administered drinking water containing HMDA for 15 days.[34,35] The target doses for rats were 100, 200, 400, 600, and 800 mg/kg/day; the actual doses received were 96, 189, 357, 449, and 545 mg/kg/day for males and 126, 263, 422, 517, and 634 mg/kg/day for females, respectively. The doses received by mice were 0, 36, 66, 139, 267, and 564 mg/kg/day for males and 48, 116, 208, 391, 632 mg/kg/day for females respectively. Absolute thymus weights were decreased in male rats at the high dose level as compared to the control. Liver weights were decreased in females at the 422 mg/kg/day dose level and above as compared to the control. Corresponding abnormal histopathology was not detected in either the thymus or liver, however. No adverse effects were observed in mice including clinical signs, and gross or histologic examination of tissues. This study established NOAELs in rats of 545 mg/kg/day in males and 634 mg/kg/day in females. The NOAELs in mice were 564 mg/kg/day for males and 632 mg/kg/day in females.

F. Subchronic Toxicity

Groups of 15 Sprague-Dawley rats of each sex were exposed to aqueous aerosols of 12.8, 51.0, and 215 mg/m^3 of HMDA for 6 hr/day, 5 days/week, for 7–13 weeks (analytically determined chamber concentrations).[36] Greater than 97% of the aerosols were less than 10 μm in aerodynamic mass median diameter at all exposure concentrations. The high concentration group was terminated at the seventh week due to a high mortality rate; the mid- and low-concentration groups were treated for a full 13-week period. Reduced weight gain and respiratory irritation were observed at the mid- and high-concentration levels. At a five-week study interval, red blood cell count, hemoglobin concentration, and hematocrit were increased at the high-dose as compared to the control; the differences were statistically significant ($p \leq 0.01$) in females only. A small increase in mean corpuscular volume and a corresponding decrease in mean corpuscular hemoglobin concentration also occurred. No treatment-related differences in hematologic and clinical chemistry measurements, and organ weights were noted at the lower dose levels. Microscopic changes involving inflammation of the upper respiratory tract and lung were seen at the high concentration level only. Under the conditions of this study, the no-effect-level was 12.8 mg/m^3.

Groups of 15 Sprague-Dawley rats of each sex were fed dietary levels of 0, 50, 150, or 500 mg/kg/day of HMDA for 90 days.[5] A slight, non-statistically significant decrease in weight gain was noted at the 150 and 500 mg/kg/day dose levels. No treatment-related adverse effects were observed in hematological and clinical chemistry parameters or histopathological examination of tissues.

Groups of 10 $B6C3F_1$ mice and Fischer 344 rats were exposed via whole body inhalation to 0, 1.6, 5, 16, 50, and 160 mg/m^3 of an aqueous solution of HMDA dihydrochloride for 13 weeks.[32] The pH of the test material was 4.5 to 5.5. Samples from 34 major organs and tissues were collected from the control and high-dose group animals and examined microscopically. Nasal and laryngeal tissues were examined in lower dose groups in order to identify a no-effect level. Histopathological changes indicative of irritation of the upper respiratory tract were noted in both species at the 16 mg/m^3 exposure concentration and above and included minimal to mild focal erosion, ulceration, inflammation and hyperplasia of the laryngeal epithelium, in addition to degeneration of the olfactory and respiratory nasal epithelium. The severity of effects occurred in a dose-related manner. No other target specific organ effects were identified. The NOAEL for respiratory effects was 5 mg/m^3 HMDA dihydrochloride (1.6 mg/m^3 or ~0.3 ppm as HMDA) in both rats and mice.

G. Chronic Toxicity and Carcinogenicity

HMDA was not carcinogenic in a group of 10 mice (strain and sex not specified) in a skin painting study.[37] In this study, a 1% solution of HMDA in benzene was applied to the back of the neck 3 times/week for four months. No additional information is reported.

H. Other

None.

V. HUMAN USE AND EXPERIENCE

Typically, worker exposure to HMDA is limited to specific tasks and is therefore, of short duration. Personal sampling of workers handling HMDA in DuPont Canadian manufacturing operations was between 0.02–0.07 ppm.[3] The collection periods ranged from 10–30 minutes. Sampling in various Monsanto manufacturing operations in the U.S. indicates that exposures are typically less than 0.5 ppm under normal operating conditions.[25]

In an older report, typical 8-hr, time weighted average exposure concentrations measured at a nylon manufacturing site were generally below 1 ppm (4.8 mg/m^3) with infrequent excursions as high as 4.31 ppm (20.5 mg/m^3).[38] No adverse effects were reported. However in another early report, moderate conjunctival and upper respiratory tract irritation was observed in 8 of 20 workers who were exposed to HMDA at concentrations of 7 to 28 ppm; baseline levels ranged from 0.4 to 1.2 ppm under normal operating conditions.[39] In addition, acute hepatitis accompanied by dermatitis was attributed to HMDA exposure in one worker. Exposures involved both synthesis of HMDA and use in nylon production and adipic nitryl hydrogenation and ranged from 2.0 to 5.5 mg/m^3 (0.4 to 1.2 ppm) during normal operations and from 32.7 to 131.5 mg/m^3 (6.7–27.6 ppm) during autoclave discharging and filling operations. Information on concurrent exposures and possible employee lifestyle factors relating to the systemic effects were not addressed.

There is anecdotal information suggesting that HMDA may be an allergen (skin and/or respiratory) in industrial settings.[40–42] However, exposure in these reports was to multiple chemicals and is not well characterized.

VI. RATIONALE

Occupational exposure to hexamethylenediamine would most likely occur by dermal contact and inhalation of dust, vapor and aerosol forms. HMDA is strongly alkaline in solution and severely irritating to the skin, eyes and respiratory tract upon direct contact. In acute testing, it is slightly toxic by the oral and dermal routes of exposure. Workers were reported to experience eye and upper respiratory tract irritation at airborne concentrations of between approximately 33 mg/m^3 (7 ppm) and 133 mg/m^3 (28 ppm).

In a 13-week inhalation study utilizing aerosolized aqueous solutions of HMDA, the no-effect-level in rats was 12.8 mg/m^3 HMDA. At 51 mg/m^3, which was the lowest observed effect level, respiratory irritation and weight loss were observed. A NOEL of 5 mg/m^3 was established in a 13-week study in which the chloride salt of HMDA was used; the approximate HMDA equivalent NOEL was 1.6 mg/m^3 or 0.3 ppm. Hydrochloride ion would be liberated as a dissociation product in this study and the extent to which this would affect the results of this portal of entry effect is unknown. There is no evidence that the salt is the predominant commercial form as opposed to the amine. Therefore, the 13-week study of the amine itself appears to be the more relevant study upon which to base the OEL.

The available data suggest that HMDA is not mutagenic and is not a developmental toxicant except at concentrations much greater than those that induce respiratory effects. Carcinogenic potential has not been adequately investigated.

The basis for establishing an occupational exposure limit is avoidance of eye and respiratory tract irritation. Based on the animal studies and human experience with HMDA, an exposure limit of 1 ppm should prevent irritation and related effects. The information needed to establish a STEL is not available at this time.

The dermal LD_{50} suggests that HMDA may be absorbed through the skin, although not at levels typically seen in chemicals assigned skin notations. Systemic effects have been reported in animals following subacute dermal application of HMDA, however the study design and investigator observations suggest that oral exposure likely occurred. Hepatitis has also been reported in a single worker exposed both by inhalation and dermal contact. However, potential confounding factors are not addressed. Therefore, a skin notation is not assigned based on the available weight of evidence.

HMDA does not meet the criteria for notation as a dermal sensitizer, since testing is negative in laboratory animals and anecdotal reports of dermal sensitization in humans are not adequately reported.

VII. RECOMMENDED OEL

8-hr TWA: 1 ppm (~5 mg/m^3)

VIII. REFERENCES

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