Current Intelligence Bulletin 6

October 24, 1975

HEXAMETHYLPHOSPHORIC TRIAMIDE (HMPA)

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
CENTER FOR DISEASE CONTROL

NATIONAL INSTITUTE FOR OCCUPATIONAL
SAFETY AND HEALTH
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20852

October 24, 1975

Dear Colleague:

The enclosed background material on Hexamethylphosphoric Triamide has been prepared by the Office of Occupational Health Surveillance and Biometrics, National Institute for Occupational Safety and Health to alert members of the occupational health community to new information on a potential occupational hazard.

Your comments and suggestions for changes to future reports are solicited.

Sincerely yours,

J. William Lloyd, Sc.D.
Director
Office of Occupational Health
Surveillance and Biometrics

Enclosure

HEXAMETHYLPHOSPHORIC TRIAMIDE (HMPA)

Summary

The National Institute for Occupational Safety and Health (NIOSH) has received a report from an American producer of hexamethylphosphoric triamide (HMPA), a synthetic organic chemical, indicating that malignant tumors have been produced in laboratory animals by exposure to HMPA.

In light of the potential risk of human exposure to this chemical in the work environment, the National Institute for Occupational Safety and Health is advising the occupational health community of these findings.

Introduction

The E.I. du Pont de Nemours and Company (Du Pont) reported to the National Institute for Occupational Safety and Health in a letter dated September 24, 1975, that nasal tumors (squamous cell carcinoma) have been observed in rats exposed to hexamethylphosphoric triamide. NIOSH has also been advised that Du Pont has notified its customers and employees of these findings.

Background

HMPA is a colorless liquid with a density of 1.03 g/ml and a boiling point of 232°C. Synonyms for hexamethylphosphoric triamide include ENT 50882, hempa, hexametapol, hexamethylphosphamide, hexamethylphosphoramide, hexamethylphosphoric acid triamide, hexamethylphosphorotriamide, hexamethylphosphotriamide, HMPA, HMPT, HPT, phosphoric tris (dimethyamide), phosphoryl hexamethyltriamide, tris (dimethylamino) phosphine oxide, and tris (dimethylamino) phosphorous oxide.(1)

Hexamethylphosphoric triamide is a material possessing unique solvent properties and is widely used as a solvent, in small quantities, in organic and organo-metallic reactions in laboratories. (2,3) This is the major source of occupational exposure to HMPA in the United States.

Du Pont, the major manufacturer of hexamethylphosphoric triamide in the United States, periodically produces HMPA at its Chambers Works, Deepwater, New Jersey. Other producers of HMPA in the United States include Chemical Samples Company and Fike Chemical Company. None of Du Pont's HMPA is marketed; all is used internally at its Spruance Plant in Richmond, Virginia, as a processing solvent in the production of Kevlar* aramid fiber. Du Pont reports that Kevlar contains less than 1 ppm (w/w) of the HMPA which is so firmly held by the fiber that Du Pont believes there is no hazard to customers or employees handling the final fiber product.

Hexamethylphosphoric triamide had been manufactured and distributed in the past by Dow Chemical Company (as DORCOL) and Eastman Chemical Products, Inc. (as Inhibitor HPT). Both firms have advised NIOSH that they discontinued these products several years ago.(4) HMPA has been evaluated for use as an ultraviolet light inhibitor in polyvinyl chloride formulations, as an additive for antistatic effects, as a flame retardant, and as a de-icing additive for jet fuels.(4,5,6)

Hexamethylphosphoric triamide has also been extensively investigated as an insect chemosterilant.(7,8)

Toxicity

Human:

There are no data available on the toxic effects of hexamethylphosphoric triamide in humans.

*Kevlar is a registered trademark of the Du Pont Company.

Animal:

HMPA is known to have a variety of toxic effects on laboratory animals. Acute toxic effects seen in rats fed HMPA include kidney disease, severe bronchiectasis and bronchopneumonia with squamous metaplasia and fibrosis in lungs.(9,10) In rabbits, repeated application of HMPA to the skin caused dose related weight loss, altered gastro-intestinal function and apparent nervous-system dysfunction.(11) Testicular atrophy and aspermia have been observed in rats following oral treatment with HMPA.(9,12) Oral treatment with HMPA has also been highly inhibitory to testicular development in cockerels.(13)

HMPA is known to produce mutagenic effects in fruit flies (Drosophila melanogaster).(14) However, studies of the effects of HMPA on human(15) and mice chromosomes(16) showed no greater frequency of HMPA induced chromosomal aberrations when compared with controls.

Preliminary results of an inhalation toxicity study of HMPA, recently released by Du Pont, show nasal tumors in rats exposed daily to 400 and 4,000 parts per billion (ppb) HMPA after 8 months of exposure. In some cases, the tumors originating from the epithelial lining of the nasal turbinate bones filled the nasal cavity and penetrated into the brain. No nasal tumors were reported among rats exposed to 50 ppb HMPA and controls.

Prior to the Du Pont observations, the only other known report of tumors associated with exposure to HMPA was a long-term feeding study by Kimbrough. While lung tumors were observed, the results of this study were inconclusive because the tumor incidence among HMPA exposed rats was not greater than among the control rats.(17)

Occupational Exposure

It is estimated that 5,000 people are occupationally exposed to hexamethylphosphoric triamide. More than 90 percent of these exposures are in research laboratories.

Permissible Occupational Exposure

There is no current Occupational Safety and Health Administration, Department of Labor standard for hexamethylphosphoric triamide exposure.

Producers and Distributors

The following is a list of the major producers and distributors of hexamethylphosphoric triamide:

Producers	Location
E.I. du Pont de Nemours & Co., Inc.	Deepwater, NJ
Chemical Samples Company	Columbus, OH
Fike Chemical Company	Nitro, WV

Distributors*	Location
Aldrich Chemical Company	Milwaukee, WS
J.T. Baker Chemical Company	Phillipsburg, NJ
Bodman Chemicals	Aston Township, PA
Chemical Samples Company	Columbus, OH
Eastman Organic Chemicals	Rochester, NY
E.M. Laboratories, Inc.	Elmsford, NY
Fike Chemical Company	Nitro, WV
Fisher Scientific Company	Pittsburgh, PA
Guardian Chemical Corporation	Hauppauge, NY
MCB Manufacturing Chemists	Cincinnati, OH
Orgmet	E. Hampstead, NH
Peninsular Chemical Research, Inc.	Gainesville, FL
Polyscience, Inc.	Warrington, PA

*Includes domestic and imported HMPA

SOURCE: Personal communications with representatives of chemical manufacturers, October, 1975

BIBLIOGRAPHY

1. CHEMLINE, National Library of Medicine, Bethesda, Maryland, October, 1975

2. Fieser, M. and Fieser, L.F.: Reagents for Organic Synthesis, John Wiley and Sons, Inc., New York, 4:244, 1974; 3:149, 1972; 2:208, 1969; 1:430, 1967

3. Chemical Abstracts, Chemical Substances Index, Chemical Abstracts Service, Columbus, Ohio, Vol. 81, 1974

4. Personal communication with representatives of Dow Chemical Company, Midland, Michigan, and Eastman Chemical Products, Inc., Kingsport, Tennessee

5. Eastman Technical Data Sheet No. X-203, Eastman Chemical Products, Inc., Kingsport, Tennessee

6. The Merck Index, 8th Ed., Merck and Company, Inc., Rahway, New Jersey, p. 528, 1968

7. Bull, D.L. and Borkovec, A.B.: Metabolism of Carbon-14-Labeled Hempa by Adult Boll Weevils, Arch Environ Contam Toxicol, 1(2):148-58, 1973

8. Landa, V.: Action of Chemosterilants in the Reporductive Organs and Tissues of Insects, Proc, Int Cong Entomol, 13th, 3:423-24, 1972

9. Kimbrough, R.D. and Gaines, T.B.: Toxicity of Hexamethylphosphoramide in Rats, Nature, 211:146-47, 1966

10. Kimbrough, R.D. and Sedlak, V.A.: Lung Morphology in Rats Treated with Hexamethylphosphoramide, Toxicol Appl Pharmacol, 12(1):60-7, 1968

11. Shott, L.D., Borkovec, A.B., and Knapp, W.A., Jr.: Toxicology of Hexamethylphosphoric Triamide in Rats and Rabbits, Toxicol Appl Pharmacol, 18(13):499-506, 1971

12. Jackson, H., Jones, A. R., and Cooper, E.R.A.: Effects of Hexamethylphosphoramide on Rat Spermatogenesis and Fertility, J Repro Fertil, 20:263-69, 1969

13. Sherman, M. and Herrick, R.B.: Acute Toxicity of Five Insect Chemosterilants, Hemel, Hempa, Tepa, Metepa, and Methotrexate, for Cockerels, Toxicol Appl Pharmacol, 16:100-07, 1970

14. Benes, V. and Sram, R.J.: Mutagenic Activity of Some Pesticides in Drosophila Melanogaster, Indus Med Surg, 38(12):442-44, 1969

15. Chang, T.H. and Klassen, W.: Comparative Effects of Tretamine, Tepa, Apholate, and Their Structural Analogs on Human Chromosomes in Vitro, Chromasoma, 24(3):314-23, 1968

16. Manna, G.K. and Das, P.K.: Effect of two Chemosterilants Apholate and Hempa on the Bone-Marrow Chromosomes of Mice, Can J Genet Cytol, 15(3):451-59, 1973

17. Kimbrough, R.D. and Gaines, T.B.: The Chronic Toxicity of Hexamethylphosphoramide in rats, Bull Environ Contam and Toxicol, 10(4)225-26, 1973

NIOSH

Current Intelligence Bulletin

Reprints-Bulletins 1thru18 (1975-1977)

U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
Center for Disease Control
National Institute for Occupational Safety and Health