UNITED NATIONS

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United Nations Environment Programme

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Distr.
GENERAL
UNEP/FAO/PIC/ICRC.4/13
12 December 2002

ENGLISH ONLY

Interim Chemical Review Committee
Fourth session
Rome, 3 – 7 March 2003
Item 5(b) (iii) of the provisional agenda*

INCLUSION OF CHEMICALS IN THE INTERIM PRIOR INFORMED CONSENT PROCEDURE: CONSIDERATION OF DRAFT DECISION GUIDANCE DOCUMENTS

SPINOX T/GRANOX TBC

Note by the secretariat

1. At its third session, the Interim Chemical Review Committee reviewed a proposal from Senegal and the supporting documentation collected by the Secretariat, and, taking into account each of the specific requirements set out in part 3 of annex IV of the Rotterdam Convention, concluded that the requirements of that annex had been met.

2. Accordingly, the Committee agreed, to recommend to the Intergovernmental Negotiating Committee that the severely hazardous pesticide formulations Spinox T/Granox TBC should become subject to the interim prior informed consent (PIC) procedure, and to establish an intersessional drafting group to produce a draft decision guidance document for that chemical.

3. The members of the drafting group established by the third session of the Interim Chemical Review Committee were Ms. C. Barnes and Mr. M. Ammati (Co-Chairs); Ms. Yang, Ms. N'doye, Mr. Debois, Mr. Ward, Mr. Arndt, Mr. Mayne, Mr. Ikeda, Mr. Untung, Mr. Palikhe, Mr. Sibartie, Mr. Cable, Mr. Komives and the Secretariat.

4. A detailed work plan for the development of the decision guidance document was developed by the drafting group in line with the process for developing decision guidance documents adopted by the Intergovernmental Negotiating Committee at its seventh session (decision INC-7/6). The work plan was annexed to the report of the third session of the Committee and posted on the Rotterdam Convention website. The goal was to have a draft decision guidance document available for consideration by the Committee at its fourth session in March 2003.

5. On 22 March 2002 the secretariat circulated detailed guidance to the drafting group including a summary of the results of the third session of the Interim Chemical Review Committee, a copy of the

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* UNEP/FAO/PIC/ICRC.4/1

working paper on the preparation of internal proposals and decision guidance documents for severely hazardous pesticide formulations and a list of the relevant supporting documentation. The co-chairs of the drafting group prepared an internal proposal, based on the submitted information and the supporting documentation and in consultation with the secretariat. This proposal and the draft working paper were circulated to members of the drafting group for comments on 23 May 2002. The documents were amended in the light of the comments received.

6. The draft decision guidance document on Spinox T/Granox TBC and the working paper were circulated to all members of the Interim Chemical Review Committee and observers[1] to the third session of the Committee on 26 July 2002. Reponses were received from members of the committee and two observers (Germany and Mexico) as well as Crop Life International, the Pesticides Action Network (PAN UK) and the World Health Organization (WHO). The draft decision guidance document on Granox TBC/Spinox T and the working paper were amended in the light of the comments received.

7. A status report on the work of the drafting group, including a compilation of the comments and the amended draft decision guidance document were circulated to drafting group members 11 October 2002. As a result of this last round of comment several minor editorial changes were incorporated in the draft decision guidance document. A tabular summary of all of the comments received and how they were addressed will be available at the fourth session for the Interim Chemical Review Committee as document UNEP/FAO/PIC/ICRC.4/INF.3.

8. Annexed to this note is a copy of the draft decision guidance document on DNOC as submitted to the secretariat by the drafting group.

I. ISSUES TO CONSIDER IN REVIEWING THE DRAFT DECISION GUIDANCE DOCUMENT ON SPINOX T/GRANOX TBC

A. Availability of additional relevant information

9. In the course of preparing the decision guidance document no information or risk evaluations concerning these specific formulations have been made available to the secretariat or members of the drafting group.

10. No information on chemical or non-chemical alternatives to the use of Spinox T or Granox TBC as a seed treatment on peanuts has been submitted to the secretariat.

B. Response of the ninth session of the Intergovernmental Negotiating Committee to issues identified at the third session of the Interim Chemical Review Committee.

11. At the third session of the Interim Chemical Review Committee several of its members expressed concern over the implications of including a single specific formulation with identified percentages of the active ingredients in the interim PIC procedure and felt that further guidance from the Intergovernmental Negotiating Committee was necessary to determine how such listings should be considered in the future. This issue was brought to the attention of the ninth session of the INC.

12. The Intergovernmental Negotiating Committee (INC) noted that the specific formulation identified in a proposal submitted in accordance with Article 6 was the basis for listing a severely hazardous pesticide formulation. The INC agreed:

(i) that formulations containing the active ingredient or ingredients at or above the specified concentrations and in the same formulation type would also be subject to the interim PIC procedure, if supported by the technical documentation supporting the proposal and that

[1] 16 countries, two non-governmental organizations and two intergovernmental organizations.

a footnote to that effect could be added, or some other type of explanatory guidance could be provided;

(ii) that in the particular case of Granox TBC and Spinox T, all powdered formulations containing the active ingredients would be covered. The listing could be such that the constituent active ingredients (Benomyl, Carbofuran and Thiram) would be explicitly identified, along with the concentration levels, the appropriate CAS numbers and the formulation type (dustable powder), with an appropriate footnote or other explanatory guidance.

13. At the ninth session of the Intergovernmental Negotiating Committee (INC) one representative expressed his profound concern that a Task Group was undertaking work on the review of the proposals on the severely hazardous pesticide formulations Granox TBC and Spinox T when there was no established international trade in the substances. He considered that the international trade requirement was applicable to the totality of the Convention. He believed that the INC should provide guidance to ensure that the listing of a severely hazardous pesticide formulation that was not the object of international trade did not constitute a precedent that could deter countries from ratifying the Convention. It was observed that the issue did not require a decision at the current time, since the ICRC first needed to prepare a draft decision guidance document, which would have to be submitted to a future meeting of the INC for approval.

ANNEX

Operation of the interim Prior Informed Consent procedure
for banned or severely restricted chemicals in international trade

Decision Guidance Document

Granox TBC and Spinox T

Interim Secretariat for the Rotterdam Convention on the Prior Informed Consent Procedure for Certain Hazardous Chemicals and Pesticides in International Trade

UNEP

Mandate

The Rotterdam Convention on the Prior Informed Consent Procedure for Certain Hazardous Chemicals and Pesticides in International Trade was adopted at the Conference of Plenipotentiaries held in Rotterdam on 10 and 11 of September 1998. The same Conference also adopted a Resolution on interim arrangements in order to operate an interim PIC procedure between the time of the adoption of the Convention and its entry into force, and to prepare for its effective operation once it enters into force.

Relevant background text on the development of the Granox TBC and Spinox T Decision Guidance Document to be inserted.

Disclaimer

The use of trade names in this document is primarily intended to facilitate the correct identification of the chemical. It is not intended to imply any approval or disapproval of any particular company. As it is not possible to include all trade names presently in use, only a number of commonly used and published trade names have been included in this document.

While the information provided is believed to be accurate according to data available at the time of preparation of this Decision Guidance Document, the Food and Agriculture Organization of the United Nations (FAO) and the United Nations Environment Programme (UNEP) disclaim any responsibility for omissions or any consequences that may flow therefrom. Neither FAO or UNEP shall be liable for any injury, loss, damage or prejudice of any kind that may be suffered as a result of importing or prohibiting the import of this chemical.

The designations employed and the presentation of material in this publication do not imply the expression of any opinion whatsoever on the part of FAO or UNEP concerning the legal status of any country, territory, city or area or of its authorities or concerning the delimitation of its frontiers or boundaries

ABBREVIATIONS WHICH MAY BE USED IN THIS DOCUMENT

(N.B. Chemical elements and pesticides are not included in this list)

<	less than
≤	less than or equal to
<<	much less than
>	greater than
≥	greater than or equal to
>>	much greater than
µg	microgram
a.i.	active ingredient
AchE	acetylcholinesterase
ACGIH	American Conference of Governmental Industrial Hygienists
ADI	acceptable daily intake
ADP	adenosine diphosphate
ALT	alanine amino-transferase
AOEL	acceptable operator exposure level
ARfD	acute reference dose
ATP	adenosine triphosphate
BBA	Biologische Bundesanstalt für Land- und Forstwirtschaft
BOEL	biological operator exposure limit
b.p.	boiling point
BSI	British Standards Institution
bw	body weight
^{o}C	Degree Celsius (centigrade)
CA	Chemicals Association
CAS	Chemical Abstract Service
CCPR	Codex Committee on Pesticide Residues
ChE	cholinesterase
CHO	Chinese hamster ovary
d	day
D	dust
DP	dustable powder
EC_{50}	effect concentration, 50% (median effective concentration)
ED_{50}	effect dose, 50% (median effective dose)
EHC	Environmental Health Criteria
ERL	extraneous residue limit
FAO	Food and Agriculture Organization of the United Nations
g	gram
GAP	good agricultural practice
GL	guideline level

ABBREVIATIONS WHICH MAY BE USED IN THIS DOCUMENT
(N.B. Chemical elements and pesticides are not included in this list)

h	hour
ha	hectare
IARC	International Agency for Research on Cancer
IC_{50}	inhibition concentration, 50%
ICSC	International Chemical Safety Card
i.m.	intramuscular
i.p.	intraperitoneal
IPCS	International Programme on Chemical Safety
IPM	integrated pest management
ISO	International Organisation for Standardisation
IRPTC	International Register of Potentially Toxic Chemicals
IUPAC	International Union of Pure and Applied Chemistry
JMPR	Joint FAO/WHO Meeting on Pesticide Residues (Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and a WHO Expert Group on Pesticide Residues)
k	kilo- (x 1000)
kg	kilogram
K_{oc}	organic carbon/water partition coefficient
K_{ow}	octanol/water partition coefficient
l	litre
LC_{50}	lethal concentration, 50%
LD_{50}	lethal dose, 50%
LD_0	lethal dose, 0%
LD_{100}	lethal dose, 100%
LD_{LO}	lowest lethal dose
LOAEL	lowest observed adverse effect level
LOD	limit of detection
LOEL	lowest observed effect level
Log P	logarithm of the octanol/water partition coefficient
m	metre
mg	milligram
ml	millilitre
m.p.	melting point
mPa	millipascal
MRL	maximum residue limit
MTD	maximum tolerated dose
NCI	National Cancer Institute (United States of America)
ng	nanogram
NOAEL	no-observed-adverse-effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
OECD	Organisation for Economic Co-operation and Development

ABBREVIATIONS WHICH MAY BE USED IN THIS DOCUMENT
(N.B. Chemical elements and pesticides are not included in this list)

OHS	Occupational Health and Safety
OP	organophosphorus pesticide
P	same as K_{ow}
Pa	pascal
PHI	pre-harvest interval
PIC	Prior Informed Consent
POEM	predictive operator exposure model
POP	Persistent Organic Pollutant
ppm	parts per million (used only with reference to the concentration of a pesticide in an experimental diet. In all other contexts the terms mg/kg or mg/l are used).
RfD	reference dose (for chronic oral exposure. Comparable to ADI)
SMR	standardised mortality ratio
STEL	short term exposure limit
TADI	temporary acceptable daily intake
TER	toxicity/exposure ratio
TLV	threshold limit value
TMDI	theoretical maximum daily intake
TMRL	temporary maximum residue limit
TWA	time weighted average
ULV	ultra low volume
UNEP	United Nations Environment Programme
USEPA	United States Environmental Protection Agency
UV	ultraviolet
VOC	volatile organic compound
WHO	World Health Organisation
wt	weight

Decision guidance document for severely hazardous pesticide formulations causing human health problems

Granox TBC and Spinox T

Published: Draft November 2002

1. Identification

Name of the hazardous pesticide formulations: GRANOX TBC and SPINOX T

Name of the active ingredients and relative amount of each active ingredient in the formulations:

Active Ingredient	percentage in formulation	CAS number
benomyl	7	17804-35-2
carbofuran	10	1563-66-2
thiram	15	137-26-8

Type of formulation: DP (dustable powder)

Trade names and names of the producers, if available;

SPINOX T is formulated by:
S.P.I.A.
Louga Plant

B.P. 1806-Dakar, Senegal

GRANOX TBC is formulated by:
Senchim-AG
BP 21236 Dakar, Senegal

2. Reason for inclusion in the PIC procedure

The severely hazardous pesticide formulations of "GRANOX TBC" and "SPINOX T" are subject to the Rotterdam Convention. The two products have identical active ingredients, namely:

Benomyl, concentration of 7%
Carbofuran, concentration of 10%
Thiram, concentration of 15%

These formulations were found to cause problems under conditions of use in Senegal, consistent with the provisions of Article 6 and Annex IV of the Convention.

There may be other formulations marketed under the names of GRANOX or SPINOX containing different combinations of these or other active ingredients. It is only those dustable powder formulations containing the above noted combination of active ingredients at or above the specified concentrations that are subject to the PIC procedure.

3. Description of common and recognized pattern of use of the formulation in the reporting country

Permitted uses:

The formulations were registered in Senegal as a peanut seed treatment only.
The recommended application rate was 100 g of formulation per 25 kg oil peanuts or 40 kg edible peanuts.

Restrictions in handling or use:

At the time the products were first registered in Senegal, there were no restrictions on use or application, aside from the limitation to peanut seed treatment. The labels included the following precautionary statements on use.

SPINOX T

PRECAUTIONS

SPINOX is a toxic compound that requires the following precautions:
Store out of reach from children and animals.
If you do not have gloves, wrap your hands in plastic bags prior to mixing. Avoid handling this product where there are open wounds or cuts on hands.
Do not drink, or smoke or eat during application.
Avoid to breath the dust during the mixing, apply with the back to the wind.
Wash carefully all the tools that have been used for mixing.
Never eat treated seeds even if they have been rinsed or if they are without skin

GRANOX TBC

PRECAUTIONS

Store out of reach of children and animals.
For application, use preferably tools not intended for cooking or for animals.
Do not apply this product where there are open wounds or cuts on hands.
Do not drink, eat or smoke during application avoid to breath the dust during the mixing, apply with the back to the wind.
Wash your hands and face carefully after application with water and soap.
Wash the tools used.
Do not eat the treated seeds. Death hazard, even if skin is removed.

Availability/applicability of protective clothing:

No protective clothing or equipment was available to the farm workers in the reported incidents, nor was it specifically required on the GRANOX label. While not specifically recommending the use of gloves, the SPINOX label suggests that if gloves are not available, hands could be wrapped with plastic bags prior to mixing.

Actual uses:

The information available indicates that the use of the formulation at the time the reported incidents occurred reflected common usage in the country; that is, application to peanuts. This includes up to two applications, one to peanuts in the shell while in storage and a second treatment of shelled peanuts at sowing.

4. Description of the incident(s) including adverse effects and way in which the formulation was used

The following information was taken from the epidemiological study of the reported incidents and the completed incident report forms submitted by Senegal (SNGE 2000 and Annex I).

Location of incidents:

The adverse incidents occurred in the agricultural areas of the Kolda region in Senegal.

The incidents were reported from an area of approximately 40 Km^2 within the Kolda and Sedhiou districts, centred around the Sare Sama village in the Kolda district. In an epidemiological study the cases were assigned to four distinct areas identified according to the nearest health-post zone: Sare Bidji, Ndora, Diana Malari and Tankon. It is a very isolated area connected to the main district town by tracks impassable by ordinary car during the rainy season.

Peanut farming is the predominant agricultural activity in the Kolda region with a cultivated area of about 70, 000ha. No incidents were reported in surrounding peanut-growing regions where the formulations were not available.

Main activity at the time of incident:

The reported incidents were concentrated in peanut farming areas during the period of intensive field labor with a maximal peak in August when all farmers received the seeds and started or finished sowing. All the reported incidents involved farmers who had taken part in peanut seed treatment. The peanuts were treated twice: the first treatment was during storage, while the peanuts were still in their shell; the second treatment was to the shelled peanuts at the time of sowing.

Application method:

Farmers use a sowing machine to scatter peanut seeds on the ground, by using the following procedure:

- the pesticide is mixed with the seeds in the sowing machine
- workers mix the pesticide and the seeds with their hands
- the sowing machine is pulled by animals and pushed in shifts by workers

Route of exposure:

Farmers were exposed to the formulation through three different routes:

- **By mouth:** Exposure can be through hand to mouth activity (such as eating with contaminated hands) or directly by using the mouth to remove the shell from treated peanuts prior to sowing.

- **Inhalation:** during seed treatment prior to storage, during seed preparation (shelling), during mixing of the formulation with the seeds, and during sowing of the treated seeds. People handling the powder are reported to inhale the pesticide product when filling the seeder with pesticide and seeds or by walking behind the seeder during operation.

- **Through the skin:** during treatment and shelling of the seeds, loading of the seeder, and while unclogging the sowing machine

Description of the adverse effects observed:

There were five deaths in the 22 reported incidents. The exposed individuals exhibited three or more of the following symptoms: abdominal pain, chest pain, coughing, dizziness, dyspnea, fatigue, fever, gastric pain, headache, insomnia, abnormalities of urine (unspecified), oedema, pain in limbs, shivers, swelling in limbs, tachycardia, rhinitis and vomiting (Annex I).

Relationship of observed adverse effects to recognized acute toxicological effects of the active ingredient(s):

An examination of the toxicology of the active ingredients indicates that many of the severe symptoms observed are usually associated with only one of the components in the formulation: the carbamate, carbofuran.

Carbofuran – Carbofuran is a carbamate pesticide of very high toxicity. It is an acute poison, absorbed by inhalation of dust and spray mist; from the gastrointestinal tract; and, to a lessor extent through the intact skin. Early symptoms of poisoning may include headache, weakness, giddiness and nausea. Later there may be excessive sweating, stomach pains, excessive salivation, blurred vision (miosis – pupillary constriction) and muscle twitching, tremor, diarrhoea and vomiting. Typical symptoms reported among occupationally exposed formulators and applicators involved blurred vision, nausea, excessive perspiration and a sense of weakness. Uneventful recovery is reported to occur with a few hours even without therapy but it was faster when atropine was administered.

It was noted that symptoms reported in the incidents in Senegal did not reflect the full range of those typically associated with cholinesterase inhibition. Consequent to exposure to carbamates, symptoms such as miosis and excess salivation are typically of short duration. Given that the data were collected some time after exposure, those symptoms would not be expected to have been observed. In addition, it was noted that the actual reporting form used to collect the data may have influenced the symptoms reported, since it did not list the full range of symptoms representative of cholinesterase inhibition. The reported respiratory problems and chest pain may be related to lung oedema, normally a symptom of severe carbamate poisoning. Supplementary information detailing the nature and scope of the illness arising from the use of the formulations was not available due to inadequate record keeping in health centers and posts in the region.

Thiram – Thiram is a dithiocarbamate of slight acute toxicity and potential long term toxic effects. It may be absorbed from the gastrointestinal tract; by inhalation of spray mist or dust; and through intact skin. Early symptoms of poisoning may include dizziness, confusion, drowsiness, lethargy, ataxia, headaches, or coma, nausea, vomiting, diarrhoea and stomach pains; muscle weakness and paralysis (ascending); respiratory paralysis; and skin rash and eye irritation. However, alcohol increases thiram toxicity and there have been very few cases of thiram systemic poisoning leading to death without known alcohol involvement. Increased skin sensitivity unrelated to alcohol use is becoming more common especially in tropical countries, in association with thiram use.

Benomyl – Benomyl is a benzimidazole fungicide. Acute toxicity of benomyl is low, but it has the potential of causing dermal sensitization. Signs of acute poisoning following ingestion or inhalation may include abdominal cramps, dullness, sweating, nausea, vomiting and salivation. No inadvertent poisoning of agricultural or forestry workers has been documented. Benomyl caused contact dermatitis and dermal sensitisation in some farm workers.

Extent of incident (number of people affected):

There were a total of 22 separate incident reports for SPINOX T and GRANOX TBC.

For SPINOX T, 12 individuals were affected: 10 males, one female, one unknown, all ranging in age from 19 to 48 years. Two deaths occurred as a result of the exposure to SPINOX T (Annex I).

For GRANOX TBC, 10 individuals were affected, all male, ranging in age from 22 to 60 years. Three deaths occurred as a result of the exposure to GRANOX TBC (Annex I).

5. Any regulatory, administrative or other measure taken, or intended to be taken, by the proposing Party in response to such incidents

The Government of Senegal reported its plans to take the following measures:

- Inform health personnel of risks, clinical symptoms and remedies for pesticide poisonings.
- Strengthen surveillance system for pesticide poisonings.
- Inform agricultural workers on proper use of pesticides and provide personal protective equipment (masks and gloves) to those farm workers and seed recipients handling treated seeds.

6. WHO classification of the formulation.

Classification of the formulation according to the most hazardous constituent of the mixture (Annex III)		Classification of the formulation through application of the recommended formula (Annex III)	
Dermal	Oral	Dermal	Oral
Class III (slightly hazardous)	Class Ib (highly hazardous)	Class III (slightly hazardous)	Class II (moderately hazardous)

The calculations are based on the WHO recommended classification of pesticides by hazard and Guidelines to classification 2000-2002. They represent the hazard classification for dermal or oral exposure to a solid formulation.

Oral LD_{50} values on rat (Source WHO 2001)

Benomyl (unlikely to represent an acute hazard)	LD_{50} > 5,000 mg/kg bw
Carbofuran (Class Ib – highly hazardous)	LD_{50} 8 mg/kg bw
Thiram (Class III, slightly hazardous)	LD_{50} 560 mg/kg bw

Dermal LD_{50} values on rat (Sources as noted) [2]

Benomyl (unlikely to represent an acute hazard)	LD_{50} > 5,000 mg/kg bw
Carbofuran	LD_{50} > 500 mg/kg bw
Thiram	LD_{50} > 1000 mg/kg bw

7. Existence of handling or applicator restrictions for the formulation in other countries

No other country reported use of the specific formulation; therefore, no information on applicator restrictions for the formulation in other countries was available.

8. Information on incidents related to the formulation in other countries

No information on incidents related to the formulation in other countries was available.

9. Information on incidents related to other formulations of the pesticide

No specific information on incidents associated with other formulations with combinations of the three actives ingredients was available.

A systematic collection of data on incidents associated with each active ingredient was not undertaken. However, the U.S. Environmental Protection Agency reported that "…reviews based on data from California and Poison Control Centers suggest that carbofuran had a relatively high frequency and rate of poisoning among agricultural workers**."**

10. Information on other formulations of the active ingredient(s) in the country reporting the incident and in other countries.

In reviewing the responses to a general request for information on GRANOX TBC and SPINOX T, it was noted that this specific formulation was not reported as registered in any country other than Senegal.

In the responses that were received by the Secretariat, 27 countries as well as one regional economic organization reported that no dustable powder formulations of carbofuran were permitted for use in those countries (Bhutan, Canada, Chile, People's Republic of China, Colombia, Costa Rica, Czech

[2] Source of LD50 values: benomyl, FAO/WHO Pesticide Data Sheet No. 87 (Annex II); carbofuran, JMPR 1996 p 35 UNEP/FAO/PIC/ICRC.3/17.Add1; thiram EXTOXNET information profile on thiram UNEP/FAO/PIC/ICRC3/17.Add1 p 82.

Republic, Estonia, Finland, Israel, Republic of Korea, Latvia, Lesotho, Malaysia, Mexico, New Zealand, Papua New Guinea, Peru, Samoa, Switzerland, Tanzania, Thailand, Trinidad and Tobago, Turkey, United States of America, Vietnam, Zimbabwe, European Union).

China further stated that while carbofuran was registered for use as a seed coating, it was not used as a dustable powder and only low toxicity formulations were allowed to be marketed.

Two countries, Burkina Faso and the Gambia, indicated that similar formulations containing 10% carbofuran, 7% benomyl, 7% captafol were in use as seed treatments.

There are a wide variety of formulations of the individual active ingredients alone and in combination with other active ingredients registered/permitted for use in a wide range of both developed and developing countries.

Information on the handling or operator restrictions for the individual active ingredients may be found in Section 4 of the Pesticide Data Sheets in Annex II (from Section 7).

11. Physico-chemical properties of the formulation

No data on the specific formulation is available.

Information on the physico-chemical properties of the individual actives may be found in Section 1.3 of the Pesticide Data Sheets in Annex II.

12. Summary of toxicological properties

Data are not available on the toxicological properties of the formulations.

Information on the toxicological properties of the individual active ingredients may be found in sections 2.1 and 2.2 of the Pesticide Data Sheets in Annex II

13. Alternative pest-control practices

Spinox/Granox contain two fungicides and one insecticide, each of which are broad spectrum products. There are a number of alternative methods for pest control involving both chemical and non-chemical strategies including alternative technologies available, depending on the individual crop-pest complex under consideration. Countries should consider promoting, as appropriate, integrated pest management (IPM) strategies as a means of reducing or eliminating the use of hazardous pesticides. Advice may be available through National IPM focal points, the FAO, agricultural research or development agencies.

It is essential that, before a country considers substituting alternatives, it ensures that the use is relevant to its national needs and the anticipated local conditions of use.

Where it has been provided by governments, information on alternatives may be found on the Rotterdam Convention Website: www.pic/int

Annex I Information on reported incident from incident report

The Secretariat received two proposals verified to meet the requirements of Part 1 of Annex IV from Senegal. The original proposals were supported by a total of 89 Pesticide Incident Report forms (Part B of the proposals). The Secretariat found that 22 of the 89 forms submitted were complete and concerned incidents that reflect the uses of the two formulations as identified on the submitted labels. Based on these 22 forms, two summaries were prepared and circulated in PIC Circular XIV (12 December 2001). This annex contains a translation into English of a synopsis of the key elements in the 22 submitted incident forms considered by the Interim Chemical Review Committee at its third session.

PART B - PESTICIDE INCIDENT REPORT FORM

I. Product identity: *What formulation was used when the incident took place*

1. **Name of the formulation:** ***Granox TBC (10 cases)***.
2. Name of the active ingredient or ingredients in the formulation: *Thiram + Benomyl + Carbofuran*.
3. Relative amount of each active ingredient in the formulation: *Thiram 15% + Benomyl 7%+ Carbofuran 10%*
4. Trade name and name of producer, if available: *Granox TBC (producer: Senchim AG*).
5. Type of formulation: *Dustable powder (DP).*
6. Attach copy of the label(s), if available: *Labels are available, detailed information can be found in Section 3 of the DGD.*

II. Description of the incident: *How the formulation was used.*

7. Date of incident: *from July to September 2000 with a maximal peak in August.*
8. Location of incident: *districts Kolda and Sedhiou of Senegal*
9. Sex: *10 males* Age: *from 22 to 60 years*
10. Main activity at time of exposure: *peanut seed treatment*.
11. Protective clothing used during application: *no in all 10 cases*
12. Information on how product was being used: *Field/garden in all 10 cases*.

    List the animals/crop(s)/stored products treated if relevant: *peanuts*

    Application method: *by hand in 9 cases and 1 case unknown*.

Application rate (or use patterns, e.g. l/ha):

- *one application as seed treatment and another at sowing 9/10 cases*
- *one application as seed treatment 1/10 cases*

Duration of the exposure period:

- *seed treatment 0.5 to 3h in all 10 cases*
- *sowing 3-4 half days 6/10 cases*
  3-4 days 3/10 cases
  7-8 days 1/10 cases

Amount/level of potential exposure:

- *1-2 bags 4/10 cases*
- *3 or more bags 6/10 cases*

Did exposure occur to product as purchased? *Yes in all 10 cases*

Was more than one pesticide mixed together for application? *In all 10 cases a single formulation containing three active ingredients (thiram, benomyl, carbofuran) was used*

13. If more than one pesticide formulation/active ingredient was used at the same time, please respond to points i) to iv) below for each formulation/active ingredient.

I) Was the pesticide in its original container? *Yes in all 10 cases*

ii) Was the label available? *Yes in all 10 cases*
If yes, was exposed individual able to read and understand label? *No in all 10 cases*

iii) Does the label include the reported use? *Yes in all 10 cases*

iv) Is the reported incident typical of how the formulation is generally used? *Yes in all 10 cases*

14. Climatic conditions under which the incident occurred: *Hot and humid in all 10 cases*

15. Were there other individuals involved in the same incident? *Yes in all 10 cases*.

16. Include any other details.

III. Description of adverse effects:

17. Individual's reaction :

Three deaths with individuals showing three or more of the following symptoms: dyspnea, chest pain, tachycardia, coughing, rhinitis, abdominal pain, vomiting, diarrhea, icter (jaundice), tiredness, oedema, heat in the chest and abdomen, modification of urine (unspecified), dizziness, fever, hallucination.

18. Route of exposure:
    - *mouth, skin, inhalation (6 cases)*
    - *skin, inhalation(2 cases)*
    - *mouth, skin, inhalation, eyes (2 cases)*

19. How soon after starting handling the formulation were the adverse effects observed*:
    - *a few hours 1/10 cases*
    - *3 days 1/10 cases*
    - *2.5 to 3.5 months after starting handling the pesticides 8/10 cases*

    **The interim Chemical Review Committee considered that the time after starting to handle the pesticide was not always the same as the time between the last exposure and observation of the adverse effects.*

IV. Management:				
20.	Treatment given:	*No in 1 case*	*Yes in 7 cases*	*Unknown in 2 cases*
	First aid administered:	*No in 1 case*	*Yes in 3 cases*	*Unknown in 6 cases*
	Hospitalization:	*No in 7 cases*	*Yes in 2 cases*	*Unknown in 1 case*

PART B - PESTICIDE INCIDENT REPORT FORM

I. Product identity: *What formulation was used when the incident took place*

1. **Name of the formulation:** ***Spinox T (12 cases)***.
2. Name of the active ingredient or ingredients in the formulation: *Thiram + Benomyl + Carbofuran*.
3. Relative amount of each active ingredient in the formulation: *Thiram 15% Benomyl 7% Carbofuran 10%*
4. Trade name and name of producer, if available: *Spinox T (producer: SPIA).*
5. Type of formulation: *Dustable powder (DP).*
6. Attach copy of the label(s), if available: *Labels are available, detailed information can be found in Section 3 of the DGD.*

II. Description of the incident: *How the formulation was used.*

7. Date of incident: *one case in February, one case in April and others from June to September 2000 with a maximal peak in August.*
8. Location of incident: *districts Kolda and Sedhiou of Senegal*
9. Sex: *10 males, one female and 1 unknown* Age: *from 19 to 48 years.*
10. Main activity at time of exposure: *peanut seed treatment*.
11. Protective clothing used during application: *no in all 12 cases*
12. Information on how product was being used: *Field/garden in all 12 cases*.

    List the animals/crop(s)/stored products treated if relevant: *peanuts*.

    Application method: *by hand in 11 cases and 1 case unknown*.

    Application rate (or use patterns, e.g. l/ha):
    - *one application as seed treatment and another at sowing 6/12 cases*
    - *2-3 applications total as seed treatment and/or sowing 5/12 cases*
    - *more than 3 applications total as seed treatment and sowing 1/12 cases*

    Duration of the exposure period:
    - *seed treatment: 0.5-3 hours 9/12 cases*
    - *sowing: 2-5 half days 7/12 cases*
      3-4.5 days 2/12 cases
    - *unspecified: 3 days 1/12 cases*
      4-5 hours over 3-4 days 2/12 cases

Amount/level of potential exposure:

- *1-2 bags 6/12 cases*
- *3 or more bags 5/12 cases*
- *unknown 1/12 cases*

Did exposure occur to product as purchased? *Yes in all 12 cases*

Was more than one pesticide mixed together for application? *In all 12 cases a single formulation containing three active ingredients (thiram, benomyl, carbofuran) was used.*

13. If more than one pesticide formulation/active ingredient was used at the same time, please respond to points i) to iv) below for each formulation/active ingredient.

I) Was the pesticide in its original container? *Yes in all 12 cases*

ii) Was the label available? *Yes in all 12 cases*
If yes, was exposed individual able to read and understand label? *No in 11 cases*

iii) Does the label include the reported use? *Yes in 11 cases*

iv) Is the reported incident typical of how the formulation is generally used? *Yes in all 12 cases*

14. Climatic conditions under which the incident occurred: *Hot and humid in all 12 cases*

15. Were there other individuals involved in the same incident? *Yes in all 12 cases*.

16. Include any other details.

III. Description of adverse effects:

17. Individual's reaction:
Two deaths with individuals showing three or more of the following symptoms:
fever, dyspnea, oedema, tachycardia, coughing, rhinitis, abdominal pain, modification of urine (unspecified), shiver, chest pain, dizziness, insomnia, headache, diarrhea, anorexia, gastric pain
pain in left arm, vomiting, tiredness.

18. Route of exposure:

- *mouth, skin, inhalation (7 cases)*
- *skin, inhalation (4 cases)*
- *mouth, inhalation (1 case)*

19. How soon after starting handling the formulation were the adverse effects observed:

- *2 days 1/12 cases*
- *1 to 4 weeks 2/12 cases*
- *1 to 2 months 4/12 cases*
- *3 to 4 months 5/12 cases*

**The interim Chemical Review Committee considered that the time after starting to handle the pesticide was not always the same as the time between the last exposure and observation of the adverse effects*

IV. Management:				
20.	Treatment given:	*No in 1 case*	*Yes in 9 cases*	*Unknown in 2 cases*
	First aid administered:	*No in 1 case*	*Yes in 2 cases*	*Unknown in 9 cases*
	Hospitalization:	*No in 7 cases*	*Yes in 2 cases*	*Unknown in 3 cases*

For further information, the Designated National Authority for Senegal is:

Monsieur le Directeur
Direction de l'Environnement
Ministère de l'Environnement et de la Protection de la Nature
Dakar, BP 6557
23, Rue Calmette
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Telex 3248 COMIDES SG

Annex II Safety data sheet on pesticide active ingredient

WHO/FAO DATA SHEET ON PESTICIDES No. 87

BENOMYL

It must be noted that the issue of a Data Sheet for a particular pesticide does not imply endorsement of the pesticide by WHO or FAO for any particular use, or exclude its use for other purposes not stated. While the information provided is believed to be accurate according to data available at the time when the sheet was compiled, neither WHO nor FAO are responsible for any errors or omissions, or any consequences therefrom.

CLASSIFICATION:
Primary use: Systemic fungicide
Secondary use: Acaricide, mite ovicide
Chemical group: Benzimidazole carbamate

1.0 GENERAL INFORMATION

1.1 COMMON NAME: Benomyl (ISO)

1.1.1 Identity:
IUPAC chemical name: Methyl 1-[(butylamino)carbonyl]-1H- benzimidazol-2-ylcarbamate
CAS chemical name: Carbamic acid, [1-(butylamino)carbonyl]- 1H-benzimidazol-2-yl]-, methyl ester.
CAS registry number: 17804-35-2
RTECS registry number: DD6475000
Molecular formula: $C_{14}H_{18}N_4O_3$
Relative molecular mass: 290.3
Structural formula:

Trade names and synonyms: Benlate^{R};Tersan^{R}; Fungicide 1991; methyl 1-(butylcarbamoyl)-2-benzimidazolecarbamate.

1.2 SYNOPSIS: Benomyl is a systemic, broad spectrum benzimidazole carbamate fungicide. Acute toxicity is low, and there is no evidence of accumulation. It is only mildly irritant to skin and eyes, but sensitizes skin. Foetotoxic and teratogenic effects have been observed in laboratory animals following gavage administration of high doses, but not following dietary exposure. Inhalation and oral exposure reduced spermatogenic activity in laboratory animals.

1.3 SELECTED PROPERTIES

1.3.1 Physical characteristics: A tan-coloured odourless crystalline solid which decomposes at 140 °C just after melting. Technical benomyl is greater than 98% (w/w) pure.

1.3.2 Solubility: In water at 25 °C and pH 5 its solubility is 3.6 mg/L. Soluble in several organic solvents, especially heptane and chloroform (40 and 9.4 g/100 g solvent at 25 °C respectively).

1.3.3 Stability: Rapidly hydrolysed in dilute aqueous solutions and in soil to butyl isocyanate and the fungicide methyl-2-benzimidazole carbamate (carbendazim). Decomposed by strong acids and alkalis. Stable to light.

1.3.4 Vapour pressure: Negligible (less than 5×10^{-6} Pa).

1.4 AGRICULTURE, HORTICULTURE AND FORESTRY

1.4.1 Common formulations: Wettable powder (50%) and oil dispersion (50%). In combination with other pesticides as a wettable powder (10-50%) or as a dust (6%).

1.4.2 Pests mainly controlled: Controls a wide range of fungal diseases of fruits, nuts, vegetables, field crops, turf and ornamentals. Powdery mildew, apple scab and grey mould fungus are well controlled. It is also effective against mites.

1.4.3 Use pattern: Effective as a pre-harvest systemic fungicide, and as a post-harvest dip or dust treatment for the protection of fruits, seeds and vegetables in storage. Compatible in mixtures with non-alkaline pesticides.

1.4.4 Unintended effects: Toxic to fish and to earthworms.

1.5 PUBLIC HEALTH PROGRAMMES: No recommended usage.

1.6 HOUSEHOLD USE:

1.6.1 Common formulations: Wettable powder (50%), wettable powder (2%) in combination with other pesticides.

1.6.2 Pests mainly controlled: Powdery mildew, botrytis, fusarium basal rot, black spot and blossom rot.

1.6.3 Use pattern: As a spray application to ornamentals, domestic fruit, trees and lawns. Application procedures and re-application intervals should be made according to manufacturers' directions.

2.0 TOXICOLOGY AND RISKS

2.1 TOXICOLOGY - MAMMALS

2.1.1 Absorption route: Benomyl is readily absorbed after oral and inhalation exposure, but much less following dermal exposure.

2.1.2 Mode of action: Benomyl and its main metabolite carbendazim bind to microtubuli, an essential structure of all cells, thereby interfering with their functions (cell division, intracellular transports, etc.). Selective toxicity of benomyl is thought to be due to its higher affinity for fungal as compared with mammalian microtubuli.

2.1.3 Excretion products: Benomyl is almost completely transformed and excreted in the urine as methly(5-hydroxy-1H-benzimidazol-2-yl)-carbamate (5-HBC) and to a less extent as carbendazim. 5-HBC is the major metabolite in milk.

2.1.4 Toxicity, single dose:
Oral LD_{50} Rat (M & F) „ 10 000 mg/kg b.w. (peanut oil) Rat (M & F) „ 10 000 mg/kg b.w. (aqueous suspension of Benlate^{R,} 53%a.i.)

Dermal LD_{50} Rabbit (M & F) 10 000 mg/kg b.w. (50% w.p.)

Inhalation LC_{50} - 4 hour exposure Rat >4.01 mg/L (50% w.p.) Dog >1.65 mg/L (50% w.p.) Oral administration of benomyl to rats and inhalation exposure to dogs caused testicular toxicity. Doses were >100 mg/kg and 1.65 mg/L for oral and inhalation exposure respectively.

Primary irritancy: Mild erythema was observed following application of an aqueous suspension of 25% benomyl to shaved guinea pig skin. Mild conjunctival irritation was observed in rabbit eyes following instillation of 10 mg of a dry powder formulation (5 mg a.i.) or 0.1 ml of an oil suspension (10 mg a.i.).

2.1.5 Toxicity, repeated doses:
Oral: Gavage studies in rats of various age showed that benomyl (200 mg/kg/day for 10 days and 45 mg/kg/day for about 80 days) caused reduced sperm count and various histopathological lesions of testes and epididymus indicating disruption of all stages of spermatogenesis.

Inhalation: Nose exposure of rats to benomyl (6 h/day for 90 days) caused degeneration of olfactory epitelium at 50 mg benomyl/m^3.

Dermal: Skin exposure of rabbits to 50% benomyl formulation equivalent to 1000 mg/kg (6 h/day, 5 days/week for 3 weeks) caused mild erythema and moderate desquamation of the sites of application. Testicular toxicity (degeneration of spermatogenic elements) was observed at microscopic examination. Benomyl was found to produce sensitization in guinea pigs.

Cumulation of compound: No evidence of cumulative residues was seen in the tissues of laboratory and domestic animals.

Cumulation of effects: No evidence of cumulative effects was observed in rats following gavage, dietary or inhalation exposure.

2.1.6 Dietary studies:
Short term: No signs of toxicity were observed in rats following 90 days administration of benomyl up to and including 2500 mg/kg/diet. In a 90-day study, beagle dogs received 0, 100, 500 and 2500 mg/kg/diet (up to 84 mg/kg b.w./day). Minor changes in clinical chemistry and some histopathological lesions observed, at the high dose level only, were probably not due to benomyl.

Long term: Administration of up to and including 2500 mg/kg diet to rats for two years was without adverse effect on growth, clinical chemistry, haematologic or histopathologic parameters. No adverse effects on clinical chemistry parameters or haematological indices were observed in male and female CD-1 mice receiving up to 5000 mg/kg/diet for two years. Compound related changes were found in the absolute and relative liver weights for males (highest dose) and females (up to and including 1500 mg/kg diet). Male mice had decreased testes weights and testes degeneration at the highest dose.

2.1.7 Supplementary studies of toxicity:

Carcinogenicity: Rats were exposed up to 2500 mg/kg benomyl in the diet for two years and no oncogenic effects were detected. Mice were exposed to 0, 500, 1500 and 5000 mg/kg/diet for two years. The incidence of hepatocellular adenomas and carcinomas in female mice was increased in a dose-dependent manner. In male mice, the number of hepatocellular adenomas and carcinomas were significantly increased at 500 and 1500 mg/kg but not at 5000 mg/kg dose. The increased number of lung alveolar carcinomas in male mice was still within the range of historical controls.

Teratogenicity: A mouse gavage study (0, 50, 100 and 200 mg/kg per day on days 7 to 17 of gestation) showed teratogenic effects at all dose levels. Abnormalities included; exencephaly, hydrocephaly, cleft palate, hydronephrosis, polydactyly, oligodactyly, umbilical hernia, fused ribs, fused vertebrae and short/kinky tail. Teratogenicity was also observed in a rat gavage study (0, 3, 10, 30, 62.5 and 125 mg/kg per day on days 7 to 16 of gestation). Malformations included, microphthalmia, anophthalmia and hydrocephaly. The NOEL was 30 mg/kg benomyl. In another study in rats the NOEL for similar teratogenic effects was found to be 31.2 mg/kg. In a rat study aimed at evaluating the effects of low levels of benomyl as the pups aged the compound was administered by gavage at dose levels of 0, 15.6, and 31.2 mg/kg per day from day 7 of gestation to day 15 of lactation). No teratogenicity was found but testes weight was significantly reduced in males given 31.2 mg/kg. A further gavage study in rats produced similar teratogenic effects at 62.4 mg/kg per day on day 7 - 21 of gestation. The incidence of these effects increased when a semipurified protein- deficient diet was given together with the same level of benomyl. Some malformations (primarily hydrocephaly) also appeared at the lower dose when the same diet was provided.

Reproduction: No adverse effect was observed in a three generation reproduction study with ChR-CD rats receiving 2500 mg/kg diet (the maximum dose administered). Pre-pubertal exposure of Sprague-Dawley rats to 10 daily gavage doses of 200 mg technical benomyl/kg b.w./day in oil had no effect on the time of puberty onset or on the sperm count at that time. However, the same regimen caused depression of the total epididymal and vas deferens sperm counts at doses of 200 or 400 mg/kg b.w./day in adult rats. At the 400 mg/kg b.w./day dose the testes weights were maintained but showed evidence of hypospermatogenesis. Dietary administration of 1, 6.3 or 203 mg/kg (diet) for 70 days had no effect on reproductive behaviour of adult Wistar rats. Decreased ejaculate sperm concentration was observed in the high dose group and testes weights were decreased at all doses. Both effects were reversed during a 70 day recovery period. Permanent reductions were observed in the size of testes and male accessory glands in 100 day old offspring of Wistar rat dams receiving 31.2 mg benomyl/kg b.w./day on gestation day 7 through to day 15 of lactation. Reduced spermatogenic activity has been reported in rats following acute inhalation exposure, acute and sub-chronic oral exposure and dogs following a single four hour inhalation exposure (section 2.1.4).

Mutagenicity: In a dominant lethal mutation study administration of upto 203 mg benomyl/kg/diet for 46-53 days to Wistar rats, or 2500 mg/kg/diet for 7 days to ChR-

CD rats did not induce mutations. Intraperitoneal administration of 1000 mg benomyl/kg b.w. to rats induced mitotic arrest in bone-marrow cells within four hours of dosing. Serum from these rats collected 30 minutes after dosing was cytotoxic to mammalian cell lines *in vitro*. Orally administered doses of 1000 mg/kg b.w. did not affect the bone marrow, and the serum was only weakly cytotoxic. Benomyl was not mutagenic in *Escherichia coli* WP2 hcr, or *Salmonella typhimurium,* nor in mitotic gene conversion studies in *Saccharomyces cerevisiae,* but was a mitotic spindle poison in *Aspergillus nidulans* .

2.2 TOXICOLOGY - MAN

2.2.1 Absorption route: No specific information published but animal data suggest rapid absorption from the gastro- intestinal tract, and by the inhalation route. Benomyl is probably absorbed only slowly through intact skin.
2.2.2 Dangerous doses:
Single: No published information available.
Repeated: No published information available.

2.2.3 Observations on occupationally exposed workers: No inadvertent poisoning of agricultural or forestry workers has been documented. Benomyl caused contact dermatitis and dermal sensitization in some farm workers. Cross-sensitization between benomyl and other pesticides such as diazinon, daconil, saturon and 2-bordeaux has been reported. Blood profiles from workers involved in the manufacture of benomyl were not different from those of a control group of workers. Workers exposed for 1-95 months during benomyl manufacture were examined for reproduction performance. There was no reduction in fertility as shown by the birth rates, which were generally higher than those of the control populations.

2.2.4 Observations on exposure of the general population: No published information available. With good agricultural practice, exposure of the public to hazardous quantities of benomyl is unlikely.

2.2.5 Observations on volunteers: No published information available.

2.2.6 Reported mishaps: None reported.

2.3 TOXICITY - NON-MAMMALIAN SPECIES

2.3.1 Fish:
LC_{50} (96 hour): Carp 7.5 mg/L
Fathead minnow 2.2 mg/L
Bluegill 1.3 mg/L
Rainbow trout 0.17 mg/L
Channel catfish 0.031 mg/L

2.3.2 Birds:
LC_{50} (5 days): Mallard duck > 10 000 mg/kg diet
Bobwhite quail > 10 000 mg/kg diet
Body weight gain, feed consumption and egg production in Leghorn hens were unaffected by 25 mg benomyl/kg diet (as Benlate^{R} 50% w.p.) for 28 days. No residues were found in the fat or breast tissue. A low concentration of the methyl 5-hydroxy-metabolite was found in the eggs during exposure, but not 7 days after cessation of exposure.

2.3.3 Beneficial insects:
Benomyl is not toxic to bees.

2.3.4 Other species:
LC_{50} : *Daphnia magna* 0.64 mg/L
Exposure of earthworms to residues or suspensions of benomyl may have a delayed lethal effect. Low concentrations on the foliage may suppress feeding. Reduced populations of earthworms have been reported in benomyl treated orchards.

3.0 FOR REGULATORY AUTHORITIES - RECOMMENDATIONS OF COMPOUND

3.1 RECOMMENDED RESTRICTIONS ON AVAILABILITY [For definition of categories see the 'Introduction to Data Sheets']. All liquid formulations of 50% or less and all solid formulations - Category 5

3.2 TRANSPORT AND STORAGE
Formulations in Category 5: Should be stored and transported in clearly labelled leakproof containers out of the reach of children, away from food and drink.

3.3 HANDLING
Formulations in Category 5: Handling of large quantities of solid formulations (2 kg bags or greater) requires use of a dust mask and protective clothing (see section 4.1.3 - 4.1.4). For handling small quantities and liquid formulations no facilities other than those required for handling of any chemical are required.

3.4 DISPOSAL AND/OR DECONTAMINATION OF CONTAINERS Decontamination of containers is probably not practical due to the low water solubility of benomyl. Containers must be disposed of in an approved manner. Care must be taken to avoid contamination of water sources.

3.5 SELECTION, TRAINING AND MEDICAL SUPERVISION OF WORKERS
Formulations in Category 5: Warning of workers to minimize contact is essential particularly in view of the sensitizing effects of benomyl.

3.6 ADDITIONAL REGULATIONS RECOMMENDED IF DISTRIBUTED BY AIRCRAFT
All formulations: Benomyl is normally not distributed by aircraft. If it is, pilots and loaders should have special training in application methods. All workers must wear a dust mask, overalls and impermeable gloves.

3.7 LABELLING Formulations in category 5 - Minimum cautionary statement. This formulation contains the fungicide benomyl which is poisonous if swallowed or if the dust is inhaled. Keep out of reach of children and pets, and well away from foodstuffs or animal feeds.

3.8 RESIDUES IN FOOD Maximum levels have been recommended for a variety of agricultural products and foodstuffs by the FAO/WHO Joint Meeting on Pesticide Residues on Food and the Environment. In 1983 the JMPR established an Acceptable Daily Intake (ADI) of 0-0.02 mg/kg/b.w.

4.0 PREVENTION OF POISONING IN MAN AND EMERGENCY AID

4.1 PRECAUTIONS IN USE

4.1.1 General: Benomyl is a benzimidazole fungicide. Acute toxicity of benomyl is low, but it has the potential of causing sensitization.

4.1.2 Manufacture and formulation: TLV 10 mg/m^3. Dusts should be controlled, preferably by mechanical means. Protective equipment for respiratory tract and skin is necessary.

4.1.3 Mixers and applicators: Light respiratory protection should be used when handling dusty formulations. For all formulations clean overalls and gloves should be used to prevent skin contamination. When opening the container and when mixing, care should be taken to avoid contact with the eyes and mouth. Mixing if not mechanical, should always be carried out with a paddle of appropriate length. The applicator should avoid working in spray mist and avoid contact with the mouth. Splashes must be washed from the skin or eyes immediately with large volumes of water. Before eating, drinking or smoking, hands and exposed skin should be washed.

4.1.4 Other associated workers: Persons exposed to benomyl and associated with its application should wear protective clothing and observe the precautions described above in 4.1.3. under "Mixers and Applicators".

4.1.5 Other populations likely to be affected: Subject to 4.2 below, other persons are not likely to be exposed to hazardous amounts of benomyl.

4.2 ENTRY OF PERSONS INTO TREATED AREAS

No exclusion from treated areas is indicated.

4.3 DECONTAMINATION OF SPILLAGE AND CONTAINERS Residues in containers should be buried in a deep dry pit (>0.5 m) taking care to avoid contamination of water sources. Spillage of liquid formulations should be contained and absorbed by absorbent material. This material, or spillage of dry formulations, should be collected and buried in a deep dry pit. Care must be taken to avoid contamination of water sources. Residues should be washed from the spillage site with water and detergent.

4.4 EMERGENCY AID

4.4.1 Early symptoms of poisoning: No details reported.

4.4.2 Treatment before person is seen by physician, if these symptoms appear following exposure: The person should stop work immediately, remove contaminated clothing and wash contaminated skin with soap and water and flush with large volumes of clean water. If the eyes are contaminated, they should be flushed with large volumes of clean water.

5.0 FOR MEDICAL AND LABORATORY PERSONNEL

5.1 MEDICAL DIAGNOSIS AND TREATMENT IN CASE OF POISONING

5.1.1 General information: Benomyl is a benzimidazole fungicide of low acute toxicity. At high doses benomyl has been shown in animals to be teratogenic and to cause testicular changes.

5.1.2 Symptoms and signs: No cases of human poisoning have been recorded.

5.1.3 Laboratory: No tests in humans to measure exposure have been reported.

5.1.4 Treatment: Symptomatic, because no specific antidote is available. In the case of skin contamination the exposed area should be washed with soap and water. If the compound has entered the eyes they should be washed with copious volumes of isotonic saline or water.

5.1.5 Prognosis: Unknown.

5.1.6 References to previously reported cases: No reports.

5.2 SURVEILLANCE TESTS: There are no readily available field techniques to determine the degree of exposure.

5.3 LABORATORY METHODS

5.3.1 Detection and assay of compound and residues: Assay methods may not distinguish between benomyl and methyl 2- benzimidazole carbamate, which forms rapidly when benomyl is in aqueous solution. Douch PGC (1973), *Xenobiotica*, 3(6), 367-383. Kirkland JJ, Holt RH, Pease HL (1973), J Agric Food Chem, **21(3)**: 368-371. Pressley TA, Longbottom JE (1982), The determination of benomyl and carbendazim in Municipal and Industrial Wastewater. Method 631. EPA-600/4-82-012. PB82-156068. Teubert W, Stringham R (1984), J Assoc Off Anal Chem **67(2)**: 303-305.

5.3.2 Other tests in case of poisoning: None.

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DATA SHEET ON PESTICIDES No. 56

CARBOFURAN

CLASSIFICATION:
Primary use: Insecticide
Secondary use: Nematocide
Chemical Group: Carbamate
Date issued:

1. GENERAL INFORMATION

1.1 COMMON NAME: Carbofuran (ISO, BSI and ANSI)

1.1.1 Identity:

IUPAC: 2,3-dihydro-2,2-dimethylbenzofuran-7-yl methylcarbamate
CAS No. 1: 2,3-dihydro-2,2-dimethyl-7-benzofuranyl methylcarbamate
CAS Reg. No.: 1563-66-2
Molecular formula: $C_{12}H_{15}NO_3$
Molecular weight: 221.3
Structural formula: _Structural formula;pest56.bmp

1.1.2 Synonyms: Bay 70143; Carbofuran; Curaterr^R; ENT 27,164; FMC 10242; Furadan^R; Niagara 10242^R; Yaltoxi^R.

1.2 SYNOPSIS: Carbofuran is a broad spectrum, non-cumulative carbamate insecticide; a cholinesterase inhibitor with contact and stomach action and highly toxic to mammals. It is a systemic with no phytotoxic action.

1.3 SELECTED PROPERTIES

1.3.1 Physical characteristics - Carbofuran is a colourless (white) crystalline solid. It has a melting point of 150-152°C, a density (d^{20}_4) of 1.180. The technical material contains 98.8% active ingredient. It is non-corrosive and non-flammable.

1.3.2 Solubility - Water 700 mg/l, 25°C 1-methyl-2-pyrrolidione 300 g/kg, 25°C Dimethylformamide 270 g/kg, 25°C Dimethylsufoxide 250 g/kg, 25°C Acetone 150

g/kg, 25°C Acetonitrile 140 g/kg, 25°C Methylene chloride 120 g/kg, 25°C Cyclohexanone 90 g/kg, 25°C Benzene 40 g/kg, 25°C Ethanol 40 g/kg, 25°C Carbofuran is virtually insoluble in conventional solvents of agricultural formulations.

1.3.3 Stability - It is stable under neutral or acidic conditions but unstable in alkaline media.

1.3.4 Vapour pressure - 2.66 x 10^{-6} kPa (2 x 10^{-5} mmHg), 33°C 1.33 x 10^{-5} kPa (1 x 10^{-4} mmHg), 50°C

1.4 AGRICULTURE, HORTICULTURE AND FORESTRY

1.4.1 Common formulations - Flowables (100, 120, 300, 350, 480 g a.i./l) granules (20, 30, 50, 100 and 150 g a.i./kg).

1.4.2 Pests controlled - Carbofuran is effective against a wide range of foliar-feeding and soil pests including nematodes, corn rootworm, rice water weevil, wireworms, sugar-cane borer, alfalfa weevil, alfalfa snout beetle, armyworms, European corn borer, flea beetle, aphids, thrips, hornworms and others.

1.4.3 Use pattern - Carbofuran may be applied to alfalfa, corn, peanuts, peppers, strawberries, tobacco, bananas, sorghum, potatoes, cottonwood trees, sugar-cane, and rice. It may be applied to foliage at 0.25-1.0 kg a.i./ha; in a 7 inch band or in seed furrows at planting time at 0.5-4.0 kg/ha; and, as a soil treatment incorporated into the top 1 inch of soil. On rice, apply before or within 21 days after flooding. It is compatible with other non-alkaline pesticides and fertilizers.

1.4.4 Unintended effects - Carbofuran is not phytotoxic when used as directed.

1.5 PUBLIC HEALTH USE - No recommended use.

1.6 HOUSEHOLD USE - No recommended use.

2. TOXICOLOGY AND RISKS

2.1 TOXICOLOGY - MAMMALS

2.1.1 Absorption - Carbofuran may be absorbed from the gastrointestinal tract; minimally through the intact skin; and, by inhalation of spray mists or dusts.

2.1.2 Mode of action - Carbofuran is a reversible, direct inhibitor of cholinesterases through carbamoylation of the esteratic site of the enzyme. Accumulation of acetylcholine at nerve synapses and myoneural junctions causes the toxic effects. The carbamoylated enzyme undergoes spontaneous and rapid reactivation. Carbofuran and its ester metabolites are active.

2.1.3 Excretion products - The metabolism and excretion of carbofuran have been well studied in rats, mice and lactating cows. The per oral dose is rapidly absorbed, degraded and eliminated. In mammals mixed function oxidases are chiefly responsible for metabolism; 3-hydroxycarbofuran and 3-ketocarbofuran are the most common carbamate metabolites. 3-Hydroxy-N-hydroxycarbofuran is also produced to some extent in all the test animals except the mouse. Hydrolysis of the carbamoyl ester bond also occurs, producing 3-ketocarbofuran phenol followed by carbofuran phenol and 3-hydroxyphenol. These degradation products are primarily excreted as conjugates of glucuronic acid and sulfate.

In rats, 87% of the radioactivity from carbonyl ^{14}C labelled carbofuran (p.o.) is eliminated within 48 hours, 45% as $C0_2$ in expired air, 38% in urine and 4% in faeces. When ring-labelled carbofuran is fed to cows and rats, nearly all of the ^{14}C is eliminated in urine (92% in 32 hours), none is exhaled and less than 3% is found in faeces. In milk cows, less than 3% is found in milk following per oral and fistula administration.

2.1.4 Toxicity, single dose

Oral LD_{50}:
Rat (M, F) 8.8 mg/kg bw (technical)
Rat (weanling male) 8.06 mg/kg bw (technical)
Rat (weanling female) 5.91 mg/kg bw (technical)
Dog +15.38 mg/kg bw (technical)
Mouse 14.4 mg/kg bw (technical)
Cat 2.5-3.5 mg/kg bw (technical) Rabbit 7.5 mg/kg bw (technical)
Guinea-pig 9.2 mg/kg bw (technical)

Dermal LD_{50}:
Rat 2 000 mg/kg bw* (technical)
Rabbit 2 000 mg/kg bw* (technical)

Inhalation LC_{50}:
1 hour
Rat (M) 0.091-0.108 mg/l (dust)
Rat (F) 0.080 mg/l (dust)
4 hours
Rat (M, F) 0.120 mg/l (50 W.P.)
Rat (M, F) 0.085 mg/l (80 W.P.)
Dog (M) 0.052 mg/l (50 W.P.)
Guinea-pig (M, F) 0.053 mg/l (75 W.P. aerosol)
Guinea-pig (M, F) 0.043 mg/l (75 W.P. dust)

I.P. LD_{50}:
Rat (M) 8.2 mg/kg bw (75% W.P.)
Rat (F) 2.8 mg/kg bw (75% W.P.) *
Manufacturer provided information.
In an acute intubation study using female rats, it was found that brain cholinesterase was more sensitive to carbofuran than plasma and erythrocyte cholinesterase respectively.

2.1.5 Toxicity, repeated doses

Oral: Groups of female rats were administered carbofuran by gavage at a dosage level of 1.0 mg/kg/day for 28 days. Cholinesterase activity was monitored at 1, 2, 6 and 24 hours after administration on days 14 and 28. Brain cholinesterase activity was the most affected, reaching maximal depression by six hours on both testing days; erythrocyte activity was least affected. The treatment activity values appeared comparable to control values at 24 hours post treatment. Similar results were observed in a 90-day intubation study with male and female rats receiving dosage levels of 0, 0.1, 0.3, 1.0 and 3.0 mg/kg bw/day. In this study, maximum erythrocyte and plasma activity depressions at the highest dosage level (3.0 mg/kg bw/day) occurred within one hour of administration after three weeks of treatment. Normal activity was re-established within 24 hours. No changes were observed at levels of 0.3 mg/kg bw or

below. These studies demonstrated the rapid and transient nature of in vivo cholinesterase depression by carbofuran.

Dermal: Groups of male and female rabbits received dermal applications of carbofuran 50% wettable powder at dosage levels of 0, 0.5, 1.0 and 2.0 mg/kg bw/day for 20 successive days. Mortality appeared to be dose-related. Decreased body weights, inflammatory skin lesions and decreased general activity were observed in all treatment groups during the test period. The lesions disappeared within five days of cessation of treatment and there were no treatment-related biochemical or histopathological changes.

Inhalation: Groups of mice and female guinea-pigs were exposed to carbofuran aerosol formulation at a concentration level of 0.01 mg/m^3 (air) for four hours a day, five days a week for three weeks. There were no compound-related changes in mortality rates, behaviour, haematology, biochemistry or histopathology.

Sensitization: No sensitization reactions were produced in guinea-pigs following challenge doses administered two weeks after daily subcutaneous injections of carbofuran.

Cumulation of compound: Carbofuran is not accumulated in body tissue.

Cumulation of effect: Carbofuran did not produce any cumulation of effect in several studies with multiple dosing.

2.1.6 Dietary studies

Short-term: Groups of male and female rats were offered varying levels of carbofuran in the diet for 90 days. Initially, carbofuran was incorporated into the diet at dosages of 0, 0.1, 0.4, 2.0, 10 and 25 mg/kg diet. Subsequently, the dietary levels of carbofuran were progressively increased on days 22-35, 36-49 and 50-90 to yield final concentrations of 0, 1.6, 6.4, 32, 160 and 1600 mg/kg diet. No mortality occurred during the study period. Intermittent tremors and episodes of incontinence were observed among females receiving the 1600 mg/kg diet. Depressed growth rates were noted at dietary levels of 100 mg/kg and above and persisted to the end of the test period at levels of 160, 400 and 1600 mg/kg diet. However, this finding appeared to be related to poor diet palatability. Haematological and urological values were unaffected and gross and microscopic pathological findings were comparable. Cholinesterase activity was not monitored. No effects were observed among the three lowest dosage groups.

A 14-day feeding study was conducted with carbofuran using groups of male and female rabbits. Dietary concentrations of 0, 70, 210 and 700 ppm did not produce mortality or untoward behavioural effects. Body weight reductions were observed within the group receiving the 700 ppm diet.

Carbofuran was administered at dosages of 0, 0.025, 0.25, 1.25, 2.5 and 5.0 mg/kg/day by gelatin capsule to groups of male and female dogs for 93 continuous days. Clinical signs of acetylcholine poisoning were observed within the groups receiving either 2.5 or 5.0 mg/kg/day. Plasma and erythrocyte cholinesterase activities were within normal limits when monitored four hours before and one hour after daily dosing. At 5.0 mg/kg, some depression of plasma and erythrocyte cholinesterase activities were observed when samples were drawn 15, 30, 45 and 60 minutes following carbofuran administration on day 72 and after extended dosing, again on day 113.

Long-term: In a two year study, groups of male and female rats were offered diets containing 0, 10, 20 or 100 ppm of carbofuran. Males exposed to 100 ppm exhibited slightly lower group mean body weights. Depressed plasma, erythrocyte and brain cholinesterase activity values were noted for animals receiving the 100 ppm diet; no effects were observed at the 10 or 20 ppm levels. There were no treatment-related effects on mortality, food consumption, ophthalmology, haematology and clinical chemistry parameters, urinalysis and histopathology. The no- effect level (NOEL) was considered to be 20 ppm. Groups of male and female mice were exposed to carbofuran at dietary concentrations of 0, 20, 125 and 500 ppm for two years. Decreased body weights were noted at the 500 ppm level during weeks 1-65 for males and weeks 1-78 for females. However, this effect was not observed at study termination. Brain cholinesterase activity was depressed at the 6, 12 and 18 month intervals and at termination for animals exposed to 125 or 500 ppm carbofuran. No treatment-related effects were reported for mortality, haematology and clinical chemistry parameters, urinalysis and histopathology. The no-effect level (NOEL) was considered to be 20 ppm.

Carbofuran was administered to groups of male and female beagle dogs via dietary inclusion for two years. Initially, carbofuran was incorporated into the diet at concentrations of 0, 1, 10, 50 and 100 ppm and a level to establish the maximum tolerated dose (100 ppm for days 1-14 and 200 ppm during days 15-267). The 50 ppm diet was increased to contain 100 ppm of carbofuran on day 143 while all of the other dietary concentrations were fortified on day 268 yielding dietary levels of 0, 2, 20, 100, 200 and 400 ppm through termination. Mortality was reported for one female exposed to the 400 ppm diet; three males in the 400 ppm dietary group were sacrificed in extremis after at least 518 days on study. At 100 ppm, occasional coughing and gagging were observed; at 200 and 400 ppm, more severe signs of cholinergic toxicity were observed daily. Reduced mean body weights were also exhibited at the 400 ppm level. There were no treatment- related effects associated with food consumption, haematology and clinical chemistry parameters (cholinesterase activity was not monitored), urinalysis and histopathology. The no-effect level (NOEL) was considered to be 50 ppm.

2.1.7 Supplementary studies of toxicity

Carcinogenicity: In the long-term rat and mouse dietary studies described in section 2.1.6, carbofuran did not demonstrate any carcinogenic or tumorigenic potential at dietary levels up to and including 100 ppm for rats and 500 ppm for mice. No evidence of carcinogenicity or tumorigenicity was observed in the dog at dietary levels up to 400 ppm.

Teratogenicity: Carbofuran was administered daily by gavage to groups of pregnant female rats at dosages of 0 (corn oil only), 0.25, 0.50 and 1.20 mg/kg/day on gestation days 6 through 15. Caesarean sections were performed on all females on day 20 of presumed gestation. Foetuses were examined for soft tissue and skeletal abnormalities. Survival was 100% in all groups. All maternal and foetal parameters were comparable among the groups. Carbofuran was not teratogenic when administered by gavage at a dosage of 1.20 mg/kg/day.

Groups of pregnant female rabbits were administered carbofuran at dosage levels of 0, 0.12, 0.50 and 2.0 mg/kg/day by gavage during gestation days 6 through 18. On gestation day 29, all surviving dams were subjected to a Caesarean section and the foetuses were examined for skeletal and soft tissue abnormalities. At the 2.0 mg/kg/day dosage group, one dam died on gestation day 11. Depressed mean maternal

body weight gains were also reported for the 2.0 mg/kg/day dosage group. All other maternal and foetal parameters were comparable among the groups. There was no evidence of teratogenicity in this study at a dosage of 2.0 mg/kg/day.

A teratology and postnatal dietary study was conducted with carbofuran in the rat. Carbofuran was incorporated into the diet at concentrations of 0, 20, 60 and 160 ppm and administered to pregnant female rats only during gestation days 6 through 19. On gestation day 20, approximately half of the dams from each dosage group were submitted to Caesarean section and the foetuses were examined for skeletal and visceral abnormalities. The remaining dams were allowed to deliver and care for the pups for 21 post-partum days. At the end of the lactation period (post- partum day 21), the dams and pups were submitted to necropsy. Mean food consumption was slightly reduced in the 160 ppm group during the treatment period. Apparent dose-related mean maternal body weight losses occurred in the 60 and 160 ppm groups during the first two days of treatment (gestation days 6 and 7) and during the first 7 days of lactation.

A statistically significant ($P < 0.05$) reduction in mean pup body weight for the 160 ppm group animals was reported on lactation days 0, 4, 7, 14 and 21. Examination of the foetuses and pups did not reveal any teratogenic response in this study at a dietary concentration of 160 ppm.

Mutagenicity: A dominant lethal test was conducted with groups of male mice receiving intraperitoneal injections of carbofuran suspended in corn oil at dosages of 0.25 and 0.50 mg/kg. A vehicle control group received corn oil only while a positive control group was administered 100 mg/kg of methyl methane- sulfonate by the same route. Immediately following treatment, each male was housed with three untreated, virgin females and allowed to mate. This procedure was repeated weekly with a new group of untreated, virgin females for a total of six consecutive weeks. Mated females were sacrificed in mid-gestation for uterine examination. Carbofuran did not affect mating ability, frequency of pregnancy, the incidence of resorptions, preimplantation losses or the number of embryos per dam. Therefore, carbofuran was not considered to be mutagenic.

Carbofuran was evaluated for its mutagenic potential in a mitotic recombination assay using Saccharomyces cervisiae D3. Weight/volume concentrations of 0.1, 0.5, 1.0 and 5.0% were tested in the presence and absence of metabolic activation; 1,2,3,4-diepoxybutane (positive control) and a negative control were also tested. Carbofuran was considered to be non-mutagenic in this assay since it did not cause an increase in the number of absolute or relative mitotic recombinants. An Ames assay was conducted with carbofuran using five tester strains of Salmonella typhimurium. Two trials were conducted with six concentrations each, ranging between 1 and 1000 µg/plate and 10 to 5000 µg/plate, both in the presence and absence of metabolic activation. Positive controls (2-anthramine and N-methyl-N'- nitro-N-nitrosoguanidine) and a negative control were also tested. There was no increase in the number of revertants per plate for any of the tester strains in the presence or absence of metabolic activation. These results indicate that carbofuran was not considered to be mutagenic.

Escherichia coli WP_2 was used in a reverse mutation assay with carbofuran. Concentrations ranging between 1 and 1000 µg/plate and 10 to 5000 µg/plate were tested in the presence and absence of metabolic activation in two trials. Positive controls (2- anthramine, AF-2 and N-methyl-N'-nitrosoguanidine) and a negative control were also evaluated. Carbofuran did not cause an increase in the number of

revertants in the presence or absence of metabolic activation and was not considered to be mutagenic.

DNA repair assays were conducted using DNA repair-proficient and repair-deficient strains of Bacillus subtilis (H17 and M45, respectively) and Escherichia coli (W3110 and p3478, respectively) to evaluate the mutagenic and genotoxic potentials of carbofuran. Concentrations of 0.01, 0.10, 1.0 and 5.0 mg/disc were used in both bacterial assays. Chloramphenicol was used as the negative control, while 1-phenyl-3,3-dimethyltriazine served as the positive control. Carbofuran was not considered to be mutagenic or genotoxic in either bacterial assay.

Carbofuran was tested to assess its ability to induce unscheduled DNA synthesis in cultured human fibroblast cells (WI-38). Concentrations of 0.1, 1.0, 10, 100 and 1000 µg carbofuran/ml solvent were evaluated in the presence and absence of metabolic activation. In addition to a negative (solvent) control, dimethylnitrosamine and 4-nitroquinoline N-oxide were used as positive contols in the presence and absence of metabolic activation, respectively. The rate of unscheduled DNA synthesis was not increased in the presence or absence of metabolic activation by carbofuran.

Reproduction: Groups of male and female rats were maintained on diets containing concentrations of 0, 20 and 100 ppm of carbofuran for three generations (two litters per generation). Reproductive and general toxicological parameters were monitored. Mean parental body weights and food consumption were consistently lower within the 100 ppm dietary group. Reduced survival of F_1a, F_2a and F_3a litters on lactation day 4 and consistently lower pup body weights in all litters occurred within the 100 ppm group.

Dehydration was noted among some of the 100 ppm group F_3a and F_3b litters.

Fertility, gestation time, general behaviour, appearance and survival (parents only) were unaffected. At the completion of each generation, all parental animals and pups from the F_2b and F_3b litters were sacrificed and necropsied. No compound-related gross or microscopic changes were reported. Carbofuran did not produce any adverse effects on reproduction. The no-effect level (NOEL) in this study was 20 ppm. A one-generation reproduction study in beagle dogs was conducted with carbofuran at dietary levels of 0, 20 and 50 ppm. Natural mating was allowed during the second oestrus cycle. Survival, behaviour, body weights, food consumption, oestrus cycles, mating performance and gestation and lactation parameters were monitored for the parental animals. At birth, litter size, pup viability, survival, nursing ability, general behaviour and physical appearance were reported for each litter. Physical and neurological examinations were also conducted on each of the pups at birth. After one week of age, the pups were examined by X- rays to evaluate skeletal structure and general development. Gross pathological examinations were performed on one male and female pup per litter.

Carbofuran did not affect reproductive performance. There were no adverse effects attributed to carbofuran in the parental animals or progeny. The no-effect level (NOEL) in this study was 50 ppm.

Neurotoxicity: Carbofuran was evaluated to determine its potential to induce delayed neurotoxicity. A group of mature hens was orally administered 38.9 mg/kg (LD_{50}) of carbofuran and observed for signs of delayed neurotoxicity for 21 days. A positive control group received TOCP orally, at a dosage of 50 mg/kg. The dosage and observation period were repeated in the surviving birds since neurotoxicity was not observed during the initial 21-day observation period. The lack of neurotoxic effect

after the second administration and 21-day observation period indicated that carbofuran does not induce delayed neurotoxicity.

2.1.8 Modification of toxicity –

Equitoxic mixtures of carbofuran and other anticholinesterase agents were administered orally to male rats to determine if a potentiation effect on acute toxicity would result. The LD_{50} values were determined for carbofuran and the other compounds (Systox, Guthion, Trithion, Ethion, Phosphamidon, Dibrom, Diazinon, EPN, Delnau, Schradan, methyl parathion, sevin, RE 5353 and Phosdrin). The theoretical additive LD_{50} value for each mixture was calculated and compared to the value obtained in vivo. The results of these trials indicated that the acute oral toxicity of carbofuran was not potentiated when administered in combination with other anticholinesterase agents.

2.2 TOXICOLOGY - MAN

2.2.1 Absorption route - Carbofuran may be absorbed from the gastrointestinal tract; through the intact skin; and, by inhalation of spraymist or dusts.

2.2.2 Dangerous doses

Single: The acute oral LD_{50} is reported to be approximately 11 mg/kg bw, the dermal LD_{50} to be 10 000 mg/kg. The probable oral lethal dose is reported to be 5-50 mg/kg bw.

Repeated: Not known; because of rapid metabolism it probably differs little from the single dangerous dose.

2.2.3 Observations on occupationally exposed workers - Typical cases involving blurred vision, nausea, excessive perspiration and a sense of weakness have been reported among formulators and applicators. Uneventful recovery is reported to occur within a few hours even without therapy but it was faster when atropine was administered.

2.2.4 Observations on exposure of the general population - No information available, if recommended agricultural practices are followed, the general population will not be exposed to hazardous amounts of carbofuran.

2.2.5 Observations on volunteers - No information available.

2.2.6 Reported mishaps - In one episode, 142 boys and girls aged 13-16 were employed to remove tassles from corn the day after a field had been erroneously sprayed with carbofuran (carbofuran is not recommended for this purpose). By early afternoon 74 teenagers complained of symptoms of carbofuran poisoning, 40 of them were treated with atropine, 28 remained in hospital for a few hours and one patient remained overnight. The onset of symptoms was rapid but mild, recovery was also rapid.

2.3 TOXICITY TO NON-MAMMALIAN SPECIES

2.3.1 Fish - Carbofuran is very toxic to fish. LC_{50} (96 hours):

Bluegill 80 µg/l
Yellow perch 147 µg/l
Brown trout 280 µg/l
Lake trout 164 µg/l
Mosquito fish 300 µg/l
Coho salmon 524 µg/l
Steelhead 600 µg/l

2.3.2 Birds - Carbofuran is very toxic to birds and has been used as an avicide.

Oral LD_{50}: Domestic hen 6.0 mg/kg bw
Bobwhite quail 5.04 mg/kg bw
Ring-neck pheasant 4.15 mg/kg bw
Japanese quail (M) 1.9 mg/kg bw
Japanese quail (F) 1.7 mg/kg bw
House sparrow 1.3 mg/kg bw
Mallard duck 36 hours old 0.37 mg/kg bw
1 week old 0.63 mg/kg bw
4 weeks old 0.51 mg/kg bw
6 months old 0.42 mg/kg bw
Quella 0.42 mg/kg bw
Red-wing blackbird 0.42 mg/kg bw

Dermal LD_{50}: House sparrow 100 mg/kg bw
Quella 100 mg/kg bw

Dietary: The cumulative LD_{50} (10 days for pheasants) was 960 mg a.i. (as 10% granular)/kg of diet.

2.3.3 Other species - Carbofuran is highly toxic to a variety of beneficial invertebrates, the LD_{50} for honeybees is 0.16 µg/bee.

3. FOR REGULATORY AUTHORITIES

3.1 RECOMMENDED RESTRICTIONS ON AVAILABILITY

(For definition of categories see the Introduction to Data Sheets)
Liquid formulations of 4% and over, Category 2
Other liquid formulations, Category 3
Solid formulations of 16% and over, Category 2
Other solid formulations, Category 3

3.2 TRANSPORTATION AND STORAGE

All formulations - Should be transported and stored in labelled impermeable containers under lock and key, and secure from access by children and other unauthorized persons. No food or drink should be stored in the same compartment.

3.3 HANDLING

All formulations - Full protective clothing (see paragraph 4.3 in part 4) should be used by those handling the compound. Adequate washing facilities should be available at all times during the handling and should be close to the site of handling. Eating, drinking and smoking should be prohibited during handling and before washing after handling.

3.4 DISPOSAL AND/OR DECONTAMINATION OF CONTAINERS

All formulations - Container must either be burned or crushed and buried below topsoil. Care must be taken to avoid subsequent contamination of water sources. Decontamination of containers in order to use them for other purposes should not be permitted.

3.5 SELECTION AND TRAINING AND MEDICAL SUPERVISION OF WORKERS

All formulations - Pre-employment medical examination of workers necessary. Workers suffering from active hepatic or renal disease should be excluded from contact. Pre-employment and periodic cholinesterase test for workers desirable. Special account should be taken of the workers' mental ability to comprehend and follow instructions. Training of workers in techniques to avoid contact is essential.

3.6 ADDITIONAL REGULATIONS RECOMMENDED IF DISTRIBUTED BY AIRCRAFT

All formulations - Pilots and loaders should have special training in application methods and early symptoms of poisoning, and must wear a suitable respirator. Use of flagmen not recommended. Flagmen, if used, should wear protective clothing and be located well away from the dropping zone.

3.7 LABELLING

All formulations - "DANGER - POISON" (skull and cross-bones insignia). Carbofuran is a carbamate compound which inhibits cholinesterase enzymes. It is extremely toxic. Contact with the skin, inhalation of dust or spray, or swallowing should be avoided. Wear protective gloves, clean protective clothing, and a respirator of the organic-vapour type when handling this material. Bathe immediately after work.

Ensure that containers are stored under lock and key. Empty containers must be disposed of in such a way as to prevent all possibility of accidental contact with them. Keep the material out of reach of children and well away from foodstuffs, animal feed and their containers.

In case of contact, immediately remove contaminated clothing and wash the skin thoroughly with soap and water; for eyes, flush with water for 15 minutes. If poisoning occurs, call a physician. Atropine sulfate is a specific antidote and repeated doses may be necessary. Artificial respiration may be needed.

3.8 RESIDUES IN FOOD

Maximum residue levels - Maximum residue levels have been recommended by the Joint FAO/WHO Meeting on Pesticides Residues.

4. PREVENTION OF POISONING IN MAN AND EMERGENCY AID

4.1 PRECAUTIONS IN USE

4.1.1 General - Carbofuran is a carbamate pesticide of very high toxicity. It is an acute poison, absorbed by inhalation of dust and spray mist; from the gastrointestinal tract; and, to a lesser extent, through the intact skin. Most formulations should be handled by trained personnel wearing suitable protective clothing.

4.1.2 Manufacture and formulation - TLV - (ACGIH) 2.5 mg/m^3. Formulation should not be attempted without advice from the manufacturer. Although volatility is low, vapour and dusts should be controlled preferably by mechanical means. Protective equipment for the skin and respiratory protection is necessary.

4.1.3 Mixers and applicators - When opening the container and when mixing, protective impermeable boots, clean overalls, gloves and a respirator should be worn.

Beware of possible positive pressure build-up, especially with liquid formulations in metal containers with inverted pour spouts. Mixing, if not mechanical, should always be carried out with a paddle of appropriate length. When spraying tall crops or during aerial application, a respirator should be worn as well as an impermeable hood, protective clothing, boots and gloves. The applicator should avoid working in spray mist and avoid contact with the mouth. Particular care is needed when equipment is being washed after use. All protective clothing should be washed immediately after use, including the inside of the gloves. Splashes must be washed immediately from the skin or eyes with large quantities of water. Before eating, drinking or smoking, hands and other exposed skin should be washed.

4.1.4 Other associated workers (including flagmen in aerial operations) - Persons exposed to carbofuran and associated with its applications should wear protective clothing and observe the precautions described above in 4.1.3 under "Mixers and applicators".

4.1.5 Other populations likely to be affected - With good agricultural practice subject to 4.2 below, other populations should not be exposed to hazardous amounts of carbofuran.

4.2 ENTRY OF PERSONS INTO TREATED AREAS –
Unprotected persons should be kept out of treated areas for at least one day.

4.3 SAFE DISPOSAL OF CONTAINERS AND SPILLAGE –
Residues in containers should be emptied in a diluted form into a deep pit taking care to avoid contamination of ground waters. The empty container may be decontaminated by rinsing two or three times with water and scrubbing the sides. An additional rinse should be carried out with 5% sodium hydroxide solution which should remain in the container overnight. Impermeable gauntlets should be worn during this work and a soakage pit should be provided for the rinsings. Decontaminated containers should not be used for food and drink. Spillage of carbofuran and its formulations should be removed by washing with 5% sodium hydroxide solution and then rinsing with large quantities of water.

4.4 EMERGENCY AID

4.4.1 Early symptoms of poisoning - Early symptoms of poisoning may include headache, weakness, giddiness and nausea. Later there may be perspiration, stomach pains, blurred vision, excessive salivation, slurred speech, and muscle twitching, tremor, diarrhoea and vomiting.

4.4.2 Treatment before person is seen by a physician, if these symptoms appear following exposure - The person should stop work immediately, remove contaminated clothing and wash the affected skin with soap and water, if available, and flush the area with large quantities of water. If swallowed, vomiting should be induced immediately if the person is conscious. In the event of collapse, artificial respiration should be given, preferably by mechanical means. If mouth-to-mouth resuscitation is used vomit may contain toxic amounts of carbofuran. If the eyes are contaminated, flush them with water for at least 15 minutes. If carbofuran is inhaled, remove victim to fresh air immediately.

5. FOR MEDICAL AND LABORATORY PERSONNEL

5.1 MEDICAL DIAGNOSIS AND TREATMENT IN CASES OF POISONING

5.1.1 General information - Carbofuran is a carbamate insecticide of very high toxicity. It is absorbed from the gastrointestinal tract and by inhalation, and only to a limited extent through the intact skin. Its mode of action is by reversible inhibition of acetyl cholinesterase. Erythrocyte cholinesterase is more inhibited than plasma cholinesterase. Symptoms of mild poisoning are short lasting and in case of occupational over-exposure occur without delay and at doses well below the fatal dose. Because of its rapid metabolism and excretion it does not accumulate in the tissues.

5.1.2 Symptoms and signs - Symptoms of poisoning include excessive sweating, headache, chest tightness, weakness, giddiness, nausea, vomiting, stomach pains, salivation, blurred vision, slurred speech and muscle twitching. Paraesthesia and mild skin reactions have also been reported. Diagnosis can be based on a recent history of activities and non-reactive pupils of the eyes.

5.1.3 Laboratory - Because carbofuran is a reversible inhibitor of cholinesterase, measurements of cholinesterase activity should be made by a method which minimizes the reactivation of inhibited enzyme. Erythrocyte cholinesterase determination is more informative than either plasma or whole blood cholinesterase, but the enzyme will only be inhibited for a short time (few hours) after exposure. The presence of metabolites of carbofuran in urine is also indicative of exposure.

5.1.4 Treatment - If the pesticide has been ingested, unless the patient is vomiting, rapid gastric lavage should be performed using 5% sodium bicarbonate, if available. For skin contact, the skin should be washed with soap and water. If the compound has entered the eyes, they should be washed with isotonic saline or water. Since the symptoms of poisoning with carbofuran are of short duration, atropine treatment is usually not necessary by the time the patient reaches a place where this antidote is available. Where there are manifest symptoms 1-2 mg of atropine sulfate (adult dose) may be given intramuscularly or even intravenously and repeated as necessary. Care should be taken to avoid overdosage of atropine, especially when treating children. In extreme cases, if the patient is unconscious or is in respiratory distress, oxygen may be required. Provide patient support as required, including; suction of secretions, maintenance of airways, intravenous fluids pro re nata and bladder catheterization. Morphine, aminophylline, phenothiazines, reserpine, furosemide and ethacryoic acid are condraindicated. Pralidoxime chloride is of doubtful value but if muscle weakness is severe a dilute solution may be given cautiously intravenously. If convulsions occur diazepam may be given, the patient must be monitored for respiratory depression and hypotensive reactions.

5.1.5 Prognosis - If the acute toxic effect is survived, the chances of complete recovery are very good.

5.1.6 References of previously reported cases - Okeefe, M. & Pierse, C. (1980), Bull. Environs Contam. Toxicol., 25, 777.

5.2 SURVEILLANCE TESTS –

Due to rapid reactivation of inhibited enzymes, determination of blood cholinesterase levels is of little, if any, practical value in determining when workers should be withdrawn to prevent over-exposure. Minor complaints, such as headache and nausea, generally cause the worker to stop work and thus prevent further exposure. The worker then quickly recovers, particularly if appropriate decontamination procedures are followed.

5.3 LABORATORY METHODS

5.3.1 Detection and assay of compound –
Chapman, R. A. & Robinson, J. R, (1977) J. Chromatogr., 140, 209. Cooke, R. F. et al. (1969) J. Agric. Food Chem., 17, 277. Cooke, R. F. (1973) Anal. Methods Pestic. Plant Growth Regul., 7, 187.

5.3.2 Other tests in cases of poisoning - Cholinesterase levels in blood are unreliable as a routine test to detect poisoning by carbofuran. However, shortly after absorption inhibition of erythrocyte cholinesterase may be demonstrated by an appropriate method. In plasma; Ellman, G. et al. (1961) Biochem. Pharmacol., 7, 88. In whole blood; Fleischer, J. et al. (1956) Arch. Indust. Hyg., 14, 510; Wilheim, K. et al. (1973) Bull Wld. Hlth, Org., 48, 235.

DATA SHEETS ON PESTICIDES No. 71

THIRAM

It must be noted that the issue of a Data Sheet for a particular pesticide does not imply endorsement of the pesticide by WHO or FAO for any particular use, or exclude its use for other purposes not stated. While the information provided is believed to be accurate according to data available at the time when the sheet was compiled, neither WHO nor FAO are responsible for any errors or omissions, or any consequences therefrom.

CLASSIFICATION:
Primary use: Fungicide
Secondary use: Repellent and bacteriocide
Chemical group: Dithiocarbamate

1. GENERAL INFORMATION

1.1 COMMON NAME
Thiram (ISO, BSI; exception USSR (TMTD) and JMAF (thiuram))

1.1.1 Identity;
IUPAC: Tetramethylthiuram disulfide
CAS: Tetramethylthioperoxydicarbonic diamide
CAS Reg. No.: 137-26-8
Molecular formula: $C_6H_{12}N_2S_4$
Molecular weight: 240.4
Structural formula:

1.1.2 Synonyms
Accelorator thiuram[R]; Aceto TETD[R]; Arasan[R]; Cyuram[R]; ENT 987; Ekagom[R]; Faltitram[R]; Fernacol[R]; Fernasan[R]; Fernide[R]; Hermal[R]; Hermat TMT[R]; Heryl[R]; Kregasan[R]; Mercuram[R]; Methyl thiuram; Methyl tuads; Nobecutan[R]; Nomersan[R]; Normersan[R]; Panoram[R]; Polyram ultra[R]; Pomarsol[R]; Pomasol[R]; Puralin[R]; Rezifilm[R]; Royal TMTD[R]; Sadoplon[R]; Spotrete[R]; SQ1489[R]; Tersan[R]; Thillate[R]; R 686 Thiosan[R]; Thiotex[R]; Thiramid[R]; Thirame[R]; Thirasan[R]; Thiurad[R]; Thiuram; Thiuramyl[R]; Thylate[R]; Thirampa[R]; Tiuram; Tiuramyl[R]; TMTD; Trametan[R]; Tripomol[R]; TTD[R]; Tuads[R]; Tulisan[R]; USAF B-30; USAF EK-2089; USAF P-5; Vancide[R]; Vuagt[R]; Vulcafor[R]; Vulkacit MTIC[R].

1.2 SYNOPSIS

Thiram is a dithiocarbamate; a fungicide with good avian and mammalian repellent properties; and a metabolic poison of low acute toxicity to mammals and a skin irritant. It also causes alcohol intolerance. It is also used as a promoter of vulcanization in the rubber industry, an activator in plastics manufacturing and as a chemosterilant in plastic film dry wound dressing. It is not phytotoxic when used as directed.

1.3 SELECTED PROPERTIES

1.3.1 Physical characteristics

Thiram is a colourless, odourless crystalline compound which melts at 155-156°C. It has a density (d^{20}) of 1.29. It is non- corrosive.

1.3.2 Solubility

In water, 30 mg/l at room temperature. It is slightly soluble in ethanol and diethyl ether and soluble in acetone, chloroform, benzene and carbon disulfide.

1.3.3 Stability

Thiram readily decomposes under acidic and alkaline conditions and under prolonged exposure to air, heat or moisture. It supports combustion if ignited but is non-explosive. 1.3.4 Vapour pressure Negligible at room temperature.

1.4 AGRICULTURE, HORTICULTURE AND FORESTRY

1.4.1 Common formulations

These include a wettable powder, 30-900 g a.i./kg; a colloidal suspension, 500 g/l; a dust seed treatment, 600 g a.i./kg; foliar dusts, 10-700 g a.i./kg; granule preparations, 22.5-50 g/kg; and a 10 g a.i./l paint-on preparation. It is also available in combination with phenylmercury dimethyldithiocarbamate, malachite green, phenylmercury acetate, gamma BHC, thiophanate and zineb a various concentrations. Mercury-containing formulations are no longer cleared for use in many countries.

1.4.2 Pests controlled

May be used as a repellent against rabbits, mice, deer, birds, chipmunks, moles and squirrels and as a fungicide in the control of several plant diseases.

1.4.3 Use pattern

As an animal repellent it may be applied undiluted with a brush to the lower trunks of trees and ornamentals; diluted as a spray on forest nursery stock and ornamentals; and diluted as a dip for bundles of forest, fruit and ornamental planting stock. When used as a dip, root contact must be avoided. Hang bundles to dry topside down. Dry thoroughly before planting. Do not use on those parts of the plant that are to be used as food when used as a repellent agent. As a fungicide, it may be used as a dust or a slurry for treatment of seeds of a large variety of food crops, apply after the seeds have cured (for peanuts apply immediately after shelling); as a foliar-spray treatment of apple, banana and peach trees and on (celery, tomato, strawberry and turf plants. For foliar treatment a spreader-sticker additive is recommended and it may be applied to bulbs and tubers of several ornamental and food plants. Thiram is compatible with common insecticides and fungicides.

1.4.4 Unintended effects: Thiram is not phytotoxic.

1.5 PUBLIC HEALTH USE

Thiram is a chemosterilant used in the manufacture of plastic dry-wound dressings and vulcanized rubber and plastic medical devices. It was also used as an ingredient in antiseptic sprays, soaps, etc.

1.6 HOUSEHOLD USE

Thiram is one of a broad spectrum of fungicides available for home-garden use and as an animal repellent.

2. TOXICOLOGY AND RISKS

2.1 TOXICOLOGY - MAMMAL

2.1.1 Absorption route

Thiram is rapidly absorbed from the gastrointestinal tract, through the intact skin, and by inhalation of spray mist and dust.

2.1.2 Mode of action

Thiram and other dithiocarbamates are metabolic poisons. Their acute toxic effects are largely similar to those of carbon disulfide, supporting the conclusion that the common metabolite of these compounds is responsible for their toxicity. This conclusion is supported by the findings that most dithiocarbamates of very low toxicity are poorly absorbed and that a large portion of an oral dose is excreted in the faeces unchanged. The exact mode of action is unclear; it involves intracellular action of metabolites of carbon disulfide, causing microsome injury and cytochrome P-450 injury accompanied by increased heme-oxygenase activity. A wide variety of factors including monoamine-oxidase inhibition, abnormal vitamin B_6 and tryptophan metabolisms, and cellular deprivation of zinc and copper have been cited as causes of the subcellular injuries.

In contrast to carbon disulfide, thiram also causes thyroid dysfunctions in vertebrates. This effect is thought to be a result of metabolic release of atomic sulfur in the follicular cells, causing inhibition of tyrosine iodination and ultimately hormone synthesis. A single dose of thiram causes a transient dysfunction; repeated doses can cause goitres. Other cellular enzymes may be similarly affected.

Thiram induces an alcohol intolerance similar to that of Antabuse (disulfiram) either by inhibiting acetaldehyde dehydrogenase or through the formation of a quaternary compound with the ethanol.

2.1.3 Excretion products

The metabolism and excretion of thiram has not been extensively studied; insight can be gained from pooled information of other dithiocarbamate studies, especially disulfiram. The initial degradation probably occurs in the gastrointestinal tract where the parent compound is reduced to dimethyldithiocarbamic acid which is rapidly absorbed and further metabolized by hepatic enzymes. A portion of the acid will be excreted unchanged as a glucuronide. Further metabolism may also yield dimethylamine and carbon disulfide residues. Only a small portion of the *peroral* dose has been found as carbon disulfide in the blood of rats (0.003%). Clearly a hig portion of the parent compound may be metabolized to carbon disulfide, whereas the small portion recovered in the blood represents only that portion of the dose not lost through the pulmonary route nor involved in tissue reactions.

Dimethyldithiocarbamate may also be degraded to dimethylthiocarbamate, sulfate ion and formaldehyde following methylation and oxidation reactions in body tissues in general. Dimethylthiocarbamic acid is excreted as a glucuronide.

2.1.4 Toxicity, single dose;
Oral LD_{50}:

Rat (M, F) 560 mg/kg bw
Rat (M, F) 630 mg/kg bw (as a 20% suspension in propylene glycol)
Mouse 1350 mg/kg bw
Rabbit 210 mg/kg bw
Sheep 225 mg/kg bw

Animals killed with a single oral dose showed hyperaemia and focal ulcerations of the gastrointestinal tract; focal necrosis of the liver and the renal tubules; patchy demyelination and ascending flaccid paralysis. Poisoning is characterized by eosinopenia, depression, adynamia and convulsions of the clonic type.

Dermal; Single applications of 1000-2000 mg/kg bw to rats and 500-1000 mg/kg bw to rabbits did not produce skin irritation or other toxic effects. In guinea-pigs thiram was found to be a primary skin irritant. See section 2.1.7 "Sensitization".

Intraperitoneal

LD_{50}: Mouse 2.50 mg/kg bw The most susceptible species is probably the rabbit.

2.1.5 Toxicity, repeated dose;
Oral: See sections 2.1.6 (Dietary studies) and 2.1.7 (Carcinogenicity).

Dermal:

Repeated dermal application, 50 mg/kg bw, to rabbits did not prove irritating

Cumulation of compound:

Thiram has significant cumulation properties. At 0.1-0.005 x LD_{50} the cumulation coefficient is 2.1- 2.85.

2.1.6 Dietary studies
Short-term: In an 80-day feeding study in rats 5.0 mg/kg bw per day in males and 6.0 mg/kg bw in females were found to be the no-effect levels. Patchy alopecia was observed in some males and females at dosage levels of 20 mg/kg bw per day and over. Paralysis and atrophy of the hind legs of females was observed at 67 mg/kg bw per day. In a 13-week dietary study male rats were fed thiram at dosage levels of 30, 58 and 132 mg/kg bw per day. Dose-dependent reductions in body weight and food consumption were observed. At the highest dose there was an increase in BUN, SGOT and SGPT values, evidence of testicular damage and atypical spermiogenesis were observed; five of the 20 animals in this dose group died within 13 weeks. At 58 mg/kg bw per day only BUN increases were observed.

In an 80-week study male rats were found to consume 5, 20 and 52 mg of thiram/kg bw per day, and females 6, 26 or 67 mg/kg bw per day. Dose-dependent decreases in body weight and food consumption were observed in males starting at 5 mg/kg bw and in females starting at 26 mg/kg bw.

There were no treatment-related mortalities and moderate to severe clinical signs of toxicity were observed only among the females in the highest dosage group. There

were no other adverse effects. In a one-year diet study in dogs the no-effect level was found to be 4.0 mg/kg bw per day.

Long-term: In a two-year dietary study in rats the no-effect level was found to be approximately 4.9 mg/kg bw per day. At 2500 ppm there: was 100% mortality within 17 weeks. General weakness, ataxia and occasional paralysis were observed at 300 and 1000 ppm but there was no treatment-related mortality, Thiram caused an increase in squamous epithelial metaplasia in the thyroid and fatty infiltration in males. There was a reduction in incidences of spontaneous nephritis in both sexes.

2.1.7 Supplementary studies of toxicity

Carcinogenicity: Thiram is classified as an equivocal tumorigen with no known carcinogenic effect. It did not alter the incidence or latent period of spontaneous rumours also seen in the control rats in the several dietary studies described above. Also, no clear carcinogenic effect was demonstrated in several studies of mice (C57 BL) given the highest tolerated doses in a 77-week intubation-dietary study, a five-week intubation study and after a single subcutaneous injection (4.6 mg/kg bw)

N-nitrosodimethylamine, a known carcinogen (in mice, rats, rabbits, hamsters and guinea-pigs), was produced from thiram under simulated stomach conditions in the presence of nitrite. The possibility of this transformation of carcinogenic potential occurring *in vivo* under normal dietary conditions is unknown.

Mutagenicity: Thiram was mutagenically active on base- substitution sensitive *S. typhimurium* strains TA1535 and TA100, the effect was abolished in the presence of rat liver microsomes, L-cysteine and glutathion; in TA1535 and TA98 strains following metabolic activation only; in mitotic recombination assays with ***B. subtilis;*** and in mice given 100 mg/kg bw p.o. causing an increase in chromosomal aberrations in bone marrow cells. Teratogenicity; Thiram p.o. was shown to be teratogenic, at high doses causing adult injury, in rats (400 mg/kg bw on days 6-15 of gestation); in mice (250 mg/kg bw on days 6-15 of gestation); and in hamsters at 250 mg/kg bw on days 7 or 8 of gestation. The pattern of foetal defects was not well defined; many changes are suspected to result from retardation of growth. In hamsters the combined effects of thiram and the solvent DMSO were possibly synergistic. In mice simultaneous administration of L-cysteine and thiram tended to abolish the teratogenic effect of thiram.

Reproduction: Thiram was found to have adverse effects on reproduction and to be embryotoxic in mice, rats and hamsters at high dosage levels toxic to the adults. In a three-generation dietary study in rats 100 mg/kg bw per day had no adverse effects on reproduction or foetal development. In a single generation study in rats, 50 mg/kg bw per day, from gestation day 16 to post-partum day 21, caused reduced pup growth and survival. These effects were prevented when the pups were transferred to untreated lactating dams. In an inhalation study in rats 3.8 mg/m^3 of air for 6 hours per day, 5 days per week for 4.5 months, caused reproductive malfunction: prolonged oestrus cycles, decreased conception rates, decreased fertility and reduced foetal weights. In mice 132 mg/kg bw p.o. per day for 13 weeks caused male infertility; 96 mg/kg bw for 14 days delayed oestrous cycles. These adverse effects were reversed when treatment ceased.

Neurotoxicity: Animals killed by single oral doses of thiram showed patchy demyelination in the central nervous system, initially in the cerebellum and medulla. Rats fed 300 mg/kg bw per day had clonicotonic convulsions and showed calcification in the cerebellum, hypothalamus and medulla oblongata. In another study eight out of 24 female rats fed 67 mg/kg bw per day for 80 weeks developed severe signs of

neurotoxicity including ataxia and ascending paralysis; degeneration of axis cylinders and presence of macrophages in the bundle of the sciatic nerve were observed

Metabolism: Thiram has been shown to be an inhibitor of many enzymes. It induces accumulation of acetaldehyde in the bloodstream following ethanol or paraldehyde treatment. In inhibits the *in vitro* conversion of dopamine to noradrenalin in cardiac and adrenal medulla preparations. It depresses some hepatic microsomal demethylation reactions, microsomal cytochrome P-450 content and the synthesis of phospholipids. Thiram has also been shown to have moderate inhibiting action on decarboxylases and, in fish, muscle acetylcholinesterases.

Sensitization: Thiram was found to be a primary skin irritant with a threshold limit value of 5% in a 24-hour occluded patch test in guinea-pigs and it was also shown to have moderate contact hypersensitivity potency in a guinea-pig maximization test. 2.1.8 Modification of toxicity In mammals the teratogenic and embryotoxic effects of thiram are at least partly overcome by simultaneous treatment with L-cysteine or glutathion. Potentiation of the teratogenic effect occurs with the solvent DMSO.

2.2 TOXICOLOGY - MAN

2.2.1 Absorption

Thiram can be absorbed from the gastrointestinal tract, through the skin and by inhalation of dust and fine spray mist.

2.2.2 Dangerous doses

There is no information on doses leading to illness.
Single: Thiram has been given a toxicity rating of 4 (Gosselin), the probable oral lethal dose for humans is 50-500 mg/kg bw. Alcohol, regardless of the route of absorption of thiram, increases thiram toxicity and is probably the cause of most systemic poisonings involving thiram.
Repeated: No information is available. Since thiram is cumulative the repeated dangerous dose is likely to be much smaller than the single dose.

2.2.3 Observations on occupationally exposed workers

Numerous studies of industrial and agricultural workers have been published. There have been very few cases of thiram systemic poisoning leading to death without known alcohol involvement. Increased skin sensitivity unrelated to alcohol use, once thought to be uncommon, is becoming increasingly more common, especially in tropical countries, in association with thiram use.

In one industrial study of men and women between 20 and 50 years of age, who had been exposed to TMTD for several years, ocular manifestations were common. The initial symptoms, lachrymation and photophobia, were temporary and were followed by chronic conjunctivitis in 14% of those examined, enlargement of retinal blood vessels (in 34%), reduced visual acuity, delayed dark adaptation and reduced corneal sensitivity.

In another study, in addition to ocular manifestations, tachycardia, thoracic pain and coughing, epistaxis, dermal lesions, myocardial dystrophy, liver dysfunction, astenia and goitre have been found. A single case of thyroidal adenocarcinoma in a person exposed to thiram has been reported. Many cases of poisoning have involved alcohol interaction with thiram, especially in agricultural workers and formulators. The symptoms of this poisoning include gastric pain, nausea, vomiting, hypertension and hyper-irritability, fine tremors, fever and moderate lymphopenia.

2.2.4 Observations on exposure of the general population
The use of thiram in the manufacture of many rubber and plastic products (e.g., shoes) and as a fungicide in recreational areas (e.g., golf courses and bowling greens) presents considerable opportunity for exposure of sensitive individuals to the compound. Thiram is considered to be a borderline allergen requiring several exposures to produce sensitization. For further details see section 4.1.5.

2.2.5 Observations of volunteers
Thiram has been used in several medicinal products and soaps. Systemic poisonings and contact dermatitis have not been commonly seen in these studies (see section 4.1.5 for more details). Oral doses of 0.5-1.5 g per person per day for several weeks have been tolerated without ill-effect provided alcohol was avoided.

2.2.6 Reported mishaps
There is no published information available on intentional poisoning involving thiram. Most accidental systemic poisonings due to thiram have also included alcohol consumption. In most cases, though the symptoms were severe enough to warrant hospitalization, the recovery was uneventful and complete in three to four days. In one incident, a fatality occurred following the mixing of seed and thiram with a spade. The worker, who was exposed for approximately 10 hours, fell ill and though treated in hospital he died four days later

2.3 TOXICITY TO NON-MAMMALIAN SPECIES

2.3.1 Fish
No information available.

2.3.2 Birds
Thiram is moderately toxic to most birds; the acute and chronic toxic effects are similar to those found in mammals. It has been shown to be teratogenic and to interfere in normal reproductive physiology and behaviour in domestic fowl. The effect in the young birds appears to be more severe than in older birds.
Oral LD_{50}:
Mallards 2800 mg/kg bw
Pheasants 673 mg/kg bw
Red wing blackbird 300 mg/kg bw
Domestic sparrow 100 mg/kg bw
Common grackle 100 mg/kg bw

2.3.3 Other species: No information available.

3. FOR REGULATORY AUTHORITIES - RECOMMENDATIONS ON REGULATION OF COMPOUND

3.1 RECOMMENDED RESTRICTIONS ON AVAILABILITY
(For definition of categories, see the Introduction to Data Sheets)
All liquid formulations over 28%, Category 3.
All other liquid formulations, Category 4.
All solid formulations over 11%, Category 4.
All other solid formulations, Category 5.

3.2 TRANSPORTATION AND STORAGE

Formulations in categories 3 and 4 –

Should be transported or stored in clearly labeled, rigid and leak-proof containers and away from containers of food and drink. Storage should be under lock and key and secure from access by unauthorized persons and children.

Formulations in Category 5 - Should be transported or stored in clearly labeled leak-proof containers out of reach of children and away from food and drink.

3.3 HANDLING

Formulations in categories 3 and 4 - Protective clothing (see part 4) should be provided for those handling concentrates. Adequate washing facilities should be available close at hand. Eating, drinking and smoking should be prohibited during handling and before washing after handling. Adequate ventilation must be maintained. Formulations in Category 5 - No special facilities other than those for handling of any chemical need be required. Adequate ventilation must be maintained.

3.4 DISPOSAL AND/OR DECONTAMINATION OF CONTAINER

If not decontaminated container must either be burned or crushed and buried below topsoil. Care must be taken to avoid subsequent contamination of water sources. Container may be decontaminated (for method see paragraph 4.3 and part 4). Decontaminated containers should not be used for any other purpose.

3.5 SELECTION, TRAINING AND MEDICAL SUPERVISION OF WORKERS

Formulations in categories 3 and 4 - Pre-employment medical examination for workers desirable. Workers suffering from activ hepatic or renal disease should be excluded from contact. Pre- employment and periodic cholinesterase tests for workers desirable. Training of workers in techniques to avoid contact and the need for strict abstention from alcohol use prior to and after thiram use are essential. Formulations in Category 5 - Warning of workers to minimize contact and about the dangers of alcohol use prior to and after thiram use is essential.

3.6 ADDITIONAL REGULATIONS RECOMMENDED IF DISTRIBUTED BY AIRCRAFT

All formulations - Pilot and loaders should have special training in application methods and early symptoms of poisoning. Flagmen, if used, should wear a broad brimmed hat, a facial mask and coveralls, and be located well away from the dropping zone.

3.7 LABELLING

Formulations in categories 3 and 4 - Minimum cautionary statement "WARNING - POISON" (skull and cross-bones insignia). Thiram is a dithiocarbamate; a metabolic poison of slight acute toxicity and has potential long-term toxic effects. A primary irritant, avoid contact with skin and eyes. Inhalation of dust or spray, or swallowing may be fatal. Wear protective gloves, clean protective clothing, and a particle respirator (3 micron capability) type when handling this material. Bathe immediately after work. Ensure that containers are closed and stored under lock and key. Empty containers must be disposed of in such a way as to prevent all possibility of accidental contact with them. Keep the material out of reach of children and well away from foodstuffs, animal feed and their containers. Maintain adequate ventilation during use. In case of contact immediately remove contaminated clothing and wash the skin thoroughly with soap and water; for eyes, flush with water for 15 minutes. If poisoning occurs, call a physician. Avoid alcohol use for at least 10 days. There is no specific antidote, treatment must be symptomatic.

Formulations in Category 5 - Minimum cautionary statement - This formulation contains thiram, it is poisonous if swallowed. Keep the material out of reach of children and well away from foodstuffs, animal feed and food containers. Maintain adequate ventilation during use. Avoid alcohol use prior to and after thiram use

3.8 RESIDUES IN FOOD

Maximum residue levels - Maximum residue levels have been recommended by the Joint FAO/WHO Meeting on Pesticide Residues.

4. PREVENTION OF POISONING IN MAN AND EMERGENCY AID

4.1 PRECAUTIONS IN USE

4.1.1 General

Thiram is a dithiocarbamate of slight acute toxicity and potential long-term toxic effects. In addition to its inherent toxicity it induces an alcohol intolerance similar to that of Antabuse (disulfiram), a related dithiocarbamate. It may be absorbed from the gastrointestinal tract; by inhalation of spray mist or dust; and through the intact skin. A primary irritant, avoid contact to skin and eyes; spills must be washed immediately from the skin and eyes. Adequate ventilation is essential.

4.1.2 Manufacture and formulation

TLV 5 mg/m3, ACGIH. Formulation should not be attempted without advice from the manufacturer. Although volatility is low vapour and dusts should be controlled preferably by mechanical means. Protective equipment for the skin and self-contained respiratory protection is essential. Adequate ventilation is also essential.

4.1.3 Mixers and applicators

When opening the container and when mixing, care should be taken to avoid contact with the mouth and eyes. Maintain adequate ventilation during handling; a self-contained breathing apparatus, coveralls and gloves should be worn. Mixing, if not mechanical, should always be carried out with a paddle of appropriate length. The applicator should avoid working in spray mists and avoid contact: with the mouth. Splashes must be washed immediately from the skin or eyes with large quantities of water. Before eating, drinking or smoking, hands and other exposed skin should be washed.

4.1.4 Other associated workers (including flagmen in aerial operations)

Persons exposed to thiram and associated with its application should observe the precautions described in section 4.1.3 under "Mixers and applicators".

4.1.5 Other populations likely to be affected

With correct application and appropriate warnings of use the general public should not be exposed to hazardous amounts of thiram. Warnings of use are essential; there are reports of contact poisoning in sensitive persons following exposure after correct horticultural applications and after continuous use of vulcanized rubber or plastic products contaminated with thiram during their manufacture

4.2 ENTRY OF PERSONS INTO TREATED AREAS

Unprotected persons should be kept out of treated areas until the spray solution is dry.

4.3 DECONTAMINATION OF SPILLAGE AND CONTAINERS

Residues in containers should be dissolved in a combustible solvent (alcohol, benzene, etc.) and burned in a furnace. The empty containers may be decontaminated by rinsing two or three times with a combustible solvent, the rinse burned. An additional rinse should be carried out with 15% calcium hypochlorite solution which should remain in the container overnight; neutralize and dispose of the rinse in a deep pit or into a sewer with abundant water. Impermeable gauntlets should be worn during this work and a soakage pit should be provided for the rinsings. Decontaminated containers should not be used for any other purpose. Spillage of thiram and its formulations should be removed by washing with 15% calcium hypochlorite solution and then rinsing. with large quantities of water. Neutralize the rinse fluid and drain into a deep pit or sewer with abundant water.

4.4 EMERGENCY AID

4.4.1 Early symptoms of poisoning

Early symptoms may include dizziness, confusion, drowsiness, lethargy, ataxia, headaches, or coma; nausea, vomiting, diarrhoea and stomach pains; muscle weakness and paralysis (ascending); respiratory paralysis; and skin rash and eye irritation.

4.4.2 Treatment before person is seen by a physician, if these symptoms appear following exposure

The person should stop work immediately, remove all contaminated clothing, and wash the affected skin or hair with soap and water. Flush contaminated eyes with fresh water for 10-15 minutes. If the compound was ingested and if the victim is alert, induce vomiting if it has not already occurred. Provide artificial respiration if required and preferably by mechanical means. Prevent consumption or other contact with alcohol. Contact a doctor immediately, give supportive care and remove the victim to hospital as quickly as possible.

5. FOR MEDICAL AND LABORATORY PERSONNEL

5.1 MEDICAL DIAGNOSIS AND TREATMENT IN CASES OF POISONING

5.1.1 General information

Thiram is a dithiocarbamate pesticide of slight acute toxicity and some potential long-term effects (e.g., mutagenicity, teratogenicity and tumorigenicity). It is used as an industrial water antifouling agent and in several manufacturing processes. It is absorbed from the gastrointestinal tract; by inhalation of dust or spray mist; and through the intact skin. Thiram induces alcohol intolerance similar to that of Antabuse (disulfiram).

5.1.2 Symptoms and signs

Symptoms of poisoning include nausea, vomiting, abdominal pain, diarrhoea, anorexia and weight loss; headaches, lethargy, dizziness, ataxia, confusion, drowsiness and coma; suppression of tendon reflexes; initial hypotonia progressing to flaccid paralysis (Landry's syndrome); respiratory paralysis; and severe dermatitis and eye inflammation.

5.1.3 Laboratory
Due to rapid metabolism and excretion, detection of thiram in the blood is generally not possible. Detection of thiram metabolites and xanthurenic acid in the urine may confirm absorption but will not necessarily reflect the degree of poisoning. Skin testing may be useful in identifying sensitization to the compound. Treatment should not be deferred pending laboratory results.

5.1.4 Treatment
There is no specific antidote; provide symptomatic and supportive treatment. For contact poisoning remove all contaminated clothing and wash the affected skin and hair with soap and water; flush contaminated eyes with fresh water for 10-15 minutes. If thiram has been ingested, if the patient is alert and if vomiting has not already occurred, induce vomiting preferably with Syrup of Ipecac. Continue to observe patient for signs of depression of consciousness level and/or respiration. If these signs occur, gastric intubation, aspiration and lavage should be performed immediately. Lavage with isotonic saline or sodium bicarbonate solution should be followed by activated charcoal by intubation to limit absorption of any residual thiram in the gastrointestinal tract. If the irritant properties of thiram have not already induced a bowel movement, give a mild cathartic (e.g., magnesium sulfate). Intravenous administration of glucose and ascorbic acid (0.2 g/min up to one gram total) may be useful to accelerate the excretion of unreacted, absorbed thiram. Provide artificial respiration i necessary, preferably by mechanical means. In extreme cases, if the patient is unconscious or in respiratory distress, oxygen should be provided. The patient should avoid fats, oils and lipid solvents which might enhance absorption and prohibit all forms of ethanol consumption for at least three weeks.

5.1.5 Prognosis
If the acute toxic effect is survived the chances of complete recovery are very good.

5.1.6 References to previously reported cases
Benzugli, U. P. et al. (1976) Vrach Delo, 3, 142-145 Gunther, W. W. (1970) Med. J. Aust., 1, 1177 Hamada, T. & Horiguchi, S. (1977) Sangyo Igaku, 19(3), 112-118 Krupa, A. et al. (1971) Med. Wiejsk, 6, 29-31 Marcinkowski, T. & Manikowski, W. (1973) Med. Pracy, 24, 91-95 Olefir, A. I. (1976) Vrach Delo, 2, 105-109 Reinl, W. (1966) Arch. Toxikol., 22, 12-15 Shelly, W. B. (1964) J.A.M.A., 188, 89-92 Telintum, J. & Nater, J. P. (1974) Dermatologic (Basel), 148(1), 42-44 Tanaka, S. et al. Toxicol. Res. Directory, 5(8), 1980 Verkagen, A. (1974) Trans St. John's Hosp. Dermatol. Soc., 60(1), 86-90 Verzhanski, P.S. (1976) Gumoral'n Regul. Rodovoi Deyat. Lech. Ee Narushenii, pp. 88-91

5.2 SURVEILLANCE TESTS

There are no readily available techniques to determine the degree of exposure prior to the appearance of symptoms

5.3 LABORATORY METHODS

5.3.1 Detection and assay of compound
CIPAC Handbook (1970) Vol. 1, 672 pp.

Butler, L. C. & Staiff, D.C. (1978) J. Agric. Food Chem., 26(11), 295-296

Guslafssen, K. H. & Thompson, R. A. (1981) J. Agric. Food Chem., 29(4), 729-732

Muzhanovsky, Y. E. et al. (1979) Farm. Zh. (Kiev), (2), 54-57

Smith, R. M. et al. (1981) Analyst (London), 106-1254; 129-134

5.3.2 Other tests in cases of poisoning

Sedokur, L. K. & Luk'yanchuck, D. (1976) Xanthurenic aciduria as a specific test for dithiocarbamate intoxication, Gig. Tr. Prof. Zabol., 2, 55-56

Kashevich, L. M. (1975) Rheohepatography in the diagnosis of toxicochemical lesions of the liver in persons dealing with TMTD, Gig. Tr. Prof. Zabol., 6, 16-19.

Annex III – Calculation of the WHO Classification

Excerpted from, Recommended classification of pesticides by hazard and guidelines to classification 2000-02. WHO/PCS/01.5. World Health Organization, IPCS, Geneva**.** (WHO 2001).

Approach *b*) of the WHO Recommended Classification of Pesticides by Hazard and Guidelines to Classification 2000-2002, p. 6 "Notes on the use of the tables in classification". This method allow a classification of the formulation according to the most hazardous constituent of the mixture as if that constituent was present in the same concentration as the total concentration of all active constituents.

Approach *c*) of the WHO Recommended Classification of Pesticides by Hazard and Guidelines to Classification 2000-2002, p. 6 "Notes on the use of the tables in classification". This method uses the following weighted formula

$$\frac{C_a}{T_a} + \frac{C_b}{T_b} + \frac{C_z}{T_z} = \frac{100}{T_m}$$

Where C= the % concentrations of constituent A, B, ...Z in the mixture
T= the oral LD_{50} values of constituents A, B, ...Z
Tm= the oral LD_{50} value of the mixture.

Annex IV – References

EXTOXNET Pesticide information Profile on thiram (available through the USEPA website)(excerpted in UNEP/FAO/PIC/ICRC3/17.Add1, information on LD50 p 82)

FAO/WHO, 1996. Pesticide Residues in Food – 1996, Report No.140 (excerpted in UNEP/FAO/PIC/ICRC3/17.Add1, information on carbofuran LD50 p 35)

SNGE, 2000. Report of the research on the epidemic of an unknown etiologic illness in Kolda. Dr. Eugenia Gomes do Espirito Santo, National Service for Major Endemic Diseases (SNGE), Dr Laurence Marrama, Pasteur Institute, Dakar (IPD) Dr Kader Ndiaye, IPD, Dr Malan Coly, World Health Organization (WHO), Dr Dior Diagne, Senegal Department of Health and Environment (ISED), Dr Pape Ndour, ISED Dr Ousseynou Ba Medical region of Kolda, Regional Service for Major Endemic Diseases December 2000 . (reproduced in Annex II of UNEP/FAO/PIC/ICRC.3/17.Add3)

WHO, 2001. Recommended classification of pesticides by hazard and guidelines to classification 2000-02. WHO/PCS/01.5. World Health Organization, IPCS, Geneva**.**

A full set of the information regarding Granox TBC and Spinox T that was available to the third Session of the Interim Chemical Review Committee may be found in the following documents which are available on the Rotterdam Convention Website www.pic.int

UNEP/FAO/PIC/ICRC3/17
UNEP/FAO/PIC/ICRC3/17.Add1
UNEP/FAO/PIC/ICRC3/17.Add2
UNEP/FAO/PIC/ICRC3/17.Add3