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VOLUME I. SINGLE CHEMICALS

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ABSTRACT: This information profile on*phosphoramide (680319) is part of a group of 46 such profiles that provide information about chemicals or industrial processes considered to be potential occupational hazards. Each profile contains summary data on known and suspected health effects, the extent of worker exposure and the industrial importance of either a single chemical, class of chemicals, or a particular industrial process. The report was developed for use by occupational safety and health professionals in industry, and labor and other areas, to provide them with a synopsis of information in their workplaces.

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Physiological-effects
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INTRODUCTION

An information profile is a working paper used by the National Institute for Occupational Safety and Health (NIOSH) to assist in establishing Institute priorities. It is an initial step in determining the need to develop comprehensive documents or to initiate research. Each profile summarizes data on known and suspected health effects, the extent of worker exposure, physical and chemical properties, and the industrial importance of individual chemicals and classes of chemicals. The profile may also be used by industry, labor, and the occupational health community as a synopsis of information on each subject and to identify possible health hazards associated with their workplaces.

Although detailed literature searches are conducted using computerized and manual searching techniques to identify pertinent and recent information, not all the literature obtained is incorporated in the report due to the summary nature of the profiles. Further, literature published after 1978 may not be included in these profiles because it was generally unavailable at the time the search was completed.

HEXAMETHYL PHOSPHORAMIDE

SUMMARY

Hexamethyl phosphoramide (HMPA) is used as an ultra-violet light absorber and stabilizer for polymeric materials, as an organic and metal solvent, and as an insect sterilant. No occupational exposure or production figures are available for this chemical.

Acute toxicity data indicates that HMPA is of relatively low toxicity when ingested or applied dermally to rodents (oral, skin LD_{50} values of 2500-4500 mg/kg). HMPA exposure affects body and organ weights, testicular development, gastrointestinal and nervous systems, muscle coordination, the nasal lining, and white blood counts.

HMPA produced mutagenic effects in Drosophila, but no chromosomal aberrations have been observed in mice or humans. Rats exposed to low levels of HMPA developed nasal tumors following inhalation, but HMPA does not appear to be teratogenic or embryotoxic towards rodents. No data are available on the toxic effect of HMPA in humans.

1. Synonyms: HEMPA
Hexametapol
Hexamethyl phosphoric acid triamide
Hexamethyl phosphoric triamide
Hexamethyl phosphorotriamide
Hexamethyl phosphotriamide
Hexamethyl phosphoramide
HMPA
HMPT
HPT
Phosphoric triamide, hexamethyl
Phosphoric tris(dimethylamide)
Phosphoryl hexamethyltriamide
Tris(dimethylamine)phosphine oxide

2. Chemical Abstracts Service Number: 680-31-9

3. Registry of Toxic Effects of Chemical Substances Number: TD08750

4. Molecular Formula: $C_6H_{18}N_3OP$

5. Chemical Structure: $[(CH_3)_2N]_3PO$

6. Physical and Chemical Properties:

Molecular Weight	179.20
Physical State	Liquid
Boiling Point	98-100°C at 6 mm
Melting Point	4°C
Vapor Pressure	
Evaporation Rate	
Solubility	
Specific Gravity	
Stability	

7. Producer and User Data

Production and Trends

No data are available.

Uses

Hexamethylphosphoramide is used as an ultra-violet light absorber and stabilizer for polymeric materials (Gordon, 1970). A survey of patent literature indicates that hexamethylphosphoramide also has uses as a catalyst solvent in organic reactions (particularly for alkali metal derived silanes), as a metal and hydrocarbon solvent, and as an insect sterilant.

Producers and Users

The following two companies produce and distribute hexamethylphosphoramide (SRI, 1978):

DuPont	Deepwater, N.J.
Fike Chem.	Nitro, W.V.

Additional distributors include (Chem. Week, 1978):

Aceto Chem.
Eastern Chem.

Manufacturing Process

Hexamethylphosphoramide (HMPA) is produced by reacting phosphorus oxychloride with dimethylamine in an organic solvent such as xylene. A neutralizer, such as sodium hydroxide, is added to the reaction products and the unreacted dimethylamine is distilled off. The yield of hexamethylphosphoramide is about 95% (Miller and Lomonte, 1963).

8. Biological Effects of Exposure

a) Acute Effects

Information on LD_{50}'s in several species is contained in Table 1. These data indicate that the acute toxicity of HMPA is relatively low (Shott et al., 1971).

HMPA was applied dermally to rabbits for 24 hours and the rabbits were observed for 14 days; no systemic toxic signs were produced at doses below 3000 mg/kg (Shott et al., 1971). At 3000 mg/kg, symptoms consisted of depression, ataxia, depressed righting and placement reflexes, incoordination, absence of pain reflex, salivation, labored respiration, and prostration prior to death.

Single-comb white leghorn cockerels were observed for 4 weeks after a single oral dosage of HMPA (Sherman and Herrick, 1970). HMPA at 500 mg/kg was highly inhibitory to testicular development. The testes tubules were small and not well defined. There were large intertubular spaces filled with connective tissue. The tubule lumina were inconspicuous; spermatogonia were observed, but no spermatocytes were present. Spleen size was also significantly affected (Table 2).

b) Subchronic Effects

HMPA, when given orally to rats that were observed for 38-45 days, was more toxic to males than to females (Table 1) (Kimbrough and Gaines, 1966). Clinical symptoms were involuntary urination, mild muscle fasciculation, convulsions, and bloody urine. No significant change in red cell cholinesterase

Table 1. Acute Toxicity

Species	Route	Dose	Result	Reference
rat (male)	oral	2650 mg/kg	LD_{50}	Kimbrough & Gaines, 1966
rat (female)	oral	3360 mg/kg	LD_{50}	Kimbrough & Gaines, 1966
rat (male)	skin	3500-4500 mg/kg	LD_{50}	Kimbrough & Gaines, 1966
rat (female)	skin	3500-4500 mg/kg	LD_{50}	Kimbrough & Gaines, 1966
rabbit	skin	2600 mg/kg	LD_{50}	Shott et al., 1971
chicken	oral	835 mg/kg	LD_{50}	Sherman & Herrick, 1970

Table 2. Testes and Spleen Weights of Cockerels Given Single Oral Doses of Chemosterilants[a]

Insect chemosterilant	Dose (mg/kg)	Number of cockerels	Mean body weight[b] (g)	Mean testes weight[b] (mg)	Mean testes weight[c] (%)	Mean testes tubule diameter[d] (mm)	Mean spleen weight[b] (mg)	Mean spleen weight[c] (%)
Hempa	1000	1	317	20	0.006		440	0.14
	800	7	318[e] ± 5	38[e] ± 6	0.012		374[e] ± 26	0.12
	700	8	318[e] ± 11	59[e] ± 5	0.019		448[e] ± 25	0.14
	600	10	446 ± 12	73[e] ± [illegible]	0.016		921 ± 88	0.21
	500	10	409 ± 8	67[e] ± 4	0.016	0.046	727[f] ± 30	0.18
	250	10	396[f] ± 16	95[e] ± 16	0.023		632[e] ± 46	0.16
	100	10	424 ± 10	100[e] ± 8	0.023		664[e] ± 14	0.16
Control	1	20	451 ± 8	131 ± 5	0.029	0.099	937 ± 68	0.21

[a] Data taken 28 days after treatment.
[b] Mean ± SE.
[c] As percent of body weight.
[d] Mean values based on 50 measurements per bird and 5 birds per dosage.
[e] Significantly less than control at P<0.01.
[f] Significantly less than control at P<0.05.

occurred at any time. The testes proved to be the organ most consistantly affected. Necropsies of adult male rats, killed 40 days after receiving single doses of varying amounts by stomach tube, indicated the spermatids to be the cells of the seminiferous epithelium most affected. When a single dose of 2500 mg/kg was given to six females, no effect on the reproductive organs was observed when the animals were killed 36 days later.

Oral administration of HMPA to rats for 62 days at 100 mg/kg body weight/day or gastric intubation for 92 days at up to 50 mg/kg/day resulted in exacerbation of chronic murine pneumonia (Overcash et al., 1976).

c) Chronic Effects

i. Carcinogenicity

Zapp (1975) conducted inhalation toxicity studies with low levels of HMPA in rats. Males and females were exposed to 50, 400, and 4000 ppb (v/v) of HMPA. By the eighth month, squamous cell carcinomas, i.e., nasal tumors, were found in 5% (12/240) exposed at 4000 ppb and 2.9% exposed at 400 ppb (7/240). No tumors were observed in the control group. Similar rat exposure studies by Lee et al. (1977) produced nasal tumors after approximately 9 months at 100 ppb and 13 months at 50 ppb level. No carcinomas were detected after 1 year at 10 ppb. These results indicate a potential carcinogenic effect for HMPA in rodents.

The principal signs of toxicity in rabbits exposed to a total of 15 6-hour exposures, over a 3 week period, to HMPA at 100 and 500 mg/kg were dose-related weight loss, altered gastrointestinal function, intermittant anuria, depression, and incoordination.

ii. Mutagenicity

HMPA has been shown to produce mutagenic effects in fruitflies, Drosophila melanogaster (Benes and Sram, 1969). HMPA produced no elevation in the frequency of chromosomal aberration in mice (Manna and Das, 1973). No significant effects were found with human leukocyte chromosomes, but the researchers felt there would have been a significant effect if the sample size had been larger (Chang and Klassen, 1968).

iii. Teratogenicity and Effects on Reproduction

Shott et al. (1971) fed HMPA to rats by gastric intubation at 2, 10, and 50 mg/kg/day for 92 days. The survival data of the three test groups were similar, but a greater incidence of respiratory disease was observed in the high level test animals. A statistically significant decrease in the growth rate was observed in the 50 mg/kg/day group. Growth suppression was also evident in the 10 mg/kg/day group. The females treated at 50 mg/kg/day had a 34% increase in total white blood counts compared to the controls. A total of 17 other biochemical, hemotological, and urinal parameters were completely

comparable between the control and test animals. Neither spermatogenesis nor ovarian activity was adversely affected. No change due to HMPA was observed in the fertility, gestation, number of live births, or lactation of rats at 10-20 mg/kg/day for a total of 169 days. Also, the reproductive activity of the offspring was normal.

When HMPA was given to female rats by stomach tube at a rate of 200 mg/kg/day, abnormalities were not detected in the offspring. The dosing began 7 days before mating to undosed males and continued until the 20th day of pregnancy. The weights of each fetus and placenta, the number of animals per litter, and the number of resorption sites in the treated animals did not differ significantly from the controls (Kimbrough and Gaines, 1966).

iv. Other Effects

No data were encountered.

d) Human Effects

No data are available on the toxic effect of HMPA in humans.

9. Threshold Limit Values, OSHA Standards, NIOSH Recommended Standards

None are available.

10. Other Standards

No other standards were encountered.

11. Occupational Exposures

No data were encountered.

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TEREPHTHALIC ACID

SUMMARY

Annual production of terephthalic acid (TA), crude and purified, is 2.0-2.5 billion lbs. Crude TA is an intermediate in the manufacture of dimethyl terephthalate, and purified TA is consumed in producing polyethylene terephthalate, used for polyester fibers and films. Approximately 8637 workers are exposed to TA each year.

Terephthalic acid is relatively nontoxic. Liver and kidney function were normal in laboratory animals fed diets containing TA. Excretion was rapid and nearly complete in the urine after oral and intratracheal administration. Dermal application did not cause irritation, and both dermal and ocular exposure resulted in negligible absorption and excretion. Cardiopulmonary effects were not found in rats, although a decrease in aortic blood pressure, stimulation of respiration, and a decreased pulmonary resistance were found.