Environmental Health Criteria 76

Thiocarbamate Pesticides - a general introduction

Please note that the layout and pagination of this web version are not identical with the printed version.

World Health Organization

INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

ENVIRONMENTAL HEALTH CRITERIA 76

THIOCARBAMATE PESTICIDES - A GENERAL INTRODUCTION

This report contains the collective views of an international group of experts and does not necessarily represent the decisions or the stated policy of the United Nations Environment Programme, the International Labour Organisation, or the World Health Organization.

Published under the joint sponsorship of
the United Nations Environment Programme,
the International Labour Organisation,
and the World Health Organization

World Health Orgnization
Geneva, 1988

The International Programme on Chemical Safety (IPCS) is a joint venture of the United Nations Environment Programme, the International Labour Organisation, and the World Health Organization. The main objective of the IPCS is to carry out and disseminate evaluations of the effects of chemicals on human health and the quality of the environment. Supporting activities include the development of epidemiological, experimental laboratory, and risk-assessment methods that could produce internationally comparable results, and the development of manpower in the field of toxicology. Other activities carried out by the IPCS include the development of know-how for coping with chemical accidents, coordination of laboratory testing and epidemiological studies, and promotion of research on the mechanisms of the biological action of chemicals.

ISBN 92 4 154276 4

CONTENTS

WHO TASK GROUP ON THIOCARBAMATE PESTICIDES

Members

Dr U.G. Ahlborg, Unit of Toxicology, National Institute of Environmental Medicine, Stockholm, Sweden (Vice-Chairman)
Dr R.C. Dougherty, Department of Chemistry, Florida State University, Tallahassee, Florida, USA
Dr H.H. Dieter, Federal Health Office, Institute for Water, Soil and Air Hygiene, Berlin (West)
Dr A.H. El Sabae, Pesticide Division, Faculty of Agriculture, University of Alexandria, Alexandria, Egypta
Dr A. Furtado Rahde, Ministry of Public Health, Porto Alegre, Brazil (Chairman)
Dr S. Gupta, Department of Zoology, Faculty of Basic Sciences, Punjab Agricultural University, Ludhiana, Punjab, India[a]
Dr L.V. Martson, All Union Scientific Research Institute of the Hygiene and Toxicology of Pesticides, Polymers, and Plastics, Kiev, USSR[a]
Dr U.G. Oleru, Department of Community Health, College of Medicine, University of Lagos, Lagos, Nigeria
Dr Shou-Zheng Xue, Toxicology Programme, School of Public Health, Shanghai Medical University, Shanghai, China

Observers

Dr R.F. Hertel, Fraunhöfer Institute for Toxicology and Aerosol Research, Hanover, Federal Republic of Germany
Dr E. Kramer (European Chemical Industry Ecology and Toxicology Centre), Dynamit Nobel AG, Cologne, Federal Republic of Germany
Mr G. Ozanne (European Chemical Industry Ecology and Toxicology Centre), Rhone Poulenc DSE/TOX, Neuilly-sur-Seine, France
Mr V. Quarg, Federal Ministry for Environment, Nature Conservation and Nuclear Safety, Bonn, Federal Republic of Germany
Dr U. Schlottmann, Chemical Safety, Federal Ministry for Environment, Nature Conservation and Nuclear Safety, Bonn, Federal Republic of Germany
Dr M. Sonneborn, Federal Health Office, Berlin (West)
Dr W. Stöber, Fraunhöfer Institute for Toxicology and Aerosol Research, Hanover, Federal Republic of Germany
Dr D. Streelman (International Group of National Associations of Agrochemical Manufacturers), Agricultural Chemicals Registration and Regulatory Affairs, Rohm & Haas, Philadelphia, Pennsylvania, USA

[a] Invited but unable to attend.

Secretariat

Mrs B. Bender, International Register for Potentially Toxic Chemicals, Geneva, Switzerland
Dr A. Gilman, Industrial Chemicals and Product Safety Section, Health Protection Branch, Department of National Health and Welfare, Tunney's Pasture, Ottawa, Ontario, Canada (Temporary Adviser)
Dr L. Ivanova-Chemishanska, Institute of Hygiene and Occupational Health, Medical Academy, Sofia, Bulgaria (Temporary Adviser)
Dr K.W. Jager, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland (Secretary)
Dr E. Johnson, Unit of Analytical Epidemiology, International Agency for Research on Cancer, Lyons, France
Dr G. Rosner, Fraunhöfer Institute for Toxicology and Aerosol Research, Hanover, Federal Republic of Germany (Temporary Adviser)
Dr G.J. Van Esch, Bilthoven, Netherlands (Temporary Adviser) (Rapporteur)

NOTE TO READERS OF THE CRITERIA DOCUMENTS

Every effort has been made to present information in the criteria documents as accurately as possible without unduly delaying their publication. In the interest of all users of the environmental health criteria documents, readers are kindly requested to communicate any errors that may have occurred to the Manager of the International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland, in order that they may be included in corrigenda, which will appear in subsequent volumes.

ENVIRONMENTAL HEALTH CRITERIA FOR THIOCARBAMATE PESTICIDES

A WHO Task Group on Environmental Health Criteria for Thiocarbamate Pesticides met at the Fraunhöfer Institute for Toxicology and Aerosol Research, Hanover, Federal Republic of Germany from 20 to 24 October, 1986. Professor W. Stöber opened

the meeting and welcomed the members on behalf of the host Institute, and Dr U. Schlottmann spoke on behalf of the Federal Government, who sponsored the meeting. Dr K.W. Jager addressed the meeting on behalf of the three co-sponsoring organizations of the IPCS (UNEP/ILO/WHO). The Task Group reviewed and revised the draft criteria document and summarized the health risks of exposure to thiocarbamate pesticides.

The drafts of this document were prepared by DR L. IVANOVA-CHEMISHANSKA, Institute of Hygiene and Occupational Health, Sofia, Bulgaria, and Dr G.J. VAN ESCH of Bilthoven, Netherlands.

The efforts of all who helped in the preparation and finalization of the document are gratefully acknowledged.

* * *

Partial financial support for the publication of this criteria document was kindly provided by the United States Department of Health and Human Services, through a contract from the National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, USA - a WHO Collaborating Centre for Environmental Health Effects. The United Kingdom Department of Health and Social Security generously supported the cost of printing.

INTRODUCTION

The thiocarbamates included in this review are those that are mainly used in agriculture and form part of the large group of synthetic organic pesticides that have been developed and produced on a broad scale in the last 30 - 40 years. Thiocarbamate derivatives with pesticidal properties were developed during and after World War II.

In this introductory document, an attempt has been made to summarize the available data on the thiocarbamates used as pesticides in order to indicate their impact on man, animals, plants, and the environment. The review is not intended to be complete, and more details about certain aspects can be found in the JMPR and IARC publications.

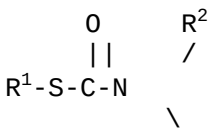
It should be noted that the design of a number of studies cited in this document, especially the earlier studies, is inadequate.

1. SUMMARY

1.1 General

Thiocarbamates are mainly used in agriculture as insecticides, herbicides, and fungicides. Additional uses are as biocides for industrial or other commercial applications, and in household products. Some are used for vector control in public health.

The general formula of thiocarbamates is:



R^3

where R^1 is an alkyl group attached to the sulfur giving *S*-thiocarbamates or to the oxygen giving O-thiocarbamates. R^2 and R^3 represent either two alkyl groups, or one alkyl and one cyclic or hexamethylene group.

A whole range of thiocarbamates is known, but it is out of the scope of this publication to give all the information on every compound. The intention is to cover the different aspects of thiocarbamates as a group, making use of publications and reports available on the compounds that are most used and best known. Data on carbamates and dithiocarbamates are not included, because these compounds have been covered in other Environmental Health Criteria documents.

1.2 Properties, Uses, and Analytical Methods

` Thiocarbamates are liquids or solids with low melting points. They are volatile compounds, and their water solubilities cover a wide range. Some thiocarbamates are stable in an acidic aqueous medium. The sequential oxidation of thiocarbamates to thiocarbamate sulfoxide and thiocarbamate sulfone decreases the hydrolytic stability.

Some physical and chemical data (chemical structure, relative molecular mass, vapour pressure, and water solubility) of individual substances are given in Annex I.

Analytical methods for the determination of thiocarbamates are outlined in the document and further details, together with physical and chemical data, can be found in the WHO Technical Report Series and the IRPTC data profiles.

1.3 Sources, Environmental Transport, and Distribution

Because of their insecticidal, herbicidal, and fungicidal properties, thiocarbamates have a wide range of uses and applications throughout the world and, thus, are produced in great quantities.

Thiocarbamates are volatile and will therefore evaporate from soil. Leaching and lateral movement in soil may take place because of their water solubility. Some photodegradation occurs.

Factors that influence the biodegradation of thiocarbamates in soil include volatility, soil type, soil moisture, adsorption, pH, temperature, and photodegradation, all of which make it unlikely that long-term contamination of the soil will occur.

Soil microorganisms contribute significantly to the disappearance of thiocarbamates from the soil. In micro-organisms and plants, thiocarbamates undergo hydrolysis followed by transthiolation and sulfoxidation to form carbon dioxide (CO_2) and compounds that enter the metabolic pool.

1.4 Environme.tal Levels and Human Exposure

Information on the environmental impact of thiocarbamates with respect to persistence and bioaccumulation in different species and food chains is limited. On the basis of the available information, it is likely that most of these compounds

are rapidly degraded.

Estimates of the exposure of the general population to thiocarbamates are not available.

1.5 Kinetics and Metabolism

As a general rule, thiocarbamates can be absorbed by the organism via the skin, mucous membranes, and the respiratory and gastrointestinal tracts. They are eliminated quite rapidly, mainly via expired air and urine.

Two major pathways exist for the metabolism of thiocarbamates in mammals. One is via sulfoxidation and conjugation with glutathione. The conjugation product is then cleaved to a cysteine derivative, which is metabolized to a mercapturic acid compound. The second route is oxidation of the sulfur to a sulfoxide, which is then oxidized to a sulfone, or hydroxylation to compounds that enter the carbon metabolic pool.

In plants, thiocarbamates are rapidly metabolized in typical oxidation reactions, e.g., thiol sulfur oxidation to the corresponding sulfoxides, reactive intermediates that are capable of reacting with sulfhydryl groups (as in glutathione, cysteine) to form conjugates. On hydrolysis, mercaptans, carbon dioxide, and alkylamines may be formed.

While thiocarbamates and their metabolic products can be found in certain organs, such as liver and kidneys, accumulation does not take place because of their rapid metabolism.

1.6 Effects on Organisms in the Environment

Soil microorganisms are capable of metabolizing thiocarbamates. From the limited information available, it seems that the thiocarbamates and their break-down products can affect enzyme activities, respiration, and nitrification, at dose levels of the order of 10 mg/kg dry soil or more.

The acute and long-term toxicities of thiocarbamates must be considered for each compound, some being more toxic than others. The acute toxicity of thiocarbamates for fish is of the order of 5 - 25 mg/litre of water.

Thiocarbamates present little or no risk for birds and honey bees.

1.7 Effects on Experimental Animals and In Vitro Test Systems

The acute oral and dermal toxicities of thiocarbamates are generally low. Only limited information concerning inhalation toxicity is available.

Some thiocarbamates, e.g., molinate, have an effect on sperm morphology and, consequently, on reproduction. However, no teratogenic effects have been observed. The results of mutagenicity studies showed that thiocarbamates containing dichloroallyl groups were highly mutagenic. Negative results were obtained with other thiocarbamates.

Adequate studies on the carcinogenicity of thiocarbamates are not available.

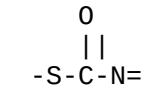
1.8 Effects on Man

Data concerning the effects of thiocarbamates on man are scarce. However, cases of irritation and sensitization have been observed among agricultural workers.

2. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, ANALYTICAL METHODS

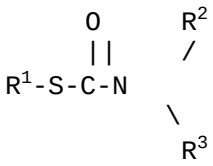
2.1 Identity

Thiocarbamates are the semi-sulfur analogues of carbamates characterized by the presence of:



They exist as salts or esters of carbamic acids. In the esters, the alkyl substituent is either attached to the oxygen (*O*-thiocarbamates) or to the sulfur (*S*- thiocarbamates).

The thiocarbamate herbicides belong to the group of *S* -thiocarbamate esters and have the general formula of:



where R^1 is an alkyl group attached to the sulfur, and R^2 and R^3 represent either 2 alkyl groups, or one alkyl and one cyclic or hexamethylene group.

The type of pesticidal activity and the chemical structures of the principle thiocarbamates are listed in Table 1. CAS numbers, chemical names, common names, molecular formulae, relative molecular mass, and selected chemical and physical properties are summarized in Annex I.

For further information on physical and chemical properties, other sources, such as the JMPR evaluations (Annex II), should be consulted.

2.2 Physical and Chemical Properties

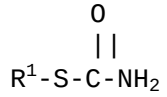
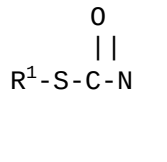
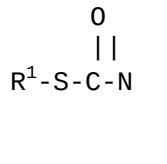
At room temperature, thiocarbamates are liquids or solids with a low melting point. As they are usually *N,N* -dialkyl substituted and have a sulfur atom in place of oxygen, they are less polar than methylcarbamates and are miscible with most organic solvents.

All thiocarbamate herbicides are volatile. Pebulate has the highest vapour pressure, followed by *S* -ethyldipropylthiocarbamate (EPTC), cycloate, molinate, butylate, diallate, and triallate (IARC, 1976; Worthing & Walker, 1983).

Thiocarbamates such as EPTC, pebulate, or diallate are very stable at pH 2 or 10. Their sulfoxide and sulfone derivatives are also stable at pH 2, but much less so at pH 10 (Casida et al., 1974).

Table 1. Chemical structures and type of pesticidal activity of the

principal thiocarbamates

Type of activity	Chemical structure	Common or other name
Insecticide		cartap
Herbicide		butylate, cycloate, diallate, EPTC, ethiolate, molinate, pebulate, thioben-carb, triallate
Fungicide		prothiocarb

The presence of a double bond in the chloroallyl group of diallate and triallate might increase, compared with that of other thiocarbamates, the possible range of reactions, e.g., the introduction of hydroxyl groups on the two-carbon atoms or methylation and methoxylation (Schuphan & Ebing, 1977).

2.3 Analytical Methods

Analysis for pesticide residues consists of sampling the environmental material or matrix, extracting the pesticide residue, removing interfering substances from the extract, and identifying and quantifying the pesticide contaminant. The manner in which the matrix material is sampled, stored, and handled can affect the results. Care should be taken to ensure that samples are truly representative, and that the pesticide residues to be measured are not degraded or the sample further contaminated during handling and storage. Many methods of detection are available, and the one chosen depends on the physical and chemical properties of the pesticide as well as on the equipment available.

A detailed review of all aspects of such analytical procedures is beyond the scope of this document. However, a brief summary of some of the procedures is given below.

A variety of techniques has been used for the determination of thiocarbamate herbicide residues. Hughes & Freed (1961) used gas-liquid chromatography (GLC) for the measurement of minute amounts of EPTC in crops. This method is also being used for the determination of other thiocarbamates. Another method in use is a colorimetric procedure based on the determination of the amine after hydrolysis of the thiocarbamate with concentrated sulfuric acid (Batchelder & Patchett, 1960).

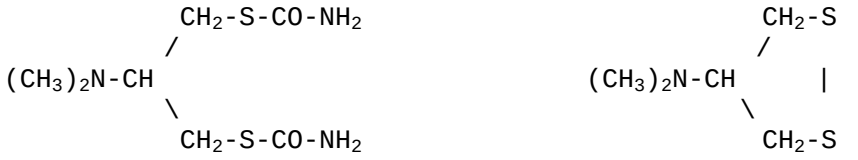
Other methods are available for the determination of EPTC: a

specific method based on gas chromatography (GC) and a method based on Kjeldahl nitrogen determination. The recommended method is GC when EPTC is determined with reference to a sample of known composition (Patchett et al., 1964). EPTC residues have also been determined by radiotracer techniques (Fang & Theisen, 1959), by GC (Hughes & Freed, 1961), and by colorimetry (Batchelder & Patchett, 1960). The GC method has mainly been used in the analysis of soil samples, but the method can also be used in the analysis of some crops. For routine crop sample analyses, the colorimetric method is preferred, because of its proved reliability and the low background values for a wide range of sample types. If the equipment is available, a GC method involving a microcoulometric detector for sulfur can be used.

3. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

3.1 Natural Occurrence

Cartap is a commercial insecticide developed from a zoogenic substance, nereistoxin, which was found by Nitta in the body of the marine segmented worm *Lumbrineris (Lumbriconereis) heterepoda,* and isolated in 1934 (Okaichi & Hashimoto, 1962; Sakai, 1969). The chemical structure of these two compounds are as follows:



cartap

nereistoxin

3.2 Man-Made Sources

Thiocarbamates are widely used throughout the world and are produced in great quantities, mainly as herbicides and fungicides.

4. ENVIRONMENTAL TRANSPORT, DISTRIBUTION, AND TRANSFORMATION

Like all pesticides, thiocarbamates can reach the soil via many routes, ranging from direct application to drift from foliage treatment. Generally, these compounds are not persistent and undergo various types of degradation.

4.1 Transport and Distribution Between Media

4.1.1 Soil

4.1.1.1 Persistence and volatilization

Several factors are known to determine the persistence of herbicides in soil. These include uptake and degradation by soil microorganisms, pH, temperature, loss through physical processes (volatilization, leaching), and chemical changes (photodecomposition, chemical reaction). Volatilization is an important mechanism in the loss of thiocarbamate herbicides from soil (Anderson & Domsch, 1980). The loss of EPTC is greater from moist soils than from dry. Loss through evaporation correlates significantly with the amount of organic matter present in the soil, the clay content, and leaching. Consequently, these factors affect the herbicidal activity (Gray

& Weierich, 1968; Fang, 1975).

The persistence of thiocarbamates in soil, expressed as the approximate half-life in moist soil, is given in Table 2 (Gray, 1971).

Fang (1975) reported that, during the first 15 min following spraying on the soil surface, 20% of the applied EPTC disappeared from dry soil, 27% from moist soil, and 44% from wet soil. The losses were 23%, 49%, and 69%, respectively, after 1 day and 44%, 68%, and 90%, respectively, after 6 days. Incorporation to a depth of 5 - 7.5 cm prevented severe loss of EPTC from soil.

Cycloate was the least volatile of 5 herbicides tested, followed by molinate, pebulate, vernolate, and EPTC in order of increasing volatility. Increasing the temperature from 1.7 °C to 37.7 °C caused an increase in the loss of vernolate from moist and wet soils. The effect was more pronounced as the soil moisture content increased (Fang, 1975).

Table 2. Persistence of thiocarbamate herbicides in moist soil under simulated summer growing conditions

Herbicide	Half-life in moist loam soil (21 - 32 °C) (weeks)[a]	Half-life in Regina heavy clay (25 °C) (weeks)[a]
EPTC	1	4 - 5
Vernolate	1 - 2	2 - 3
Pebulate	2	2 - 3
Butylate	3	-
Molinate	3	-
Cycloate	3 - 4	-
Diallate	> 4	5 - 6
Triallate	-	10 - 12

[a] From: Stauffer Chemicals SA (1978).

4.1.1.2 Leaching

Quantitative leaching tests conducted in soils contained in glass columns showed that thiocarbamate herbicides leach downwards in direct relation to their water solubilities. Molinate leached to the greatest depth followed by EPTC, vernolate, pebulate, cycloate, and butylate in decreasing order. Molinate and EPTC leached downwards to a depth of 22.5 - 37.5 cm in sandy soil when incorporated in the upper 7.5 cm of soil at 11.2 kg/ha and leached with 20 cm of water, but the other compounds stayed near the top 7.5 - 15 cm of soil when leached with 20 cm of water. Leaching depth also decreased as the organic matter content of the soil increased. In peat soil (containing 35% organic matter), none of the thiocarbamate herbicides leached out of the treated zone. The leaching data indicated that, in most soils, the thiocarbamates stayed in the upper 7.5 - 15 cm of soil. Under most conditions, the compounds would disappear through microbial action before they could reach

the deeper layers of soil by leaching (Gray & Weierich, 1968; Gray, 1971).

4.1.1.3 Lateral movement

The lateral movement of thiocarbamates was studied by placing the compounds on filter paper discs, placed in the soil together with weed seeds. Using ryegrass or oats as test species, EPTC, vernolate, and pebulate moved laterally to form a circle of weed control about 10 - 12.5 cm in diameter. Molinate, cycloate, and butylate gave smaller zones of weed control. The thiocarbamates also moved laterally more than most other commercial herbicides as shown by their effect on grass weeds. However, the size of the zone depended on both the activity of the herbicide and the species tested. When a disc containing EPTC was placed 7.5 cm deep in the soil, no zone of weed control was detected. The data indicated that the thiocarbamates moved outwards spherically when applied to a concentrated spot in the soil. Because of this property of lateral diffusion, thiocarbamates, applied by injection, have an effective herbicide action (Gray, 1971).

4.2 Biotransformation

4.2.1 Microbial degradation

Soil microorganisms contribute significantly to the disappearance of thiocarbamate herbicides from the soil (Kaufman, 1967). However, the mechanism involved has not been established, though it has been postulated that these compounds could undergo hydrolysis at the ester linkage, with the formation of a mercaptan and a secondary amine. The mercaptan could then be converted into an alcohol by transthiolation, and further oxidized to an acid, prior to entering the metabolic pool. This mechanism has been proposed for the degradation of EPTC and pebulate in plants and animals (Fang et al., 1964; Kaufman, 1967) (Fig. 1).

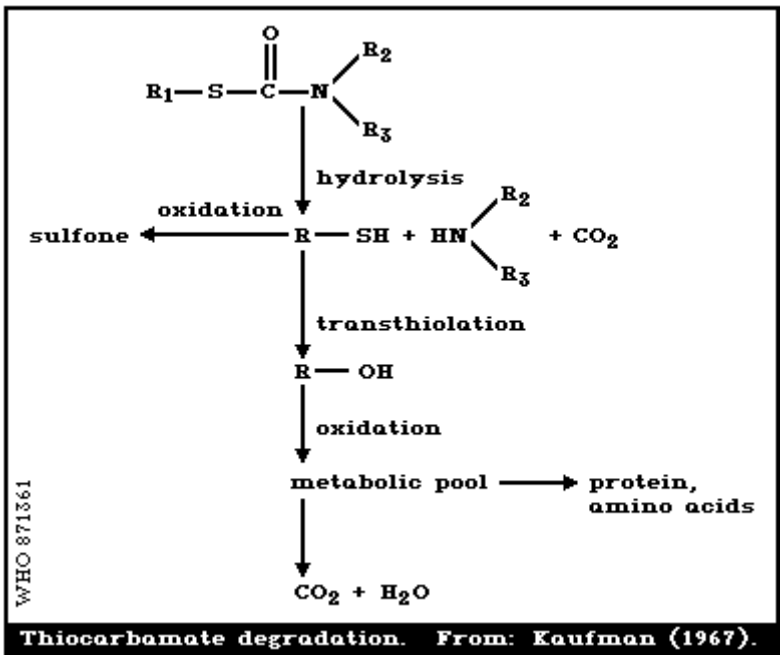
Such a mechanism, i.e., hydrolysis followed by transthiolation, could explain results observed in persistence and degradation studies on diallate, carried out by Kaufman (1967). In two separate studies, a bioassay analysis of treated soil indicated a partial loss of phytotoxicity, followed by a temporary increase in, and a subsequent complete loss of, phytotoxicity. Hydrolysis of the diallate ester linkage, followed by transthiolation of the allylic group, would result in the formation of 2,3-dichloroallyl alcohol. However, the results of unpublished studies indicate a more complex pathway involving oxidative dealkylation of the amine (Stauffer Chemicals SA, 1981).

Persistence tests in distilled water and tap water in clear glass containers showed very slow degradation of thiocarbamates by hydrolysis over a period of months. However, in pans of water containing soil, microbes, and growing plants, molinate and several other thiocarbamates disappeared rapidly within several weeks (Gray, 1971).

4.2.2 Photodegradation

Little has been reported on the photodegradation of thiocarbamates. Casida et al. (1975) exposed EPTC, butylate, cycloate, molinate, vernolate, and pebulate to sunlight on thin-

layer-chromatographic (TLC) plates. After 16 h, none of the original compounds could be recovered, but trace amounts of the corresponding sulfoxides of EPTC and pebulate were found.



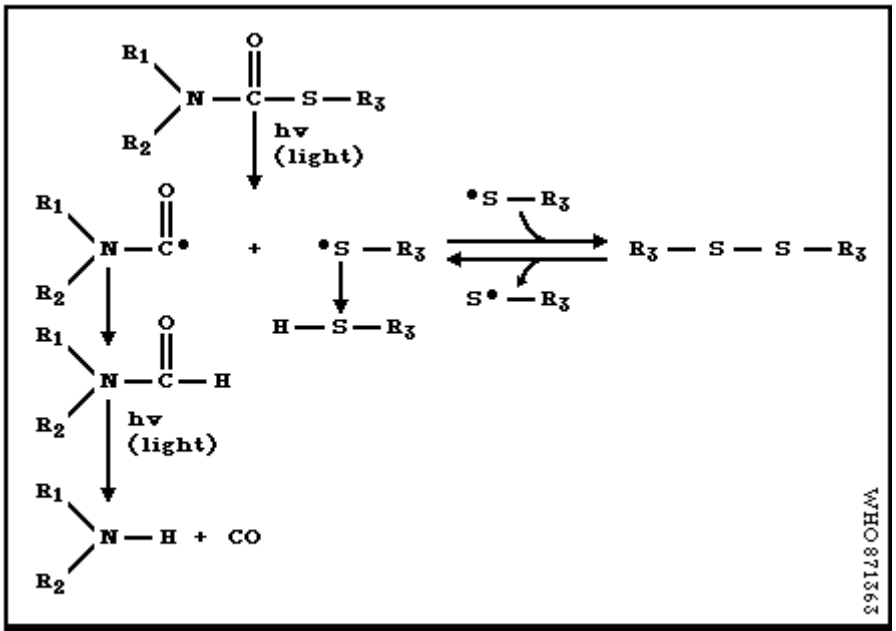
Thiocarbamate degradation. From: Kaufman (1967).

Minimum effects are to be expected on compounds in the solid state, because of poor light penetration (DeMarco & Hayes, 1979).

DeMarco & Hayes (1979) studied the photodegradation of EPTC, pebulate, and cycloate. The products identified for each herbicide were the corresponding formamide, dialkylamine, mercaptan, and disulfide, indicating a similar mode of degradation. Fig. 2 shows a possible photodegradation pathway suggested by DeMarco & Hayes (1979).

Absorption of light causes the breakage of the carbonyl C-S bond producing two radicals. These can combine with protons from the solvent giving the formamide and mercaptan. The formamide is further degraded by ultraviolet radiation (UVR) to the dialkylamine by the elimination of carbon monoxide. Collision of two mercaptan radicals would lead to the formation of a disulfide. Because the sulfur-sulfur bond is quite susceptible

to photolysis, continued exposure to UVR would result in a return to separate mercaptan radicals, and the possible reformation of the disulfide. Changes in the availability of protons could influence the concentrations of mercaptan and disulfide formed (DeMarco & Hayes, 1979).



A possible photodegradation pathway.
From: DeMarco & Hayes (1979).

5. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

Data on this subject were not available to the Task Group with the exception of some occupational exposure data mentioned in section 9.

6. KINETICS AND METABOLISM

6.1 Absorption, Distribution, and Excretion

Thiocarbamates in the form of an aerosol enter the organism mainly via the respiratory tract. Absorption through the skin and mucous membranes also occurs during occupational exposure, and through the digestive tract.

In metabolic studies on rats, administered ^{14}C-labelled pebulate orally at 0.16 - 1.95 mg/animal (average weight 235 g), the radioactivity was rapidly eliminated. An average of 51% was excreted in the first 24 h and 80% after 3 days. Approximately 55% of the radioactivity was found in expired air as carbon dioxide (CO_2), while 23% was found in the urine and only 5% in the faeces. Small amounts were detected in organs and tissues, the highest levels being found in the liver, lungs, and kidneys (Fang et al., 1964).

In a comparable study on rats, using labelled EPTC (dose levels of 0.6 - 103 mg/animal), increasing the dose led to a relative decrease in $^{14}CO_2$ output with a corresponding increase in the urinary excretion of radioactivity. Generally, $^{14}CO_2$ elimination was complete within 15 h at lower dose levels, but took approximately 35 h at higher doses (Ong & Fang, 1970).

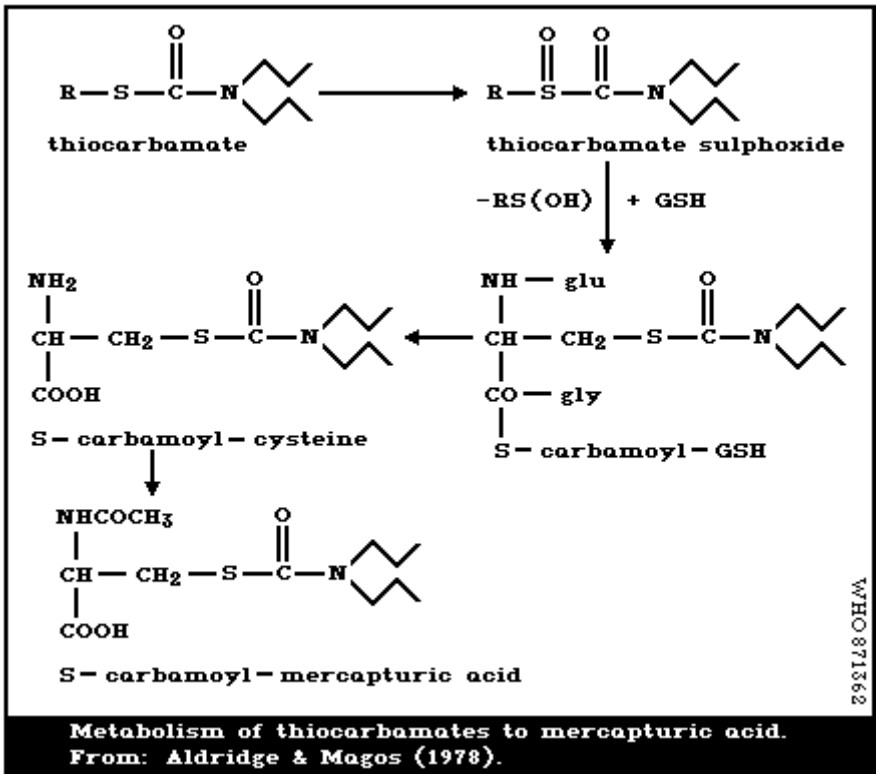
Approximately 97% of an oral dose administered to rats at 72 mg molinate/kg body weight was excreted within 48 h. The major routes of elimination were the urine (88%) and faeces (11%); less than 1% was excreted as carbon dioxide (CO_2). No differences were found between males and females. With the exception of blood, tissue residues decreased over a 7-day period from an average of 13.8% to 3.7% (DeBaun et al., 1978a).

6.2 Metabolic Transformation

6.2.1 Mammals

One of the two major metabolic pathways for thiocarbamates in mammals is sulfoxidation, followed by conjugation with glutathione (GSH) by GSH *S* -transferase. The GSH conjugate is then cleaved to the cysteine derivative, which is subsequently acetylated and excreted as *S* -carbamoyl-mercapturic acid (Hubbell & Casida, 1977; Chen & Casida, 1978). This metabolic pathway is shown in Fig. 3.

Sulfoxidation of thiocarbamates such as EPTC, molinate, pebulate, and vernolate undoubtedly represents a detoxification mechanism in mammals, the sulfoxides generally being less toxic than the parent compounds. The lower toxicity of the sulfoxides is probably attributable to the high rate of cleavage and elimination as glutathione conjugates (Casida et al., 1975).



Metabolism of thiocarbamates to mercapturic acid. From: Aldridge & Magos (1978).

The other mechanism is oxidation of the thiocarbamate molecule. Metabolism of EPTC by a mouse liver microsome NADPH system involves oxidative attack at the following sites in decreasing order of importance: sulfur, alpha-carbon of the ethyl group, alpha-carbon of the propyl group, ß-carbon of the propyl group, *y*-carbon of the propyl group, and ß-carbon of the ethyl group.

The metabolites hydroxylated at the carbons alpha to the nitrogen and sulfur decompose at physiological pH, yielding *S* -ethyl *N* -propylthiocarbamate in the case of the former, and carbonylsulfide and acetaldehyde from the latter, compound. The sulfoxide is further oxidized to the sulfone. The carbonyl-sulfide undergoes further metabolism to carbon dioxide (CO_2). These findings indicate the major involvement of the sulfoxide intermediate and also suggest that hydroxylation is an important mechanism for thiocarbamate cleavage (De Matteis & Seawright, 1973; Dalvi et al., 1974, 1975; Chen & Casida, 1978).

In mice, urea was identified as one of the many urinary metabolites. Since urea, amino acids, and small amounts of propanethiol and propanol were found in the urine, the thiolcarbamate molecule is probably hydrolysed at the ester linkage to form n-propyl mercaptan, which is then converted to propanol by a transthiolation (Fig. 1). The propanol may be oxidized to a C-3 acid and/or further broken down to a C-2 unit before entering the metabolic pool. Incorporation into tissue constituents, such as protein and amino acids, may occur (Fang et al., 1964; Ong & Fang, 1970).

The available metabolic pathways in rats differ for thiocarbamates with n-alkyl substituents as opposed to those with branched alkyl or cyclic substituents on the nitrogen. Thus, the yield of mercapturic acids and the number of metabolites are greater with the former than with the latter (Hubbell & Casida, 1977). Sulfoxides can be detected as transient metabolites in the liver of mice injected with EPTC, molinate, or pebulate, but not with butylate or cycloate (Casida et al., 1975). However, as cycloate and butylate are also oxidized to sulfoxide, the appropriate mercapturic acid $%rivatives can be detected in the urine (Hubbell & Casida, 1977).

Metabolic studies of [ring-^{14}C] molinate in the rat were carried out by DeBaun et al. (1978b). Unchanged molinate accounts for only 0.1% of the urinary ^{14}C after an oral dose of 72 mg labelled molinate/kg body weight. The major metabolic pathway involves sulfoxidation and conjugation with glutathione, giving rise to a mercapturic acid derivative that accounted for 35% of the urinary ^{14}C. Ring hydroxylation to give 3- and 4-hydroxymolinate conjugated as O-glucuronides represented approximately 26%. Hydroxylation in the 2 position of the ring, and subsequent ring cleavage, occurred only to a minor extent. Hexamethyleneimine (14.6%) and 3- and 4-hydroxyhexamethylene-imine (10.3%) were the major metabolites, presumably formed by hydrolysis of sulfoxidized molinate and its hydroxy derivatives.

6.2.2 Plants

The results of investigations with carbonyl ^{14}C-labelled materials showed that thiocarbamate herbicides are initially metabolized in plants by the typical oxidation reactions observed for other carbamate esters (Hubbell & Casida, 1977; Carringer et al., 1978; Chen & Casida, 1978), i.e., thiol sulfur oxidation to the corresponding sulfoxide. The sulfoxide is a reactive intermediate and is capable of reacting with sulfhydryl groups (e.g., in glutathione (GSH) or cysteine), to give the carbamylated derivative (Horvath & Pulay, 1980). These two conjugates were among the principal metabolites isolated from the plants. The metabolism of thiocarbamate herbicides in plants to the respective sulfoxides is of considerable theoretical importance, since the sulfoxides are believed to be responsible for the herbicidal activity of the thiocarbamates (Casida et al., 1974). Furthermore, the reaction between GSH and the thiocarbamate sulfoxide appears to result in detoxification in plants. Antidotes such as *N,N* -diallyl-2,2-dichloroacetamide, which protect plants from injury by thiocarbamate herbicides, also increase the levels of GSH and GSH *S* -transferase in the plant (Lay & Casida, 1976).

Current knowledge of the metabolism of thiocarbamates and

their mode of action is rather limited. It can be summarized as follows. Thiocarbamates are readily absorbed by plants, but do not remain as residues very long. It is generally believed that, upon hydrolysis, thiocarbamates yield mercaptan, carbon dioxide (CO_2), and dialkylamine: a further cleavage of the sulfur atom from the mercaptan is possible. Thus, the sulfur atom can be subsequently incorporated into sulfur-containing amino acids. The other part of the molecule will become carbon dioxide (CO_2) or will be incorporated into natural plant constituents.

7. EFFECTS ON ORGANISMS IN THE ENVIRONMENT

7.1 Microorganisms

Endo et al. (1982) studied the influence of cartap on the enzyme activities, respiration, and nitrification of the soil. Soil was treated with cartap-HCl to give a final concentration of 10, 100, or 1000 mg/kg (dry soil weight). The findings suggested that nitrifying organisms were affected by 100 and 1000 mg cartap, but with 10 mg, no effects on enzyme activities, respiration, or nitrification were found in soil kept under upland or flooded conditions.

7.2 Aquatic Organisms

Data concerning the toxicity of thiocarbamates for aquatic organisms are rather scarce. Acute toxicity data for fish are given in Table 3, while those for a number of aquatic invertebrates are summarized in Table 4.

7.3 Terrestrial Organisms

7.3.1 Birds

The results of a number of toxicity studies on birds, lasting from 5 days to 2 months, are summarized in Table 5. The results are expressed as LD_{50} in the diet or as no-observed-adverse-effect levels. In the species tested, the toxicity of thiocarbamates was low.

7.3.2 Honey bees

The toxicity (expressed as the LD_{50}) of EPTC, molinate, cycloate, butylate, pebulate, and vernolate for the honey bee is > 11 µg/bee. From these results, it can be concluded that these compounds are relatively non-toxic for the honey bee (Stauffer Chemicals SA, 1978).

Table 3. Acute toxicity of thiocarbamates for fish

Organism	Compound	Weight of fish (g)	Temperature (°C)	96-h LC_{50} (mg/litre)	Comments
Rainbow trout (*Salmo gairdneri*)	vernolate	-	-	9.6	
Bluegill (*Lepomis macrochirus*)	vernolate	-	-	8.4	
Mosquitofish (*Gambusia affinis*)	vernolate	-	-	14.5	Vernam
Rainbow trout	vernolate	1.3	12	4.3[b]	

(*Salmo gairdneri*)				(3.9 - 4.7)	

Table 3. (contd.)

Organism	Compound	Weight of fish (g)	Temperature (°C)	96-h LC_{50} (mg/litre)	Comments
Bluegill (*Lepomis macrochirus*)	vernolate	1.2	24	2.5[b] (1.7 - 3.7)	
Rainbow trout (*Salmo gairdneri*)	EPTC	-	-	19	
Bluegill (*Lepomis macrochirus*)	EPTC	-	-	27	
Cutthroat trout	EPTC	1.0	10	17[b] (15 - 19)	
Lake trout	EPTC	0.9	10	16.2[b] (14.8 - 17. 7)	
Rainbow trout (*Salmo gairdneri*)	molinate	-	-	1.3	
Bluegill (*Lepomis macrochirus*)	molinate	-	-	29	
Channel catfish (*Ictalurus punctatus*)	molinate	-	-	> 3	no morta
Carp (*Cyprinus carpio*)	molinate	-	-	> 2	no mort
Bluegill (*Lepomis macrochirus*)	molinate	-	-	> 1	no mort
Rainbow trout (*Salmo gairdneri*)	cycloate	-	-	4.5	
Bluegill (*Lepomis macrochirus*)	cycloate	-	-	5.6	
Mosquitofish (*Gambusia affinis*)	cycloate	-	-	10	Ro-Neet
Rainbow trout (*Salmo gairdneri*)	butylate	-	-	4.2	
Bluegill (*Lepomis macrochirus*)	butylate	-	-	6.9	
Mosquitofish (*Gambusia affinis*)	butylate	-	-	8.5	Sutan 6

Table 3 (contd).

Organism	Compound	Weight of fish (g)	Temperature (°C)	96-h LC_{50} (mg/litre)	Comments

Rainbow trout (*Salmo gairdneri*)	pebulate	-	-	7.4	
Bluegill (*Lepomis macrochirus*)	pebulate	-	-	7.4	
Mosquitofish (*Gambusia affinis*)	pebulate	-	-	10	Tillam
Rainbow trout (*Salmo gairdneri*)	diallate	-	-	7.9	
Bluegill (*Lepomis macrochirus*)	diallate	-	-	5.9	
Rainbow trout (*Salmo gairdneri*)	triallate	-	-	1.2	
Bluegill (*Lepomis macrochirus*)	triallate	-	-	1.3	

[a] Vernam 6E: herbicide formulation (vernolate).
[b] From: Johnson & Finley (1980). Other data from: Stauffer Chemicals SA (1978) and Worthing & Walker (1983).
[c] After 11 days.
[d] After 21 days.
[e] After 35 days.
[f] Ro-Neet 6E: herbicide formulation (cycloate).
[g] Sutan 6E: herbicide formulation (butylate).
[h] Tillam 6E: herbicide formulation (pebulate).

Table 4. Acute toxicity of thiocarbamates for aquatic invertebrates[a]

Organism	Compound	Stage	Temperature (°C)	96-h LC_{50} (mg/litre)
Asellus communis (isopod)	EPTC	mature	15	23[b] (15 - 36)
Gammarus fasciatus (shrimp)	EPTC	mature	15	66[b]
Cypridopsis	vernolate	mature	21	0.25[b,c] (0.15 - 0.42)
Asellus communis (isopod)	vernolate	mature	15	0.23[c] (0.16 - 0.33)
Gammarus fasciatus (shrimp)	vernolate	mature	15	14 (9.6 - 20)
Palaemonetes sp. (shrimp)	vernolate	juvenile	2.1	0.53[c] (0.14 - 2.0)

[a] From: Johnson & Finley (1980).
[b] 48-h EC_{50}.
[c] Tested in hard water (272 mg $CaCO_3$/litre).

Table 5. Toxicity of thiocarbamates for birds[a]

Product	Species	Protocol	Dose (mg/kg diet) (mg/kg diet)	Resul
EPTC	bobwhite quail	7-day dietary administration of technical EPTC	1000 - 32 000	LD_{50} no-o leve
Molinate	mallard duck	5-day dietary administration	1000 - 32 000	LD_{50}
Cycloate	bobwhite quail	7-day dietary administration of Ro-Neet 6E[b]	1800 - 56 000	LD_{50}
Butylate	bobwhite quail	7-day dietary administration	1800 - 56 000	LD_{50}
Pebulate	bobwhite quail	7-day dietary administration of technical pebulate	1000 - 18 000	LD_{50}
Pebulate	bobwhite quail	7-day dietary administration of Tillam 6E[b]	1000 - 24 000	LD_{50}
Vernolate	bobwhite quail	7-day dietary administration of technical vernolate	1800 - 24 000	LD_{50}

[a] From: Stauffer Chemicals SA (1978).
[b] Herbicide formulation.

8. EFFECTS ON EXPERIMENTAL ANIMALS AND IN VITRO TEST SYSTEMS

Yin-Tak Woo (1983) has reviewed the structure-activity relationships for the different types of thiocarbamates.

8.1 Single Exposures

Data concerning the acute toxicity of thiocarbamates are summarized in Table 6. Very few results on acute inhalatory toxicity are available.

The acute oral and dermal toxicities of thiocarbamates are relatively low. The most toxic representatives of the thiocarbamates are molinate and diallate. The toxicity of EPTC for various animal species varies significantly. The cat seems to be the most sensitive animal species. It should be noted that this may also be true for other thiocarbamates, but data on the cat are lacking.

When animals are administered high oral dose levels of thiocarbamates, signs such as anorexia, squinting, hypersalivation, lachrymation, piloerection, laboured breathing, ataxia, hypothermia, incoordination, depression, pareses, and muscular fibrillation may be observed, and convulsions followed by death may occur (Akulov et al., 1972; IARC, 1976).

Lethal doses of diallate given to rats and guinea-pigs caused restlessness within the first 2 h, followed by lack of coordination. Animals died from respiratory paralysis. Autopsy revealed vascular dilatation in the cerebrum, cerebellum, and abdominal viscera, meningeal haemorrhages, and enlarged adrenal glands (Doloshitsky, 1969).

In rabbits, a single oral dose of triallate (450 - 500 mg/kg body weight) decreased acetylcholinesterase (AChE) activity in some parts of the brain and in red blood cells. The maximum levels of inhibition were less than 20% in the brain and 42% in the red blood cells (Zhavoronkov et al., 1974).

8.2 Short- and Long-Term Exposure

8.2.1 Experimental animals

Doloshitsky (1969) carried out studies on albino rats receiving dose levels of 0.5 - 200 mg diallate/kg body weight for periods of up to 8 months. Dose levels of 20 mg/kg or more resulted in a clear increase in mortality. At 50 mg/kg body weight, 73% of the animals died within 8 months.

Table 6. Acute toxicity of thiocarbamates for experimental animals

Compound	Animal	Dose (mg/kg body weight) Oral	Dermal	Reference
Butylate	rat (male)	3500	-	Worthing & Walker (1983)
	rat (female)	3970	-	Worthing & Walker (1983)
	rabbit		> 2000	Hubbell & Casida (1977)
Diallate	rat	395		Worthing & Walker (1983)
	rat	1000		Doloshitsky (1969)
	rabbit		2000 - 2500	Worthing & Walker (1983)
	dog	510		Worthing & Walker (1983)
Triallate	rat	1471		Rappoport & Pestova (1973)
	rat	1675 - 2165		Worthing & Walker (1983)
	rabbit		8200	Worthing & Walker (1983)
Pebulate	rat	1120		Worthing & Walker (1983)
	rabbit		4640	Worthing & Walker (1983)
Vernolate	rat	1780		Stauffer Chemicals SA (1978)
Molinate	rat (male)	369		Worthing & Walker (1983)
	rat (female)	450		Worthing & Walker (1983)
	rabbit		> 4640	Worthing & Walker (1983)
Cycloate	mouse	2285		Rebrin & Alexandrova (1971)
	rat	2710		Worthing & Walker (1983)

	rabbit		> 4640	Worthing & Walker (1983)
EPTC	rat	1630	3200	Hubbell & Casida (1977)

Worthing & Walker (1983) summarized short-term toxicity tests of a number of thiocarbamates. Rats were administered 400 mg diallate/kg diet for 90 days. Weight loss, irritability, hyperactivity, and mild cardiac changes, but no deaths, occurred at 1200 mg/kg diet, the highest dose level tested. In beagle dogs, adverse effects were observed at 600 mg/kg body weight per day, but not at 125 mg/kg body weight per day. In a 2-year feeding trial, no adverse effects were observed in rats receiving 200 mg triallate/kg diet or in dogs receiving 15 mg/kg, daily. Cycloate did not induce toxicity symptoms in dogs administered 240 mg/kg daily for 90 days, and butylate was well tolerated by rats and dogs at a dose level of 40 mg/kg daily for 90 days.

Rats fed 147 mg triallate/kg body weight in the diet (one-tenth of the LD_{50}), for 1, 2, or 3 months, showed congestion, perivascular oedema, chromatolysis, and proliferation of adventitial cells in the brain. Local fatty degeneration and dystrophy in the liver and kidneys were also observed (Rappoport & Pestova, 1973).

8.2.2 Domestic animals

Sheep administered daily oral doses of diallate at 10 mg/kg body weight for 19 weeks, 25 mg/kg for 20 - 24 weeks, and 50 mg/kg for 25 and 26 weeks became ill only when the dose was increased to 50 mg/kg body weight. Cholinesterase activity remained normal. It seems that 10 mg diallate/kg body weight did not cause any toxic effects (Palmer et al., 1972).

Single oral doses of 300 mg triallate/kg and 720 mg triallate/kg body weight to sheep and pigs, respectively, decreased RNA and DNA levels in the leukocytes and increased the concentration of free nucleotides (Verkhovskiy et al., 1973).

8.3 Skin and Eye Irritation; Sensitization

Worthing & Walker (1983) summarized the skin and eye irritation potential of a number of thiocarbamates. Butylate is a mild irritant to the skin and non-irritating to eyes; cycloate is non-irritating to eyes; diallate is a moderate irritant to the skin and eyes; molinate is non-irritating to skin and moderately irritating to eyes; and triallate is moderately irritating to skin and slightly to eyes. These compounds were all tested on the skin and eyes of rabbits.

8.4 Reproduction, Embryotoxicity, and Teratogenicity

8.4.1 Reproduction

Daily administration of 3.6 mg molinate/kg body weight for 2 months to 7- to 8-week-old rats caused gonadal and spermatozoal changes. When intact females were mated with treated males, resorption, impaired fetal development, and increased lethal effects in offspring were seen. Unlike molinate, pebulate administered to male rats at 11.25 mg/kg body weight, daily, for

2 months, did not induce any gonadotoxic effects (Voytenko &

Medved, 1973).

8.4.2 Teratogenicity

Pregnant CF1 mice, Sprague Dawley rats, and golden hamsters were given cartap hydrochloride orally on days 8 - 13 (mice, hamsters) or days 9 - 15 (rats) of gestation at dose levels of 50 - 100 mg/kg body weight for mice and rats and 2 - 100 mg/kg body weight for hamsters. Mice receiving 50 mg and 100 mg, rats receiving 50 mg, and hamsters receiving 2, 10, and 50 mg/kg tolerated administration of cartap, except that maternal death occurred in rats at 50 mg/kg body weight. No significant increases in fetal abnormalities were found. Treatment of rats and hamsters with 100 mg/kg body weight resulted in maternal death and retarded growth. However, the rates of embryonal resorption and gross malformations were comparable with those in the controls. Cartap did not induce any fetotoxic or teratogenic effects in this study (Mizutani et al., 1971).

8.5 Mutagenicity and Related End-Points

Diallate and triallate were mutagenic in the Ames test, with *Salmonella typhimurium* strains TA 100 and TA 1535 (base-pair substitution mutants), but only in the presence of liver microsomal preparation, indicating the need for chemical activation. No effects were seen with strains TA 98 and TA 1538 (frameshift mutants) (Sikka & Florczyk, 1978). The mutagenic activity of these compounds seems to be related to the presence of the chloroallyl group in the molecule, which is, in fact, very similar to the known carcinogen and mutagen vinyl chloride.

Cartap was tested *in vivo* for cytogenic effects on the bone marrow cells of CF1 mice and Wistar rats. The compound was administered at levels of 10, 100, or 150 mg/kg body weight to adult male rats, in either a single dose or daily for 5 successive days. Cartap was also administered to 3-week-old rats at an oral dose of 200 mg/kg body weight or intraperitoneally (ip) at a dose of 30 mg/kg body weight. No chromosomal aberrations were found. No mutagenic effects were seen in male mice using the dominant lethal test after a single, or 5 successive, oral doses of 100 mg/kg body weight (Kikuchi et al., 1976).

Murnik (1976) showed that butylate and vernolate significantly increased the level of apparent dominant lethals in *Drosophila melanogaster*, probably because of toxicity, since genetic assays did not clearly indicate an induction of chromosomal breakage or loss. An increased frequency of sex-linked recessive lethals was found.

8.6 Carcinogenicity

Increased tumour incidence was observed in mice given diallate orally at 125 mg/kg body weight per day, from the 7th day of life, for 4 weeks, and 560 mg/kg diet for a further 73 weeks (Innes et al., 1969).

9. EFFECTS ON MAN

9.1 Occupational Exposure

Data concerning the effects of thiocarbamates on man are scarce. When soil was treated with Eptam by aircraft and tractor, the air levels of the herbicide in the working zone

ranged from 8.1 to 210 mg/m^3. Some workers reported headache and nausea, especially following exposure to 135 -210 mg EPTC/m^3 (Medved & Ivanova, 1971) and also following brief exposure to diallate. Skin irritation was also found.

10. PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES

The Joint FAO/WHO Meeting on Pesticide Residues (JMPR) and the International Agency for Research on Cancer (IARC) have evaluated the toxicity and carcinogenicity data of a few thiocarbamates. These are referred to in Annex II.

This Annex also gives the WHO recommended hazard classification. As indicated, WHO/FAO Data Sheets, IRPTC Data Profiles, and IRPTC Legal Files are not available for these thiocarbamates.

REFERENCES

AKULOV, A.A.V., VERKHOVSKIY, A.P., & YEVDOKIMOV, S.M. (1972) [Triallate poisoning of animals.] *Veterinariya*, 10: 105-106 (in Russian).

ALDRIDGE, W.N. & MAGOS, L. (1978) *Carbamates, thiocarbamates,* dithiocarbamates, Luxembourg, Commission of the European Communities (Report No. V/F/1/78/75 EN).

ANDERSON, J.P.E. & DOMSCH, K.H. (1980) Relationship between herbicide concentration and the rates of enzymatic degradation of ^{14}C-diallate and ^{14}C-triallate in soil. *Arch. environ.* Contam. Toxicol., 9(3): 259-268.

BATCHELDER, G.H. & PATCHETT, G.G. (1960) A colorimetric method for the determination of EPTC residues in crops and soils. *J.* agric. food Chem., 8(3): 214-216.

CARRINGER, R.D., RIECK, C.E., & BUSH, L.P. (1978) Metabolism of EPTC in corn (*Zea mays*). *Weed Sci.*, 26(2): 157-160.

CASIDA, J.E., GRAY, R.A., & TILLES, H. (1974) Thiocarbamate sulfoxides: potent, selective, and biodegradable herbicides. *Science*, 184: 573-574.

CASIDA, J.E., KIMMEL, E.C., OHKAWA, H., & OHKAWA, R. (1975) Sulfoxidation of thiocarbamate herbicides and metabolism of thiocarbamate sulfoxides in living mice and liver enzyme systems. *Pestic. Biochem. Physiol.*, 5: 1-11.

CHEN, Y.S. & CASIDA, J.E. (1978) Thiocarbamate herbicide metabolism: microsomal oxygenase metabolism of EPTC involving mono- and dioxygenation at the sulfur and hydroxylation at each alkyl carbon. *J. agric. food Chem.*, 26: 263-267.

DALVI, R.R., POORE, R.E., & NEAL, R.A. (1974) Studies of the metabolism of carbon disulfide by rat liver microsomes. *Life* Sci., 14: 1785-1796.

DALVI, R.R., HUNTER, A.L., & NEAL, R.A. (1975) Toxicological implications of the mixed-function oxidase catalyzed metabolism of carbon disulfide. *Chem.-biol. Interact.*, 10: 349-361.

DEBAUN, J.R., BOVA, D.L., FINLEY, K.A., & MENN, J.J. (1978a) Metabolism of [ring-^{14}C]Ordram (molinate) in the rat. I. Balance

and tissue residue study. *J. agric. food Chem.*, 26(5): 1096-1098.

DEBAUN, J.R., BOVA, D.L., TSENG, C.K., & MEN, J.J. (1978b) Metabolism of [ring-^{14}C]Ordram (molinate) in the rat. II. Urinary metabolite identification. *J. agric. food Chem.*, 26(5): 1098-1104.

DEMARCO, A.C. & HAYES, E.R. (1979) Photodegradation of thiolcarbamate herbicides. *Chemosphere*, 5: 321-326.

DE MATTEIS, F. & SEAWRIGHT, A.A. (1973) Oxidative metabolism of carbon disulfide by the rat: effects of treatments which modify the liver toxicity of carbon disulfide. *Chem.-biol.* Interact., 7: 375-388.

DOLOSHITSKY, S.L. (1969) Hygienic standardization of herbicide Avadex containing chlorine in water. *Hyg. Sanit.*, 34: 21-25.

ENDO, T., KUSAKA, T., TAN, N., & SAKAI, M. (1982) Effects of the insecticide cartap hydrochloride on soil enzyme activities, respiration, and nitrification. *J. Pestic. Sci.*, 7: 101-110.

FANG, S.C. (1975) Thiocarbamates. In: Kearney, P.C. & Kaufman, D.D., ed. *Herbicides, chemistry, degradation, and mode of* action, New York, Marcel Dekker, Vol. 1, pp. 323-348.

FANG, S.C. & THEISEN, P. (1959) An isotopic study of ethyl-*N,N* -di-n-propylthiolcarbamate (EPTC-S^{35}) residue in various crops. *J. agric. food Chem.*, 7(11): 770-771.

FANG, S.C., GEORGE, M., & FREED, V.H. (1964) Metabolism of herbicides: the metabolism of *S* -propyl-1-14C-n-butylethyl-thiocarbamate (tillam ^{14}C) in rats. *J. agric. food Chem.*, 12(1): 37-40.

FAO/WHO (1977a) *Pesticide residues in food. Report of the 1976* Joint Meeting of the FAO Panel of Experts on Pesticide Residues and the Environment and the WHO Expert Group on Pesticide Residues, Geneva, World Health Organization (FAO Food and Nutrition Series No. 9; FAO Plant Production and Protection Series No. 8; WHO Technical Report Series No. 612).

FAO/WHO (1977b) *1976 Evaluations of some pesticide residues in* food, Geneva, World Health Organization (AGP 1977/M/14).

FAO/WHO (1979) *Pesticide residues in food. Report of the 1978* Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues, Rome, Food and Agriculture Organization of the United Nations (FAO Plant Production and Protection Paper 15).

GRAY, R.A. (1971) Behaviour, persistence, and degradation of carbamate and thiocarbamate herbicides in the environment. In: *Proceedings of the California Weed Control Conference*, pp. 128-134.

GRAY, R.A. & WEIERICH, A.J. (1968) Leaching of five thiocarbamate herbicides in soils. *Weed Sci.*, 16(1): 77-79.

HORVATH, L. & PULAY, A. (1980) Metabolism of EPTC in germinating corn: sulfone as the true carbamoylating agent. *Pestic.* Biochem. Physiol., 14: 265-270.

HUBBELL, J.P. & CASIDA, J.E. (1977) Metabolic fate of the *N,N* -dialkylcarbamoyl moiety of thiocarbamate herbicides in rats and corn. *J. agric. food Chem.*, 25(2): 404-413.

HUGHES, R.E., Jr & FREED, V.H. (1961) The determination of ethyl *N,N* -di-n-propylthiolcarbamate (EPTC) in soil by gas chromatography. *J. agric. food Chem.*, 9(5): 381-382.

IARC (1976) Diallate. In: *Some carbamates, thiocarbamates, and* carazides, Lyons, International Agency for Research on Cancer, pp. 69-75 (Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, Vol. 12).

INNES, J.R.M., ULLAND, B.M., VALERIO, M.G., PETRUCELLI, L., FISHBEIN, L., HART, E.R., PALLOTTA, A.J., BATES, R.R., FALK, H.L., GART, J.J., KLEIN, M., MITCHELL, I., & PETERS, J. (1969) Bioassay of pesticides and industrial chemicals for tumorigenicity in mice: a preliminary note. *J. Natl Cancer Inst.*, 42: 1101-1114.

IRPTC (1983) *IRPTC legal file 1983*, Geneva, International Register for Potentially Toxic Chemicals, United Nations Environment Programme.

JOHNSON, W.W. & FINLEY, M.T. (1980) *Handbook of acute toxicity* of chemicals to fish and aquatic invertebrates, Washington DC, US Department of Interior, Fish and Wildlife Service.

KAUFMAN, D.D. (1967) Degradation of carbamate herbicides in soil. *J. agric. food Chem.*, 15: 582-591.

KIKUCHI, Y., HITOTSUMACHI, S., & YAMAMOTO, K.I. (1976) [Mutagenicity tests on cartap hydrochloride. In vivo cytogenetic and dominant lethal tests in mammals.] *J. Takeda Res. Lab.*, 35: 257-263 (in Japanese).

LAY, M.M. & CASIDA, J.E. (1976) Dichloroacetamide antidotes enhance thiocarbamate sulfoxide detoxification by elevating corn root glutathione content and glutathione *S* -transferase activity. *Pestic. Biochem. Physiol.*, 6: 442-456.

MEDVED, I. & IVANOVA, Z.V. (1971) [Hygienic establishment of working conditions during Eptam application in agriculture.] *Gig. i Sanit.*, 2: 29-32 (in Russian).

MIZUTANI, M., IHARA, T., KANAMORI, H., TAKATAI, O., MATSUKAWA, J., AMANO, T., & KAZIWARA, K. (1971) Teratogenesis studies with 1,3-bis(carbamoylthio)-2-(*N,N* -dimethylamino)propane hydrochloride in the mouse, rat, and hamster. *J. Takeda Res.* Lab., 30: 776-785.

MURNIK, M.R. (1976) Mutagenicity of widely-used herbicides. *Genetics*, 83: S54 (abstract).

OKAICHI, T. & HASHIMOTO, Y. (1962) The structure of nereis toxin. *Agric. biol. Chem.*, 26: 224-227.

ONG, V.Y. & FANG, S.C. (1970) In vivo metabolism of ethyl-1-14C- *N,N* -di-n-propylthiol carbamate in rats. *Toxicol. appl.* Pharmacol., 17: 418-425.

PALMER, J.S., HANFLER, M., HUNT, L.M., SCHLINKE, J.C., & GATES, C.E. (1972) Chronic toxicosis of sheep from organic herbicide

diallate. *Am. J. vet. Res.*, 33: 543-546.

PATCHETT, G.C., BATCHELDER, G.H., & MENN, J.J. (1964) Eptam. In: Zweig, G., ed. *Analytical methods for pesticides: plant* growth regulations and food additives, New York, London, Academic Press, Vol. 4, pp. 117-123.

RAPPOPORT, M.B. & PESTOVA, A.G. (1973) [Biological effects of diisopropyltrichloroallylthiocarbamate.] *Vrach. Delo*, 10: 138-141 (in Russian).

REBRIN, V.G. & ALEXANDROVA, L.G. (1971) [Toxico-hygienic characteristics of the new herbicide Ro-Neet.] *Vrach. Delo*, 12: 118-121 (in Russian).

SAKAI, M. (1969) *The chemistry and action of cartap*, pp. 15-19 Tokyo, Japan Plant Protection Society (Japanese Pesticide Information No. 6).

SCHUPHAN, I. & EBING, I. (1977) [Metabolism of thiocarbamate herbicides. I. Chemical conversion of the herbicide di-allate and synthesis of possible di-allate metabolites.] *Chemosphere*, 6(4): 173-178 (in German).

SIKKA, H.C. & FLORCZYK, P. (1978) Mutagenic activity of thiocarbamate herbicides in *Salmonella typhimurium*. *J. agric.* food Chem., 26: 146-148.

STAUFFER CHEMICALS SA (1978) *Product safety and toxicology* review. Behaviour of thiocarbamates in the environment, Geneva, Stauffer Chemicals SA (Report No. Tox-05-78-01).

STAUFFER CHEMICALS SA (1981) *Product safety and toxicology* review. Biodegradation of thiol carbamate herbicides, Geneva, Stauffer Chemicals SA (Report No. Tox-3-81-01).

VERKHOVSKIY, A.P., ZHAVORONKOV, N.I., & YEVDOKIMOV, S.M. (1973) [Changes in blood of animals poisoned by triallate.] *Veterinariya*, 9: 92-93 (in Russian).

VETTORAZZI, G. & VAN DEN HURK, G.W. (1984) *Pesticides reference* index: JMPR 1961-84, Geneva, World Health Organization.

VOYTENKO, G.A. & MEDVED, I.L. (1973) [Effect of some thiocarbamates on reproduction function.] *Gig. i Sanit.*, 38(7): 111-114 (in Russian).

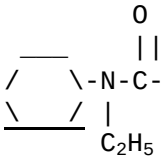
WHO (1986) *The WHO recommended classification of pesticides by* hazard. Guidelines to classification 1986-1987, Geneva, World Health Organization (Unpublished report VBC/86.1 Rev. 1).

WORTHING, C.R. & WALKER, S.B. (1983) *The pesticide manual: a* world compendium, 7th ed., Croydon, British Crop Protection Council.

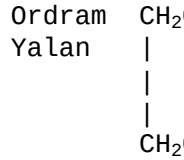
YIN-TAK WOO (1983) Carcinogenicity, mutagenicity, and teratogenicity of carbamates, thiocarbamates, and related compounds. An overview of structure-activity relationships and environmental concerns. *J. environ. Sci. Health*, C1(1): 97-133.

ZHAVORONKOV, N.I., AKULOV, A.V., ANTISEFEROV, S.D., VERKHOVSKIY, A.P., & YEVDOKIMOV, S.M. (1974) Effect of carbamates on hens. *Pestic. Abstr.*, 7: 372.

Annex I. Names and structures of selected thiocarbamates

Common name	Trade/ other name	Chemical structure	CAS chemical name/ CAS registry number	Molecular formula	
butylate	Sutan	$[(CH_3)_2CHCH_2]_2NCOSCH_2CH_3$	carbamothioic acid, bis(2-methyl-propyl)-, *S* -ethyl ester (2008-41-5)	$C_{11}H_{23}NOS$	217
cartap	Padan	$(H_2N\text{-}C(=O)\text{-}SCH_2)_2\text{-}CH\text{-}N(CH_3)_2$	carbamothioic acid, *S,S'*-[2-(dimethyl-amino)-1,3 propane-diyll ester (15263-53-3)	$C_7H_{15}N_3O_2S$	20
cycloate	Ro-Neet Eurex		carbamothioic acid, ethyl(cyclo-hexyl)-, *S* -ethyl ester (1134-23-2)	$C_{11}H_{21}NOS$	2
diallate	Avadex DATC	$[(CH_3)_2CH]_2N\text{-}C(=O)\text{-}SCH_2\text{-}C(Cl)\text{=}CHCl$	carbamothioic acid, bis(1-methyl-ethyl)-, *S* -(2,3-dichloro-2-propenyl) ester (2303-16-4	$C_{10}H_{17}Cl_2NOS$	27
EPTC	Eptam Eradicane R-1608	$[(CH_3)_2CH]_2N\text{-}C(=O)\text{-}SC_2H_5$	carbamothioic acid, bis(1-methyl-ethyl)-, *S* -ethyl ester (759-94-4)	$C_9H_{19}NOS$	1
ethiolate	Prefox	$(C_2H_5)N\text{-}C(=O)\text{-}SC_2H_5$	carbamothioic acid, diethyl-, *S* -ethyl ester (2941-55-1)	$C_7H_{15}NOS$	1

Annex I (contd).

Common name	Trade/ other name	Chemical structure	CAS chemical name/ CAS registry number	Molecular formula	
molinate	Ordram Yalan		1H-azepine-1-carbothioic acid, hexa-hydro-, *S* -ethyl ester (2212-67-1)	$C_9H_{17}NOS$	18
pebulate	Tillam PEBC	$C_2H_5\text{-}N(C_4H_9)\text{-}C(=O)\text{-}SC_3H_7$	carbamothioic acid, butylethyl-, *S* -propyl ester (1114-71-2)	$C_{10}H_{21}NOS$	2

prothio-carb	Dynone	$(CH_3)_2N\text{-}C_3H_7NH\text{-}C(=O)\text{-}SC_2H_5$	carbamothioic acid, [3-(dimethyl-amino)-propyl]-, *S* -ethyl ester (19622-19-6)	$C_8H_{18}N_2OS$
triallate	Avadex BW Far-Go	$[(CH_3)_2CH]_2N\text{-}C(=O)\text{-}S\text{-}CH_2\text{-}CCl_2\text{-}Cl$	carbamothioic acid, bis(1-methyl-ethyl)-, *S* -(2,3,3-trichloro-2-propenyl) ester (2303-17-5)	$C_{10}H_{14}Cl_3NOS$
vernolate	R-1607 Vernam	$(C_3H_7)_2N\text{-}C(=O)\text{-}SC_3H_7$	carbamothioic acid, dipropyl-, *S* -propyl ester (1929-77-7)	$C_{10}H_{21}NOS$

[a] At 20 °C.
[b] From: Worthing & Walker (1983).

Annex II, Table 1. Thiocarbamates: JMPR reviews, ADIs, Evaluation by IARC, Classification by Hazard, FAO/WHO Data Sheets, IRPTC Data profile and Legal file[a]

Compound	Year of JMPR meeting	ADI[b] (mg/kg body weight)	Evaluation by JMPR[c]: Published in: FAO/WHO	IARC[d] Evaluation of carcino-genicity	Availability of IRPTC[e]: Data profile	Legal file[g]	WHO recommended classification of pesticides by hazard[h]
Butylate							0
Cartap	1978 1976	0-0.1 0-0.5 (temporary)	1979 1977b 1977a				II
Cycloate							III
Diallate				1976			II
EPTC							II
Molinate							II
Pebulate							II
Prothiocarb							III
Triallate							III
Vernolate							II

[a] Adapted from: Vettorazzi & Van den Hurk (1984).
[b] ADI = acceptable daily intake.
[c] JMPR = Joint Meeting on Pesticide Residues (FAO/WHO).
[d] IARC = International Agency for Research on Cancer, Lyons, France.
[e] IRPTC = International Register for Potentially Toxic Chemicals (UNEP, Geneva)
[f] WHO/FAO Data Sheets on Pesticides with number and year of appearance.
[g] From: IRPTC (1983).
[h] From: WHO (1986).
The hazard referred to in this classification is the acute risk for healt
risk of single or multiple exposures over a relatively short period of time
encountered accidentally by a person handling the product in accordance w
for handling by the manufacturer, or in accordance with the rules laid down
transportation by competent international bodies.
The classification relates to the technical material and not to the formulat

Annex II, Table 2. WHO recommended hazard classification for pesticides

Class		LD_{50} for the rat (mg/kg body weight)			
		Oral		Dermal	
		Solids	Liquids	Solids	Liquids
1a	Extremely hazardous	5 or less	20 or less	10 or less	40 or less
1b	Highly hazardous	5 - 50	20 - 200	10 - 100	40 - 400
II	Moderately hazardous	50 - 500	200 - 2000	100 - 1000	400 - 4000
III	Slightly hazardous	over 500	over 2000	over 1000	over 4000
O	Unlikely to present acute hazard in normal use				

See Also:
Toxicological Abbreviations