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DuPont Haskell Global Centers
for Health and Environmental Sciences
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Room 6428
Attention: 8(e) Coordinator
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency, ICC Building
1201 Constitution Ave., NW
Washington, DC 20004



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Dear 8(e) Coordinator:

Hexamethylenediamine
124-09-4

This letter is to inform you of the results of pre-1977 DuPont studies with the above-referenced test substance. In addition, DuPont received information from a third party also with the above-referenced test substance.

DuPont's Pre-1977 Toxicity Studies - See the attached 1937 report.

Third Party Studies

Acute Dermal Study - A single dose of undiluted test substance was applied to the shaved skin of rats (5/sex) at 0, 950, 1400, 2000, 3000 or 4800 mg/kg. The application site was covered by an occlusive patch for 24 hours, after which the skin was rinsed with soapy water. Clinical signs included hypoactivity, closed eyes and low body temperature in three higher dose groups. At 2000, 3000, and 4300 mg/kg, necrosis was observed 24 hours after treatment and persisted until the time of death. At 950 and 1400 mg/kg, necrosis was observed 24 hours after treatment and recovered thereafter. Dermal LD50 (combined) = 1900 mg/kg.

Acute Algae Study - In a 72-h acute toxicity test, *Raphidiopsis subcapitata* were exposed at nominal concentrations of 0, 1, 1.8, 3.2, 5.6, 10, 18, 32, 56 and 100 mg/L. The 72-h EC50 was 56 mg/L for biomass.

Acute Fish Study - The 96 hour acute fish toxicity was tested following the EU Methods C1 guidelines. *Brachydanio rerio* (10/group) were exposed under semi-static conditions to test substance to nominal concentrations of 0, 0.46, 1.0, 2.1, 4.6, 10, 21, 46, and 100 mg/L. Test solutions were prepared by direct addition into test water. The 96-h LC50 was estimated to 68 mg/L, based on nominal concentrations under these test conditions.

This information is submitted in accordance with current guidance issued by EPA indicating EPA's interpretation of Section 8(e) of the Toxic Substances Control Act or, where it is not clear that reporting criteria have been met, it is submitted as a precautionary measure and because it is information in which EPA may have an interest.

Sincerely,

S. Sathesh Anand, Ph.D., DABT
Senior Research Toxicologist



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2. Hexamethylene Diamine

The toxicity of hexamethylene diamine was studied in rats by subcutaneous injection, oral and cutaneous administration and inhalation experiments.

Subcutaneous Injections.

Twenty white rats were given subcutaneous injections of a 10 per cent solution of pure hexamethylene diamine in doses between 96 and 465 mg. of the diamine per kilogram body weight. All animals developed severe necroses at the site of the injection and showed variable changes of weight. They were killed 8 days after the injection. In another series 20 rats were injected with 1 cc. of a 10 per cent solution of hexamethylene diamine and killed 3, 5, 8 and 15 days, respectively, after the injection, and in a third series 15 animals treated in the same way were killed in groups of five, 4, 6 and 8 weeks after the injection. All animals developed severe necroses at the site of the injection and lost weight during the experimental period.

Upon pathological examination all rats showed local ulcerations of the skin and inflammatory reactions at the site of the injection. These ulcers had little tendency to heal and were still present in animals killed 8 weeks after the injection, at which time they showed a minor amount of scar tissue.

Microscopically, those rats of the first series which had received the smallest dose showed in addition to the pathological changes of the skin, mild degeneration of the tubular epithelium of the kidney and in one instance red blood cells were found in

the capsule spaces of one kidney. All other organs (brain, lungs, heart, liver, pancreas, spleen, suprarenals, testes and epididymides) were essentially normal. The findings in the animals receiving larger doses were of similar nature but more marked.

The animals of the second and third series showed locally at the site of the injection a more or less extensive coagulation necrosis, which in the beginning is characterized by a leucocytic infiltration of mild to moderate degree and the formation of small abscesses in the periphery of the necrotic region, and the blood vessels in this neighborhood became thrombotic and the nervous elements degenerated. Only after about two weeks, attempts at regeneration became manifest, although the necrotizing processes were still progressing in other places. After a period of four weeks the epidermis forming the edge of the ulcers showed signs of proliferation and during the following four weeks the progress of healing was very slow and even after eight weeks smaller ulcers were still present.

The systemic effects of smaller doses were apparently entirely restricted to the kidneys. Only with higher doses and a longer interval between injection and death of the animals, which, on account of the slow absorption from the site of the injection, may be interpreted as prolonged exposure, did other organs also show direct or indirect toxic effects which evidently persisted unmitigated throughout the observation period of eight weeks. With doses of more than 0.5 cc. and with long intervals between

administration and time of death the regressive changes of the tubular epithelium of the kidney became more marked and the presence of erythrocytic debris and hemoglobinous globular matter in the tubuli and occasionally also in Bowman's capsule spaces during the latter part of the experimental period indicated the existence of hematotoxic processes in the body and an increased permeability of the renal cells to the decomposition products of red blood cells. The destruction of red blood cells is also indicated by the deposits of brown pigment in the phagocytes of the spleen and is responsible for the compensatory increased formation of red blood cells in the bone marrow.

The pathological findings further indicate that with extended exposure more or less extensive lesions become increasingly frequent in the heart, brain and liver. Although it is possible that these are the result of the absorption of toxic substances from the necrotic tissues, similar findings observed in animals treated with oral administration and with inhalation of the vapors of hexamethylene diamine suggest that they are produced by the chemical agent.

Oral Treatment.

In these experiments doses of 1 cc. of a 10 per cent aqueous solution were given daily to 6 white rats. All animals showed extreme discomfort throughout the experiment with disturbances of the respiration and cyanosis and behaving as though there was severe damage to the gastro-intestinal tract. One animal died after the second, 1 after the third, and 1 after the

fourth treatment. The remaining 3 animals were killed for autopsy, 1 after the second, and 2 after the fifth treatment.

Upon pathological examination the stomachs of 2 rats that had died spontaneously were markedly distended with gas; there was a slight congestion of the gastric mucosa of the lower section and in one animal multiple hemorrhages of the gastric mucosa and multiple ulcers in the other. The gastric mucosa of the 2 animals killed at the end of the experiment was mildly congested and the lungs, liver and kidneys were hyperemic.

The results of the microscopical examination of the organs of these animals may be summarized as follows: The stomach of 3 rats showed severe necrotizing processes, affecting mainly the squamous cell epithelial lining and to a lesser degree the glandular mucosa. In addition to this local effect the majority of these animals gave evidence of a systemic action of hexamethylene diamine as indicated by inflammatory and circulatory lesions as well as degenerative lesions in the brain, regressive processes in the kidneys and a proliferation of the reticulo-endothelial structures of the liver and spleen. One animal gave also indications of an irritant action on the bladder as indicated by hemorrhages into its mucosa.

These experiments indicate that the oral ingestion of hexamethylene diamine causes severe local irritation, and in addition, systemic effects resulting in damage of other vital organs.

Inhalation Experiments.

Inhalation experiments with hexamethylene diamine were

rendered difficult by the development of a white powdery material that clogged the apparatus and covered the surface of the molten amine.

Five rats were exposed to the vapors developed at 45°C. from pure hexamethylene diamine. These vapors were carried by an air current flowing at about 4 liters per minute into the bell jar containing the rats. Within 3 minutes after the beginning of the exposure the animals showed a severe irritation of the mucous membranes and the respiration became jerky. The animals were given 7 four hour exposures in 9 days and were killed for autopsy on the fourteenth day of the experiment.

Upon gross pathological examination the lungs and trachea as well as other organs of these animals were found to be normal with the exception of those of one animal that suffered from an abdominal abscess.

In a second series of experiments 5 rats were exposed on five days for 3, 5, 5, 5, and 5 hours respectively, to vapors liberated from hexamethylene diamine at 45°C. to 48°C., the air flow being 6.5 liters per minute. Soon after the beginning of the exposure the respiration became jerky and the animals became cyanotic. One animal that developed hemorrhages around the nose died during the fourth inhalation period and the other animals were killed on the eighth day of the experiment for autopsy.

Upon gross pathological examination the animal that died spontaneously showed few small subpleural hemorrhages in the

lungs, the liver was small and congested, the spleen was small and the other viscera were normal.

The outstanding histo-pathological finding in this group was a brown pigmentation in the spleen, the peripancreatic lymph nodes and the tubular epithelium of the kidney, indicating some minor destructive effect on the red blood cells. There were reactive changes of different types in the lungs but these were too variable to allow a definite conclusion in regard to the specific injurious effect of hexamethylene diamine. The same holds true for the interpretation of lesions found in the brain, liver, pancreas and kidney.

Application to the Skin.

Six white rats were treated daily on 5 days of the week on their shaved backs with a 1 per cent paste of crude hexamethylene diamine in vaseline. No precautions were taken to prevent licking. The first few applications produced erythema and scaling of the skin but these gradually disappeared and when the animals were killed on the twenty-first day of the experiment, i.e., after 16 applications, new hair had grown almost completely over the shaved area.

With the exception of mild degenerative changes in the liver cells in 3 out of 6 rats and mild to moderate regressive lesions of the renal tubules in 3 out of 6 animals, the pathological examination gave no evidence of any toxic effect in these animals.

In a second series of experiments 6 rats were similarly

treated with a 2 per cent paste of crude hexamethylene diamine. This was found to be much more irritant. Scaling of the epidermis and cracking of the skin developed after the third treatment and in 5 rats this lasted until they were killed on the ninth day of the experiment, i.e., after 7 applications had been made.

Upon autopsy the treated area showed some sero-sanguinous crusts and liver and kidneys were mildly hyperemic. Microscopically the skin showed small ulcerative defects of the epidermis, in other parts this was atrophic and contained small purulent blisters; there were also inflammatory reactions in the lower layers of the skin (subepidermal connective tissue). The only other pathological finding in these animals was a moderate degenerative change in certain parts of the kidney which, however, may not have been due to absorption of the material through the skin but due to oral ingestion of small quantities by licking the painted area.

These experiments indicate that hexamethylene diamine is strongly alkaline and extremely irritating for all tissues, especially to the mucous membranes of the eye, the respiratory tract and the gastro-intestinal tract. Systemic effects resulting in damage to the kidney may result from the various types of exposure studied in this report. Only with prolonged contact and continued absorption should toxic effects on the heart, liver, brain and red blood cells be expected.



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