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INTERIM CHEMICAL REVIEW COMMITTEE
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Item 6 (b) on the provisional agenda •

**INCLUSION OF CHEMICALS IN THE INTERIM PRIOR INFORMED CONSENT PROCEDURE - REVIEW OF PROPOSALS FOR SEVERELY HAZARDOUS PESTICIDE FORMULATIONS**

**GRANOX TBC and SPINOX T**

Note by the Secretariat

1. In September 2001 the Secretariat received proposals from the designated authority in Senegal concerning two pesticide formulations found to be causing problems under conditions of use in that country. In line with Article 6 the proposals were verified as meeting the information requirements of part 1 of Annex IV and summaries published in PIC Circular XIV (12 December 2001).

2. These proposals were brought to the attention of the eighth session of the Intergovernmental Negotiating Committee (INC-8, October 2001 (UNEP/FAO/PIC/INC8/INF9). Delegations to INC-8 were requested to review the formulations and to submit to the Secretariat by 15 December 2001 any information they might have in line with part 2 of Annex IV. A further request for the submission of this information was posted on the Rotterdam Convention website (www.pic.int).

3. In a letter dated 25 October 2001 the Secretariat requested designated national authorities review the formulations identified in the proposals and submit any information they might have available in line with part 2 of Annex IV by 15 December 2001. The following organizations were also invited provide such information: Crop Life International, the Pesticides Action Network UK (PAN UK), Pesticides Action Network Africa (PAN Africa), the Sahaelian Pesticides Committee (CSP), the International Seed Treaters Association (FIS/ASSINSEL), the formulators in Senegal (Senchim AG and S.P.I.A.) and the Peanut Collaborative Research Support Program, a US AID sponsored project in West Africa.

• UNEP/FAO/PIC/ICRC3/1

4. As of 7 January 2002, the Secretariat received replies from 16 designated national authorities in 14 countries (Bhutan, China, Colombia, Costa Rica, Czech Republic, Estonia, Finland, Israel, Democratic Republic of Korea, Latvia, Lesotho, New Zealand, Turkey, Zimbabwe), the European Commission and PAN Africa.

   (i) In all cases the designated national authorities indicated that the pesticide formulations Granox T.B.C. and Spinox T were not registered in their countries. Some designated national authorities provided information on the registration status of the individual active ingredients including a brief description of the relevant formulations and permitted uses.

   (ii) PAN Africa provided specific information on the formulations in the form of an article from the publication Pesticides and Alternatives (No. 12 November 2000). A copy of this article is annexed to the present note.

5. Only very limited formulation specific information has been provided in response to the above noted requests of the Secretariat. In the light of this and to facilitate the work of the Committee the Secretariat has collected basic information on the physical chemical and toxicological properties of the individual active ingredients contained in these formulations. In addition a classification of the hazard posed by these formulations has been proposed using the approaches specified by the WHO in the *WHO recommended classification of pesticides by hazard and guidelines to classification 2000-2002.*

6. Annexed to the present note is the formulation specific information submitted by PAN Africa, the proposed hazard class of the pesticide formulations based on the WHO classification, as well as, the information collected by the Secretariat on the individual active ingredients benomyl, carbofuran and thiram. The information on the individual active ingredients includes the most recent toxicological evaluation by the FAO/WHO Joint Meeting on Pesticide Residues (JMPR), the pesticide data sheet and International Chemical Safety Card available on the INCHEM database, as well as, the relevant EXTOXNET Pesticide Information Profile maintained by the United States Environmental Protection Agency.

7. A copy of the correspondence submitted to the Secretariat in response to the above noted requests for information has been sent to the chair of the inter-sessional task group and is available from the Secretariat on request. A complete set of this correspondence will be available at the third session of the Committee in February 2002.

# -Annexes-

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# ANNEX I – Countries where the designated national authority responded to the request for information on the formulations Granox T.B.C. and Spinox T

As of 7 January 2002, the designated national authorities in the following countries had replied to the request for information of 25 October 2001.

| Country/Organisation | Date received |
|---|---|
| Bhutan | 18 December 2001 |
| People's Republic of China | 19 December 2001 |
| Colombia | 26 November 2001 and 11 December 2001 |
| Costa Rica | 3 December 2001 |
| Czech Republic | 17 December 2001 |
| Estonia | 26 November 2001 |
| Finland | 6 December 2001 |
| Israel | 27 December 2001 |
| RDA Republic of Korea | 17 December 2001 |
| Latvia | 25 November 2001 |
| Lesotho | 18 December 2001 |
| Mexico | 20 December 2001 |
| New Zealand | 11 December 2001 |
| Turquey | 17 December 2001 |
| Zimbabwe | 8 December 2001 |
| Europan Union | 18 December 2001 |

A copy of the correspondence and attachments submitted to the Secretariat has been sent to the chair of the inter-sessional task group on these two formulations and is available from the Secretariat on request. A complete set of this correspondence will be available at the third session of the Committee in February 2002.

# ANNEX II – Calculation of the toxicity of a pesticide formulation of: 15% thiram, 7%benomyl and 10% carbofuran, on the basis of the WHO recommended classification of pesticides by hazard and Guidelines to classification 2000-2002

A- Excerpt from p.6 of *WHO recommended classification of pesticides by hazard and Guidelines to classification 2000-2002:*

**NOTES ON THE USE OF THE TABLES IN CLASSIFICATION**

(…)

4. It is not possible to include classification of mixtures of pesticides in the guidelines: very many of these are marketed with varying concentrations of active constituents. There are three possible approaches to the classification of mixtures – in order of preference:

**(a)** require the formulator to obtain reliable acute oral and dermal toxicity data for rats on the actual mixture as marketed;

**(b)** classify 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;

**(c)** apply the formula: $\frac{C_a}{T_a} + \frac{C_b}{T_b} + \ldots \frac{C_z}{T_z} = \frac{100}{T_m}$

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.

The formula can also be used for dermal toxicities provided that this information is available on the same species for all constituents. The use of this formula does not take into account any potentiation or protective phenomena.

B- Application of the three possible approaches to the classification of mixtures proposed in the WHO recommended classification of pesticides by hazard and guidelines to classification 2000-2002 to a mixture of thiram 15 %, carbofuran 10 % and benomyl 7 %.

Values for $LD_{50}$ are taken from the *WHO recommended classification of pesticides by hazard and guidelines to classification.* and they are all oral values.

**(a)** A request for additional information on the formulations Granox TBC and Spinox T has been addressed to the producers of these formulations in Senegal. As of 7 January 2002, no reply has been received.

**(b)** Carbofuran is given as the most hazardous active ingredient in the mixture: it belongs to a hazard of **class Ib** (highly hazardous), with a $LD_{50}$ of 8 mg/kg.

The total concentration of all active ingredients is 15%+10%+7%= 32%.

Result:

- A solid formulation made of 32% carbofuran (oral LD 50 8 mg/kg) corresponds to a **class Ib** hazard (highly hazardous) (see table A p.42 of the WHO recommended classification when the route is oral and the formulation is solid).

**(c)** Application of the formula:

Carbofuran (class Ib),highly hazardous: $LD_{50}$ 8 mg/kg
Thiram (class III), slightly hazardous : $LD_{50}$ 560 mg/kg
Benomyl (unlikely to present hazard) : $LD_{50}$>10 000 mg/kg

Result:

$$\frac{10}{8}\ (\text{carbofuran}) + \frac{15}{560}\ (\text{thiram}) + \frac{7}{10000}\ (\text{benomyl}) = 1.277 = \frac{100}{T_m}$$

$T_m$= 78.28 (oral $LD_{50}$ in mg/kg)

The mixture corresponds to:

- a **class II** hazard (moderately hazardous) when the route is oral and the formulation is solid.
  (see table A p.42 of the WHO recommended classification when the route is oral and the formulation is solid).

Calculations are based on the following sections 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
- p.9: Entries and abbreviations used in the table
- p. 41: Annex – How to find the hazard class of a formulation
- p.42: $LD_{50}$ values and classification of formulations when the route is oral and the formulation solid

## ANNEX III – Extract of the information specific to the formulations Granox TBC and Spinox T submitted by PAN Africa.

During August 2000 in the Kolda region in Senegal, several cases of illness characterised mainly by dyspnea and oedema of the inferior limbs and of the face was observed. A joint investigation of the Service National des Grandes endémies and the Institut Pasteur of Dakar showed that signs and symptoms suggested carbamate poisoning.

Copy of article in Pesticides & Alternatives, number 12 – November 2000 attached.

*Pesticides & Alternatives, number 12 – November 2000*

# New Cases of intoxication in Senegal

A mysterious and tragic event is taking place in the Region of Kolda since July 2000. Several farmers died there and the exact causes of the phenomenon are still unknown. Ten victims were recorded in the department of Kolda, more precisely in the rural community of Sare' Bidji (8 km from the city of Kolda). There were also 6 victims in the department of Sédhiou (rural communities of Diana Malary[1], and Tankon). According to medical authorities, there might be more victims, for rural population generally refer to traditional or empirical treatments in the first place. Others patients presenting the same signs were recorded.

Agriculture is the main activity in the rural communities of Saré Bidji, Diana Malary and Tankon. The peasants also devote themselves to livestock farming. The main crops are groundnuts, millet, rice, maize and niébé[2]. In these localities, groundnut plants are treated with pesticides. The distribution of agricultural inputs and the phytosanitary protection of seeds are in the hands of a private company, the SONAGRAINES. Most of the affected villages are peopled by a majority of Peul[3], apart from Sam Toulou, which is essentially peopled by Manjaque[4] but with a strong presence of Peul. The populations practice a traditional type of agriculture with a limited use of machines and inputs.

The accidents are first characterized by the period of occurrence, for they all coincided with the seedling of groundnuts. Furthermore, all the victims had been in contact with the treatment powder, i.e. a pesticide product called Granox[5], which is used for the protection of groundnut seedlings. Secondly, all the victims were Peul farmers, apart from one who was a Manjaque. Most of them were men (14 of the 16 victims) and their average age was 30 years. they presented the same clinical signs: edema in the face and inferior members, swelling of the abdomen, cardiac pains and respiratory difficulties entailing death within 3 days. Finally, the victims were all very active in agricultural works and they were in charge of phytosanitary protection and seedling.

The nature of the clinical signs and the fact that most of the affected persons died suggests a poisoning by pesticides as it was the case in 1996 in the villages of Boucotte and Kabrousse (Region of Ziguinchor). The inves- investigations that were carried out at the period made it possible to identify Fenitrothion as source of the intoxication. In the present case, government authorities sent a team of epidemiologists and toxicologists in the concerned localities in order to identify the causes of intoxication. PAN Africa also undertook a mission of investigation in the region of Kilda from 11 to 14 September 2000. This mission aimed at establishing a link between the poisonings and pesticides.

## FIELD INVESTIGATIONS

They consisted in interviews with survivors and victims' relatives. The investigation were carried out in the villages of Saré Bidji, Mbadany and Saré Sara in the department of Kolda. The village of Samé Kanta was chosen due to its easy accessibility for the investigations in the department of Sédhiou. The interviewers also tried to collect a maximum of information on the villages that they could not visit . The investigations were therefore completed by interviews with regional and local medical authorities and mangers of local organisms working the agricultural sector (Regional Direction for the Protection of Vegetables and SONAGRAINES)

## RESULTS

The main pesticides that re used in these villages were provided by the SONAGRAINES during the distribution of seeds.

- Proxopur or Pirimiphos methyl (which is no longer used) for the disinfection of closed metallic storage facilities ("seccos") and

| Product | Active Substance | Chemical Group | Nature of the product | Supplier |
|---|---|---|---|---|
| *Actellic (ULV)* | *Pirimiphos-methyl* | Organo-phosphorus | Insecticide | |
| *Baygon (ULV)* | *Propoxur* | Carbamate | Insecticide | SPIA |
| *Sumithion 4% (DP)* | *Fenitrothion* | Organo-phosphorus | Insecticide, Acaricide | SPIA |
| *Phostoxin (FUM)* | *Phosphine* | Inorganic Compound | Insecticide, Rodenticide | |
| *Spinox T or Granox (DP)* | *Thiram 15% + Benomyl 7% + Carbofuran 10%* | Carbamate<br>Carbamate | Fungicide<br>Fungicide, Insecticide, Acaricide, Nematicide | SPIA |

powder for open-air storage areas at a rate of 500g per ton of stored product.

- Fénitrothion 4% at a rate of 500g/ton and phosphine for the protection of seed stocks.
  According to the managers of the SONAGRAINES, Fenitrothion 1% was replaced by Fenitrothion 4% two years ago because parasites have become resistant to Fenitrothion 1%.

- Granox for the protection of seedlings at a rate of 100 grams for 100 kg of seeds.

  The product that were provided by the DPV* for the protection of subsistence crops did not reach these villages. According to the Regional Inspector of the Protection of Vegetables, they were diverted by some Village Struggle Committees of the "reference villages", which are in charge of relaying the distribution in the other villages.

**The Phytosanitary treatment seeds**

The soils are normally treated in the presence of SONAGRAINES agents. Groundnuts are treated with the shell. According to the peasants, the products are very toxic, for they have to hold their nose due to the strong odor of the product when they open the storage facilities. Granox 15% is distributed to farmers at a rate of 100g for 100kg of seeds for the protection of seedlings against granivorous birds, fungus and insects. That treatment concerns husked seeds. The seeds are treated in the sower in order to avoid consumption by human beings and animals or contamination of utensils.

According to several peasants, the products that were used this year are more toxic than those of last year.

**Safety and hygiene rules are not respected**

According to the manager of the s*ecco* of Saré Bidji, the peasants are trained to the utilization of Granox and to hygiene and safety rules. They should not manipulate products with bare hands and they are also supposed to avoid contact with wounds or inhalation of the product by having their back to the wind during manipulation, to avoid smoking during treatments or eating treated seeds etc.
However, some peasants estimated that they were not well prepared to the use of pesticides. This is certainly the reason why most of them do not respect safety instructions. Only one of the interviewed peasants protected his hands y binding them with a used cloth piece. Peasants work without protective equipment. The studies that were undertaken in the rural communities of Saré Bidji and Diana Malahary

show that peasants have dangerous practices that might lead to intoxication. Some of those practices can be quoted here:

- The consumption of seeds that were already treated with Fenitrothion 4% and Phosphine: This happened in the village of Samé Kanté where a former SONACOS worker assets that the chemical products that were used there are not toxic and that he generally consumes already treated seeds . The manager of the SONAGRAINES secco in Saré Bidji has a similar behavior and, when we asked him to show us already treated seeds, he brought a basket of groundnuts that were husked by his wife in order to prepare a meal. Traces of the product could be seen on the shells.

- Many persons take their food with their hands, which are stained with pesticides. Many peasants use their hand in order to mix powder pesticides with seeds in the sower. Other ones use a stick for that purpose, but they use their hands in order to release the disk of their sower. And yet, they do not wash their hands before eating. Some peasants also crunch seeds when they are working and, even if those seeds have not been treated the peasant' hands might have been in contact with pesticides. Some other peasants smoke while treating the seeds, which can cause intoxication. Even the manager of the SONAGRAINES *secco*, who is in charge of training the peasants, does not respect hygiene rules. We saw him manipulating seeds for direct consumption with his hands badly soiled by the Fenitrothion 4% sample that he was just showing us. Pesticides are also used for other purposes, for instance in the struggle against headlice, according to a peasant of Samé Kanta.

- Pesticides are sometimes kept within the habitations and even in places where food reserves are stocked. We met two peasants who used to keep pesticides under their bed. One of them presented symptoms of intoxication during our visit. Another one, who also had similar symptoms, kept an already-open sachet of Granox in a shoulder strap into which he often plunged his hand, for it certainly contained other things. Furthermore, several peasants showed already-open Granox sachets and declared that they were stored in their houses.

The basic hygiene and safety rules are thus ignored by the peasants who do not always realize that their behavior might be extremely dangerous. Four cases can be quoted to illustrate this assessment.

1. The case of Saré Bidji (Region of Kilda). At the beginning of the rainy season, some children poured Granox in a hive in order to kill the bees and collect honey. One of the village inhabitants suffered from chest pains and respiratory difficulties for several days after having consumed that honey.
2. The case of Samé Kanta (Department of Sédhiou. The health assistant of the village used the tray of a sower in order to stop the rainwater that was flowing from his roof. and yet the sower was already stained with Granox. The assistant realised a few minutes later that drops fell from the tray into his mouth. He was aware of the danger and immediately went to buy milk. He started feeling chest pains and

respiratory difficulties at that moment.

3. The case of Saré Sara (Region of Kolda). A patient that we met in that villag4e informed us that hid daughter one prepared already treated seeds without being aware of that fact. When they took their meal, her husband and her presented the same symptoms: swelling of legs and stomach, chest pains and respiratory difficulties.

**CONCLUSION**

The information that we collected in the villages of Saré Bidji, Mbadany, Saré Sara (Department of Kolda) and Samé Kanta (Department of Sédhiou) sparks off strong presumptions about the existence of a link between pesticides (Thirame 15% + Benomyl 7% + Carbofuran 10%, Fenitrothion, Phosphine and Propoxur) and the mysterious death cases.

Although the governmental Commission did not determine yet the causes of these death instances, the using conditions of pesticides show strong probabilities of intoxication.

Study carried out by Henry René Diouf

[1] This rural community is situated at 40 km from the city of Kolda
2 A local variety of beans
3 Local ethnic group
4 idem
5 Thiram 15% + Benomyl 7% + Carbofuran 10%
6 National Direction for the Protection of Vegetables
7 A local storage facility

## ANNEX IV: Translation of the label for the formulations GRANOX T.B.C. and SPINOX T

(Originals of the labels, in French, will be available upon demand at the meeting)

**GRANOX T.B.C.**

**15.7.10**

**Thiram 15%**
**Benomyl 7%**
**Carbofuran 10%**

**Fungicide – Insecticide**

**SHELLED PEANUT SEED TREATMENT**

DOSAGE for ½ HECTARE:

POISON

Distributed by SONAGRAINES

Campaign 1998-1999

Manufactured by
SENCHIM-AG
BP 21236 DAKAR SENEGAL

NET WEIGHT: 100g

PRECAUTIONS
1- Store out of reach of children and animals.
2- For application, use preferably tools not intended for cooking or for animals.
3- Do not apply this product where there are open wounds or cuts on hands.
4- Do not drink, eat or smoke during application avoid to breath the dust during the mixing, apply with the back to the wind.
5- Wash your hands and face carefully after application with water and soap.
6- Wash the tools used.
7- Do not eat the treated seeds.

Death hazard, even if the skin is removed

ANTIDOTE:
Atropine sulfate

**SPINOX T**

**Thiram 15%**
**Benomyl 7%**
**Carbofuran 10%**

**SHELLED PEANUT SEED TREATMENT**

DOSAGE:

1 bag of 100g for
- 25 kg oil peanuts
- 40 kg mouth peanuts

PRECAUTIONS

SINOX 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

Net weight
100 g. (SEE ICON) S.P.I.A.

LOUGA Plant
Industrial Zone
B.P.02

65 Avenue Faidherbe
B.P. 1806-Dakar

# ANNEX V – Information collected on the active ingredient benomyl (CAS N.: 17804-35-2)

5.1- JMPR Review on benomyl – Excerpt from 1995 Report
5.2- Pesticide Data Sheet on benomyl (INCHEM database)
5.3- International Chemical Safety Cards on benomyl (INCHEM database)
5.4- EXTOXNET Pesticide information Profile on benomyl (USEPA website)

# ANNEX V – Information collected on the active ingredient benomyl

***5.1 - JMPR Review on benomyl* – (Excerpt from 1995 Report)**

## TOXICOLOGY

Benomyl was evaluated toxicologically by the Joint Meeting in 1973, 1975, 1978 and 1983. In 1983 an ADI of 0-0.02 mg/kg bw was established, after a review of data on the toxicity of carbendazim and benomyl and incorporating a higher-than-normal safety factor because of the paucity of data on individual animals in many studies. The compound was reviewed by the present Meeting within the CCPR periodic review programme, with particular attention to the recent Environmental Health Criteria monograph on benomyl (EHC 148).

Benomyl is readily absorbed by animals after oral exposure and rapidly metabolized. It is eliminated in the faeces and excreted in the urine. Ninety eight per cent of the dose was excreted by 72 h after administration. The tissue distribution showed no bioconcentration. In rats, the metabolites carbendazim and methyl 5-hydroxybenzimidazol-2-ylcarbamate (5-hydroxycarbendazim) were found in the blood and in small amounts in the testes and liver. The latter compound was the main metabolite in urine. A 50% wettable powder formulation was poorly absorbed via the dermal route by rats. After a 10-h exposure, less than 2% of a single dose of 0.2 mg was excreted in the urine.

Benomyl has low acute toxicity, with an oral $LD_{50}$ in rats of >10,000 mg/kg bw. The clinical signs of toxicity after high single doses were generally non-specific. Testicular degeneration, with necrosis of germinal epithelium and aspermatogenesis, has been observed after single doses in rats (≥100 mg/kg bw orally) and dogs (1.65 mg/litre air by inhalation). Wettable powder formulations containing benomyl have been shown to be mildly irritating to rabbit skin and eyes and have also induced skin sensitization reactions in maximization tests. The WHO has classified benomyl as unlikely to present an acute hazard in normal use.

In a 90-day study, rats were given dietary doses of 0, 100, 500 or 2500 ppm benomyl. Increased liver weight was seen at 2500 ppm; the NOAEL was 500 ppm (50 mg/kg bw per day). Dogs were given dietary doses of 0, 100, 500 or 2500 ppm benomyl for three months or two years and rabbits were treated dermally, five days per week for three weeks, with 0, 50, 250, 500, 1000 or 5000 mg/kg bw per day. Hepatotoxicity was seen in the dogs but not in the rabbits; effects on male reproductive organs were seen in both rabbits and dogs. The NOAEL was 500 ppm (equal to 13 mg/kg bw per day) in dogs, and 500 mg/kg bw per day in rabbits.

In a two-year study, benomyl was administered in the diet to rats at 0, 100, 500 or 2500 ppm. Benomyl was not carcinogenic and showed no compound-related effects at dietary levels up to and including 2500 ppm (equal to 109 mg/kg bw per day). In a two-year feeding study in mice at dietary levels of 0, 500, 1500 or 5000 ppm, benomyl caused liver tumours, and a no-effect level could not be established for hepatocellular neoplasms. Male mice had decreased testicular weights and thymic atrophy at 5000 ppm. The lowest dietary level was equal to 64 mg/kg bw per day.

In rats treated by gavage for 62 days with 45 mg benomyl/kg bw per day, decreased testicular and epididymal weight, reduced caudal sperm reserves and decreased sperm production, with generalized disruption of all stages of spermatogenesis were observed. After mating with untreated females, no effect was seen on reproductive behaviour, weight of the seminal vesicles, sperm mobility, or related reproductive hormones. The NOAEL was 15 mg/kg bw per day. A lowering of male fertility

rates has been reported, but this effect was not seen consistently. A single dose of 100 mg/kg bw or more administered to rats by gavage had effects 70 days after exposure which included decreased testicular weight and atrophy of the seminiferous tubules. The NOAEL was 50 mg/kg bw per day. In a recent study of reproductive toxicity, rats received dietary doses of 0, 100, 500, 3000 or 10 000 ppm benomyl. The NOAEL was 500 ppm (equivalent to 37 mg/kg bw per day), on the basis of effects on pup survival and pup growth and on testicular changes. Fertility indices were not affected at dietary levels up to 10,000 ppm.

In a study of developmental toxicity, mice were exposed by gavage to benomyl at doses of 0, 50, 100 or 200 mg/kg bw per day on days 7-17 of gestation. There was no indication of maternal toxicity, but benomyl was teratogenic at doses of 100 and 200 mg/kg bw per day and fetotoxic at 50 mg/kg bw per day. The major abnormalities included hydrocephaly, cleft palate, and limb defects. In studies of teratogenicity, pregnant rats were exposed to benomyl at doses up to and including 125 mg/kg bw per day on days 7-16 of gestation. Benomyl was teratogenic, the major effects being microphthalmia and hydrocephaly. The Meeting concluded that the NOAELs in rats were 30 mg/kg bw per day for teratogenicity and fetotoxicity and 125 mg/kg bw per day for maternal toxicity. In rabbits, benomyl was not teratogenic at doses up to 180 mg/kg bw per day (the highest dose tested), and no effect was seen on maternal toxicity or fetotoxicity at 90 mg/kg bw per day.

Benomyl has been adequately tested for genotoxicity in a range of assays. The Meeting concluded that benomyl does not directly damage genetic material but does cause numerical chromosomal changes both *in vitro* and *in vivo* as a result of its interference with the mitotic spindle proteins.

In an epidemiological study of workers exposed to benomyl, there was no reduction in fertility, as indicated by the birth rates, among the study population. Spermatogenesis in the workers was not examined. Cases of dermal sensitization to benomyl have been reported.

An ADI of 0-0.1 mg/kg bw was established on the basis of the NOAEL of 13 mg/kg bw per day in the two-year study in dogs and applying a safety factor of 100. This ADI should be used when assessing exposure to benomyl itself. Since the use of benomyl on crops gives rise to residues of carbendazim and since the ADI for carbendazim is lower than that which would be derived from the data on benomyl, the Meeting concluded that the intake of residues in food should be compared with the ADI of 0-0.03 mg/kg bw for carbendazim.

A toxicological monograph was prepared, summarizing the data received since the previous evaluation and including summaries from the previous monograph and monograph addenda.

## TOXICOLOGICAL EVALUATION

Levels that cause no toxic effect

Mouse: <500 ppm, equal to <64 mg/kg bw per day (two-year study of toxicity and carcinogenicity)
50 mg/kg bw per day (study of developmental toxicity)
<50 mg/kg bw per day (fetotoxicity in a study of teratogenicity)

Rat: 2500 ppm, equal to 109 mg/kg bw per day (two-year study of toxicity and carcinogenicity)
500 ppm, equivalent to 37 mg/kg bw per day (study of reproductive toxicity)
30 mg/kg bw per day (teratogenicity and fetotoxicity in a study of developmental toxicity)
125 mg/kg bw per day (maternal toxicity in a study of developmental toxicity)

Rabbit: 180 mg/kg bw per day (study of developmental toxicity)
90 mg/kg bw per day (maternal toxicity and fetotoxicity in a study of developmental toxicity)

Dog: 500 ppm, equal to 13 mg/kg bw per day (one-year study)

Estimate of acceptable daily intake for humans

0-0.1 mg/kg bw (benomyl)
0-0.03 mg/kg bw (carbendazim, with which residues of benomyl in food should be compared)

Studies that would provide information valuable for the continued evaluation of the compound

Further observations in humans

Toxicological criteria for estimating guidance values for dietary and non-dietary exposure to benomyl

| Exposure | Relevant route, study type, species | Results, remarks |
|---|---|---|
| **Short-term (1-7 days)** | **Oral, toxicity, rat** | **$LD_{50}$ >10 000 mg/kg bw** |
| | **Dermal, toxicity, rabbit** | **$LD_{50}$ (50% wettable powder) >10 000 mg/kg bw** |
| | **Dermal, irritation, rabbit** | **50% wettable powder - irritating** |
| | **Ocular, irritation, rabbit** | **50% wettable powder - irritating** |
| | **Dermal, sensitization, guinea-pig** | **Positive in maximization test** |
| | **Inhalation, toxicity, rat** | **$LC_{50}$ of 50% wettable powder >4.01 mg/litre air** |
| **Mid-term (1-26 weeks)** | **Oral, 62 days, rat** | **NOAEL=15 mg/kg bw per day; reduced spermatogenesis** |
| | **Oral, developmental toxicity, rat** | **NOAEL=30 mg/kg bw per day; fetotoxicity and teratogenicity** |
| **Long-term (> one year)** | **Dietary, two years toxicity, dog** | **NOAEL=13 mg/kg bw per day; hepatotoxicity** |

***5.2- Pesticide Data Sheet on benomyl (INCHEM database)***

**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 $5 \times 10^{-6}$ 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.

**REFERENCES**

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***5.3- International Chemical Safety Cards on benomyl (INCHEM database)***

| TYPES OF HAZARD/EXPOSURE | ACUTE HAZARDS/SYMPTOMS | PREVENTION | FIRST AID/FIRE FIGHTING |
|---|---|---|---|
| FIRE | Combustible. | NO open flames. | Powder, alcohol-resistant foam, water spray, carbon dioxide. |
| EXPLOSION | | | |
| EXPOSURE | | PREVENT DISPERSION OF DUST! | |
| INHALATION | Abdominal cramps, dullness, sweating, nausea, vomiting, salivation. | Local exhaust or breathing protection. | Fresh air, rest, and refer for medical attention. |
| SKIN | Redness. | Protective gloves. | Remove contaminated clothes, and rinse and then wash skin with water and soap. |
| EYES | | Safety goggles. | First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then take to a doctor. |
| INGESTION | Nausea, vomiting (further see Inhalation). | | Rinse mouth, and refer for medical attention. |

| SPILLAGE DISPOSAL | STORAGE | PACKAGING & LABELLING |
|---|---|---|
| Sweep spilled substance into containers, then remove to safe place. | Separated from strong bases, strong acids, food and feedstuffs, dry. | Do not transport with food and feedstuffs. |

| | | |
|---|---|---|
| IMPORTANT DATA | **PHYSICAL STATE; APPEARANCE:** WHITE CRYSTALLINE POWDER , WITH CHARACTERISTIC ODOUR. | **INHALATION RISK:** A harmful contamination of the air will not or will only very slowly be reached on evaporation of this substance at 20°C. |
| | **CHEMICAL DANGERS:** The substance decomposes slowly in aqueous solution, producing methyl N-(2-benzimidazolyl)carbamate and the ethyl analog. The substance decomposes on heating or by contact with strong acids and strong bases, producing oxides of nitrogen. | **EFFECTS OF SHORT-TERM EXPOSURE:** The substance irritates the skin. Exposure could cause depression of the central nervous system and muscular uncoordination. |
| | **OCCUPATIONAL EXPOSURE LIMITS (OELs):** TLV: 0.84 ppm; 10 mg/m3 (as TWA) (ACGIH 1990-1991). | **EFFECTS OF LONG-TERM OR REPEATED EXPOSURE:** Repeated or prolonged contact with skin may cause dermatitis. Repeated or prolonged contact may cause skin sensitization. Animal tests show that this substance possibly causes malformations in human babies. |
| | **ROUTES OF EXPOSURE:** The substance can be absorbed into the body by inhalation and by ingestion. | |

| | | |
|---|---|---|
| PHYSICAL PROPERTIES | Decomposes below melting point at (without melting)°C | |
| | Relative density (water = 1): | see Notes |
| | Solubility in water: | none |
| | Vapour pressure, kPa at 20°C: | negligible |
| ENVIRONMENTAL DATA | This substance may be hazardous to the environment; special attention should be given to fish. | |

| **NOTES** |
|---|
| The substance is used as a pesticide. Relative density is unknown in literature, abortrine, Agrocite, Arilate, BBC, BC 6597, Benlat, Benlate, Benomyl 50W, BNM, D 1991, DuPont 1991, F1991, Fundasol, Fundazol, Fungicide 1991, Fungicide D-1991, Fungochrom, NS 02, Tersan, and Uzgn are trade names. |
| |

| **ADDITIONAL INFORMATION** |
|---|

***5.4- EXTOXNET Pesticide information Profile on benomyl (USEPA website)***

**E X T O X N E T**
**Extension Toxicology Network**
**Pesticide Information Profiles**

A Pesticide Information Project of Cooperative Extension Offices of Cornell University, Oregon State University, the University of Idaho, and the University of California at Davis and the Institute for Environmental Toxicology, Michigan State University. Major support and funding was provided by the USDA/Extension Service/National Agricultural Pesticide Impact Assessment Program.
EXTOXNET primary files maintained and archived at Oregon State University
Revised June 1996

# Benomyl

Trade and Other Names: Commercial names for products containing benomyl include Agrocit, Benex, Benlate, Benosan, Fundazol, Fungidice 1991, and Tersan 1991. Benomyl is compatible with many other pesticides.

Regulatory Status: Benomyl is a General Use Pesticide (GUP). The EPA categorizes it as toxicity class IV - practically nontoxic. Benomyl-containing products carry the Signal Word CAUTION.

Chemical Class: benzimidazole

Introduction: Benomyl is a systemic, benzimidazole fungicide that is selectively toxic to microorganisms and to invertebrates, especially earthworms. It is used against a wide range of fungal diseases of field crops, fruits, nuts, ornamentals, mushrooms, and turf. Formulations include wettable powder, dry flowable powder, and dispersible granules.

Formulation: Formulations include wettable powder, dry flowable powder, and dispersible granules.

Toxicological Effects:

- **Acute toxicity:** Benomyl is of such a low acute toxicity to mammals, it has been impossible or impractical to administer doses large enough to firmly establish an LD50. Thus the LD50 is greater than 10,000 mg/kg in rats and greater than 3400 mg/kg in rabbits (using a 50% wettable powder formulation). Because of its high LD50 there is a low risk for acute poisoning from this compound [1]. Skin irritation may occur for workers exposed to benomyl. Skin reactions have also been seen in rats and guinea pigs. Most organisms can become sensitized to the compound as well. Benomyl is readily absorbed into the body by inhaling the dust, but there are no reports of toxic effects to humans by this route of exposure. The inhalation LC50 in rats is greater than 2 mg/L [2].
- **Chronic toxicity:** When rats were fed diets containing about 150 mg/kg/day for 2 years, no toxic effects were observed [3]. Dogs fed benomyl in their diets for 3 months had no major toxic effects, but did show evidence of altered liver function at the highest dose (150 mg/kg). The damage progressed to more severely impaired liver function and liver cirrhosis after 2 years [6].
- **Reproductive effects:** A three-generation study on rats showed no reproductive or lactational differences at a dose of 150 mg/kg/day administered in the diet [3]. In another study in rats, the testes were the most affected sites at relatively low doses of

about 15 mg/kg/day. Male rats had decreased sperm counts, decreased testicular weight, and lower fertility rates. The animals recovered from these effects 70 days after feeding with the pesticide had stopped [3]. Reproductive effects in humans are unlikely at expected exposure levels.

- **Teratogenic effects:** Very high doses of benomyl can cause birth defects in test animals [4]. Rats fed 150 mg/kg/day in the diet for three generations showed no birth defects. No teratogenicity was observed in another study of rats given 300 mg/kg/day on days 6 to 15 of gestation [4]. At higher doses, some birth defects were noted, but they were accompanied by toxicity to the fetus [4]. In another rat study where mothers were fed 1000 mg/kg/day for 4 months, the offspring showed a decrease in viability and fertility [1]. These data suggest that benomyl is not likely to cause teratogenic effects under normal circumstances.
- **Mutagenic effects:** Conflicting negative and positive results have been found in numerous mutagenicity assays. As a result, no conclusions about the mutagenicity of benomyl can be drawn [3].
- **Carcinogenic effects:** Tumors in the livers of both male and female mice were observed in lifetime studies at doses of benomyl at 40 to 400 mg/kg/day. In a 2-year dietary study when albino rats were fed up to 2500 mg/kg/day of benomyl, there were no significant adverse effects at any dose level attributable to benomyl [1]. Based on these data, it is not possible to determine the carcinogenicity of benomyl [5].
- **Organ toxicity:** Target organs identified in animal studies included the liver and testes.
- **Fate in humans and animals:** Benomyl's metabolism has been studied in the mouse, rat, rabbit, dog, sheep, and cow. Benomyl is rapidly broken down to carbendazim, further to other compounds, such as 5-hydroxy-2-benzimidazole carbamate (5 HBC), and then eliminated. In a rat study, benomyl, carbendazim (MBC), and 5-HBC were found in rat blood in the first 6 hours. After 18 hours, only 5-HBC was present. The urine contained about 40 to 70% of the dose, and the feces 20 to 45%. No residues were found in muscle or fat. Benomyl and its metabolites do not accumulate in tissues over long-term exposure periods [2,3]. Carbendazim (MBC) and the parent compound benomyl have similar toxicological properties, but the former is not a skin sensitizer [2].

Ecological Effects:

- **Effects on birds:** In bobwhite quail and mallard ducks, the 5-day dietary LC50 for benomyl is greater than 10,000 ppm. In redwing blackbirds, the LD50 value is 100 mg/kg, which indicates that benomyl is moderately toxic to this species [4].
- **Effects on aquatic organisms:** Benomyl is highly to very highly toxic to fish. The order of susceptibility to benomyl for various fish species from least susceptible to most susceptible is catfish, bluegill, rainbow trout, and goldfish. The LC50 values for the compound in fish are 0.05 mg/L to 14 mg/L in adults, and 0.006 mg/L in catfish fry [8]. The main breakdown product, carbendazim, had the same order of toxicity as benomyl. Crayfish have an LC50 greater than 100 mg/L. The estimated bioconcentration factor (BCF) ranges from 159 in rainbow trout up to 460 in bluegill sunfish, indicating that benomyl does not tend to significantly concentrate in living tissue [8,9].
- **Effects on other organisms:** A single application of benomyl to turf grass can substantially reduce some soil dwelling organisms. The compound is very lethal to earthworms at low concentrations over a long time period. The 7-day LC50 in earthworms is 1.7 mg/L and the 14-day LC50 is 0.4 mg/L [6]. Benomyl also decreases

the mixing of soil and thatch. The effects last for up to 20 weeks [10]. Benomyl is relatively nontoxic to bees [2].

Environmental Fate:

- **Breakdown in soil and groundwater:** Benomyl is strongly bound to soil and does not dissolve in water in flooded rice fields to any significant extent [2,11]. It is highly persistent. When applied to turf, it has a half-life of 3 to 6 months and, when applied to bare soil the half-life is 6 to 12 months. Where four successive annual applications were applied, residues did not accumulate from one year to the next [6].
- **Breakdown in water:** Benomyl completely degrades to carbendazim within several hours in acidic or neutral water. The half-life of carbendazim is 2 months [1].
- **Breakdown in vegetation:** Since benomyl is a systemic fungicide, it is absorbed by plants. Once it is in the plant, it accumulates in veins and at the leaf margins [6]. The metabolite carbendazim seems to be the fungicidally active agent. Benomyl residues are quite stable, with 48 to 97% remaining as the parent compound 21 to 23 days after application [6].

Physical Properties:

- **Appearance:** Benomyl is a tan crystalline solid compound. It has little or no odor [1].
- **Chemical Name:** methyl-1-[(butylamino)carbonyl]-H-benzimidazol-2-ylcarbamate [1]
- **CAS Number:** 17804-35-2
- **Molecular Weight:** 290.62
- **Water Solubility:** 2 mg/L [1]
- **Solubility in Other Solvents:** chloroform s.; heptane s.; ethanol s.; acetone s. [1]
- **Melting Point:** Decomposes without melting above 300 C [1]
- **Vapor Pressure:** Negligible (<1 mPa) at 20 C [1]
- **Partition Coefficient:** Not Available
- **Adsorption Coefficient:** 1900 [1]

Exposure Guidelines:

- **ADI:** 0.02 mg/kg/day [12]
- **MCL:** Not Available
- **RfD:** 0.05 mg/kg/day [13]
- **PEL:** 5 mg/m3 (8-hour) (respirable fraction) [14]
- **HA:** Not Available
- **TLV:** Not Available

Basic Manufacturer:

DuPont Agricultural Products
Walker's Mill, Barley Mill Plaza
P.O. Box 80038
Wilmington, DE 19880-0038

- **Phone:** 800-441-7515
- **Emergency:** 800-441-3637

# ANNEX VI – Information collected on the active ingredient carbofuran (CAS N.: 1563-66-2)

# ANNEX VI – Information collected on the active ingredient carbofuran

## *6.1- JMPR Review on carbofuran – Excerpt from 1996 Report*

### TOXICOLOGY

Carbofuran was evaluated for toxicological effects by the Joint Meeting in 1976, 1979, 1980, and 1982. The 1980 Meeting established an ADI of 0-0.01 mg/kg bw, which was confirmed in 1982. The compound was re-evaluated at the present Meeting within the CCPR periodic review programme.

Carbofuran is rapidly absorbed, metabolized, and eliminated, mainly in the urine, after oral administration to mice and rats. After oral administration of [*phenyl*-$^{14}$C]carbofuran to rats, 92% of the radiolabel was eliminated in the urine and 3% in the faeces. Most of the radiolabel was eliminated within 24 h after treatment. With the [$^{14}$C]carbonyl-labelled compound, 45% was eliminated as [$^{14}$C]carbon dioxide. The metabolic pathway involves hydroxylation, hydrolysis, oxidation and conjugation.

Carbofuran is highly toxic after acute oral administration. The oral $LD_{50}$ values in various species ranged from 3 to 19 mg/kg bw. Carbofuran had no sensitizing potential in guinea-pigs, and no local irritation was found in rabbits after repeated dermal applications over 7 or 21 days. WHO has classified carbofuran as 'highly hazardous'.

In a 13-week study in dogs fed diets providing 0, 10, 70, or 500/250 ppm carbofuran (dose reduced because of marked toxicity), an NOAEL was not identified because inhibition of erythrocyte acetylcholinesterase activity and some clinical signs were observed at the lowest dose. In a subsequent four-week study in dogs, the only dose administered was 5 ppm, equal to 0.22 mg/kg bw per day, which was the NOAEL for clinical signs, mortality, body weight, food consumption, and cholinesterase activity in plasma and erythrocytes. In a one-year study in dogs at dietary concentrations of 0, 10, 20, or 500 ppm, the NOAEL was 10 ppm, equal to 0.3 mg/kg bw per day, on the basis of histopathological testicular changes in a single male at 20 ppm; similar changes were observed in animals at 500 ppm. There was no inhibition of erythrocyte or brain acetylcholinesterase at concentrations of 10 or 20 ppm. The overall NOAEL in these short-term studies in dogs was 5 ppm, equal to 0.22 mg/kg bw per day.

In two-year studies of toxicity and carcinogenicity at dietary concentrations of 0, 20, 125, or 500 ppm in mice and 0, 10, 20, or 100 ppm in rats the NOAELs were 20 ppm, equal to 2.8 mg/kg bw per day, in mice and 20 ppm, equivalent to 1 mg/kg bw per day, in rats, on the basis of inhibition of erythrocyte and brain acetylcholinesterase activity. There was no evidence of tumorigenicity.

In a three-generation study of reproductive toxicity in rats at dietary concentrations of 0, 20, or 100 ppm, the NOAEL was 20 ppm, equal to 1.6 mg/kg bw per day, on the basis of reduced body-weight gain in parental animals and reduced pup growth and pup survival at 100 ppm.

In an early study of developmental toxicity, rats were given carbofuran at doses of 0, 0.1, 0.3, or 1 mg/kg bw per day by gavage. An NOAEL could not be identified in this study. Dose-dependent transient clinical signs (chewing motions) were observed in the dams. In a later study in rats at oral doses of 0, 0.25, 0.5, or 1.2 mg/kg bw per day the NOAEL for maternal and fetal toxicity was 1.2 mg/kg bw per day, the highest dose tested. In a further study of teratogenicity in rats, with dietary administration of 0, 20, 60, or 160 ppm carbofuran, the NOAEL for maternal toxicity was 20 ppm, equal to 1.5 mg/kg bw per day, on the basis of a reduction in body-weight gain at 60 ppm. The NOAEL for pup toxicity, based on reduced pup weight, was 60 ppm, equal to 4.4 mg/kg bw per day. None of the studies showed teratogenic potential.

The results of an early study of developmental toxicity in rabbits at oral doses of 0, 0.2, 0.6, or 2 mg/kg bw per day showed an NOAEL of 0.6 mg/kg bw per day for maternal toxicity on the basis of clinical signs, and an NOAEL of 2 mg/kg bw per day for fetotoxicity and teratogenicity. In a subsequent study in rabbits at doses of 0, 0.12, 0.5, or 2 mg/kg bw per day, the NOAEL was 0.5 mg/kg bw per day on the basis of slightly reduced body-weight gain in dams and a slightly increased incidence of skeletal variations in pups at 2 mg/kg bw per day. These studies provided no evidence of teratogenicity.

In a 90-day study of neurotoxicity in rats at dietary concentrations of 0, 50, 500, or 1000 ppm, systemic toxicity (reduction in body-weight gain) was observed at all doses. Clinical signs of neurotoxicity were observed at 500 and 1000 ppm. No histopathological lesions in the nervous system were observed.

In a study of developmental neurotoxicity, carbofuran was administered in the diet to provide concentrations of 0, 20, 75, or 300 ppm from gestation day 6 through lactation day 10. Reductions in body-weight gain in dams and pups and in pup survival and some evidence of delayed pup development were found at 75 ppm and higher. The NOAEL was 20 ppm, equal to 1.7 mg/kg bw per day, on the basis of reduced body-weight gain in dams and signs of fetotoxicity at higher doses.

Carbofuran has been tested for genotoxicity in a wide range of tests *in vivo* and *in vitro*. The Meeting concluded that it is not genotoxic.

An ADI of 0-0.002 mg/kg bw was allocated on the basis of the NOAEL for erythrocyte acetylcholinesterase inhibition of 0.22 mg/kg bw per day in a four-week study in the most sensitive species, the dog, using a 100-fold safety factor. The use of a short-term study to determine the ADI was justified because the effect observed was reversible and acute.

A toxicobgical monograph was prepared, summarizing the data received since the previous evaluation and including summaries from the previous monograph.

## TOXICOLOGICAL EVALUATION

### Levels that cause no toxic effect

Mouse: 20 ppm, equal to 2.8 mg/kg bw per day (two-year study of toxicity and carcinogenicity)

Rat: 20 ppm, equivalent to 1 mg/kg bw per day (two-year study of toxicity and carcinogenicity)

20 ppm, equal to 1.2 mg/kg bw per day (three-generation study of reproductive toxicity)

1.2 mg/kg bw per day (highest dose tested in a study of developmental toxicity)

20 ppm, equal to 1.5 mg/kg bw per day (study of developmental toxicity)

20 ppm, equal to 1.7 mg/kg bw per day (study of developmental neurotoxicity)

Rabbit: 0.6 mg/kg bw per day (study of developmental toxicity)

Dog: 5 ppm, equal to 0.22 mg/kg bw per day (four-week study of toxicity)

Estimate of acceptable daily intake for humans
0-0.002 mg/kg bw

Studies that would provide information useful for the continued evaluation of the compound
Further observations in humans.

**Toxicological criteria for setting guidance values for dietary and non-dietary exposure to carbofuran**

| EXPOSURE | RELEVANT ROUTE, STUDY TYPE, SPECIES | RESULT, REMARKS |
|---|---|---|
| Short-term (1-7 days) | Oral toxicity, rat | $LD_{50}$ = 6-14 mg/kg bw |
| | Dermal toxicity, rat | $LD_{50}$ >500 mg/kg bw |
| | Inhalation toxicity, rat | $LC_{50}$ = 0.088-0.1 mg/litre |
| | Dermal irritation, rabbit | Not irritating |
| | Ocular irritation, rabbit | Not available |
| | Dermal sensitization, guinea-pig | Not sensitizing |
| Medium-term (1-26 weeks) | Repeated oral, 4 weeks, toxicity, dog | NOAEL = 0.22 mg/kg bw per day |
| | Repeated oral, reproductive toxicity, rat | NOAEL = 1.6 mg/kg bw per day, parental and pup toxicity |
| | Repeated oral (gavage), developmental toxicity, rat | NOAEL = 1.2 mg/kg bw per day (highest dose tested). No evidence of teratogenicity |
| | Repeated oral (feeding), developmental toxicity, rat | NOAEL = 1.5 mg/kg bw per day, maternal toxicity |
| | Repeated oral, developmental toxicity, rabbit | NOAEL = 0.6 mg/kg bw per day, maternal toxicity. No evidence of teratogenicity |

| EXPOSURE | RELEVANT ROUTE, STUDY TYPE, SPECIES | RESULT, REMARKS |
|---|---|---|
| | Repeated oral, developmental neurotoxicity, rat | NOAEL = 1.7 mg/kg bw per day |
| Long-term (≥ one year) | Repeated oral, two years, carcinogenicity, mouse | NOAEL = 2.8 mg/kg bw per day, cholinesterase inhibition. No evidence of carcinogenicity |
| | Repeated oral, two years, carcinogenicity, rat | NOAEL = 1 mg/kg bw per day, reduced body-weight gain and cholinesterase inhibition. No evidence of carcinogenicity. |

*6.2- Pesticide Data Sheet on carbofuran (INCHEM database)*

**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** - $2.66 \times 10^{-6}$ kPa ($2 \times 10^{-5}$ mmHg), 33°C $1.33 \times 10^{-5}$ kPa ($1 \times 10^{-4}$ 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.

***6.3- International Chemical Safety Cards on carbofuran (INCHEM database)***

| TYPES OF HAZARD/ EXPOSURE | ACUTE HAZARDS/SYMPTOMS | PREVENTION | FIRST AID/FIRE FIGHTING |
|---|---|---|---|
| FIRE | Not combustible, liquid formulations containing organic solvents may be flammable, gives off irritating or toxic fumes (or gases) in a fire. | | In case of fire in the surroundings: all extinguishing agents allowed. |
| EXPLOSION | Risk of fire and explosion if formulations contain flammable/explosive solvents. | | |
| EXPOSURE | | PREVENT DISPERSION OF DUST! STRICT HYGIENE! AVOID EXPOSURE OF ADOLESCENTS AND CHILDREN! | IN ALL CASES CONSULT A DOCTOR! |
| INHALATION | Dizziness, sweating.Laboured breathing, unconsciousness, vomiting, pupillary constriction, muscle cramp, excessive salivation. | Ventilation (not if powder), local exhaust, or breathing protection. | Fresh air, rest, refer for medical attention, and see Notes. |
| SKIN | | Protective gloves, protective clothing. | Rinse and then wash skin with water and soap. |
| EYES | | Safety spectacles. | First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then take to a doctor. |
| INGESTION | Abdominal cramps, diarrhoea, headache, nausea, vomiting, weakness (further see Inhalation). | Do not eat, drink, or smoke during work, wash hands before eating. | Give a slurry of activated charcoal in water to drink, induce vomiting (ONLY IN CONSCIOUS PERSONS!), rest, refer for medical attention. |

| SPILLAGE DISPOSAL | STORAGE | PACKAGING & LABELLING |
|---|---|---|
| Do NOT wash away into sewer, sweep spilled substance into containers; if appropriate, moisten first to prevent dusting, carefully collect remainder, then remove to safe place (extra personal protection: complete protective clothing including self-contained breathing apparatus). | Provision to contain effluent from fire extinguishing, separated from food and feedstuffs. Keep in a well-ventilated room. | Do not transport with food and feedstuffs.<br><br>T+ symbol<br>R: 26/28<br>S: 1/2-<br>)36/37-45<br><br>UN Hazard Class: 6.1<br>UN Packing Group: II<br>Marine pollutant. |

| | | |
|---|---|---|
| IMPORTANT DATA | **PHYSICAL STATE; APPEARANCE:**<br>COLOURLESS CRYSTALS. | **INHALATION RISK:**<br>Evaporation at 20°C is negligible; a harmful concentration of airborne particles can, however, be reached quickly on spraying or when dispersed, especially if powdered. |
| | **CHEMICAL DANGERS:**<br>The substance decomposes on heating producing toxic fumes including nitrogen oxides. | **EFFECTS OF SHORT-TERM EXPOSURE:**<br>The substance may cause effects on the nervous system , resulting in convulsions, respiratory failure. Cholinesterase inhibitor. Exposure may result in death. The effects may be delayed. Medical observation is indicated. |
| | **OCCUPATIONAL EXPOSURE LIMITS (OELs):**<br>TLV: ppm; 0.1 mg/m3 (ACGIH 1993-1993). | **EFFECTS OF LONG-TERM OR REPEATED EXPOSURE:**<br>The substance may have effects on the immune system. Cholinesterase inhibitor; cumulative effect is possible: see acute hazards/symptoms. |
| | **ROUTES OF EXPOSURE:**<br>The substance can be absorbed into the body by inhalation through the skin and by ingestion. | |

| | | |
|---|---|---|
| PHYSICAL PROPERTIES | Melting point: | 153-154°C |
| | Relative density (water = 1): | 1.2 |
| | Solubility in water, g/100 ml at 25°C: | 0.07 |
| | Vapour pressure, Pa at 33°C: | 0.0027 |
| | Octanol/water partition coefficient as log Pow: | 2.32 |
| ENVIRONMENTAL DATA | This substance may be hazardous to the environment; special attention should be given to water organisms, soil organisms, honey bees and birds. | |

| **NOTES** |
|---|
| Temperature of decomposition unknown in literature, specific treatment is necessary in case of poisoning with this substance; the appropriate means with instructions must be available, carrier solvents used in commercial formulations may change physical and toxicological properties, do NOT take working clothes home, bay 70143, Curaterr, FMC 10242, Furadan, Niagara 10242, Pillarfuran and Yaltox are trade names, if the substance is present under the form of a formulation containing hydrocarbon solvents, vomiting may not be induced. |
| Transport Emergency Card: TEC (R)-61G46<br>If the pesticide is formulated with an organic solvent, also consult the ICSC of the solvent used. |

| **ADDITIONAL INFORMATION** |
|---|
| |

***6.4- EXTOXNET Pesticide information Profile on carbofuran (USEPA website)***

**E X T O X N E T**
**Extension Toxicology Network**
**Pesticide Information Profiles**

A Pesticide Information Project of Cooperative Extension Offices of Cornell University, Oregon State University, the University of Idaho, and the University of California at Davis and the Institute for Environmental Toxicology, Michigan State University. Major support and funding was provided by the USDA/Extension Service/National Agricultural Pesticide Impact Assessment Program.
EXTOXNET primary files maintained and archived at Oregon State University
Revised June 1996

# Carbofuran

Trade and Other Names**:** Trade names include Furadan, Bay 70143, Carbodan, Carbosip, Chinofur, Curaterr, D 1221, ENT 27164, Furacarb, Kenafuran, Pillarfuron, Rampart, Nex, and Yaltox.

Regulatory Status**:** Following a Special Review, the EPA initiated a ban on all granular formulations of carbofuran which became effective on September 1, 1994. Before 1991, 80% of the total usage of carbofuran was in granular formulations. The ban was established to protect birds and is not related to human health concerns. Bird kills have occurred when birds ingested carbofuran granules, which resemble grain seeds and when predatory or scavenging birds have ingested small birds or mammals which had eaten carbofuran pellets. There is no ban on liquid formulations of carbofuran. Liquid formulations of carbofuran are classified as Restricted Use Pesticides (RUP) because of their acute oral and inhalation toxicity to humans. Granular formulations are also classified as RUP's, but for a different reason; their toxicity to birds. Liquid formulations bear the Signal Word WARNING. Granular formulations bear the Signal Word DANGER. Formulations of carbofuran are in toxicity class I - highly toxic or toxicity class II - moderately toxic.

Chemical Class: carbamate

Introduction**:** Carbofuran is a broad spectrum carbamate pesticide that kills insects, mites, and nematodes on contact or after ingestion. It is used against soil and foliar pests of field, fruit, vegetable, and forest crops. Carbofuran is available in liquid and granular formulations, but as stated avove the granule form is banned in the U.S.

Formulation: Carbofuran is available in liquid and granular formulations, but as stated above, the granular form is banned in the U.S.

Toxicological Effects:

- **Acute toxicity:** Carbofuran is highly toxic by inhalation and ingestion and moderately toxic by dermal absorption [5]. As with other carbamate compounds, carbofuran's cholinesterase-inhibiting effect is short-term and reversible [5]. Symptoms of carbofuran poisoning include: nausea, vomiting, abdominal cramps, sweating, diarrhea, excessive salivation, weakness, imbalance, blurring of vision, breathing difficulty, increased blood pressure, and incontinence. Death may result at high doses

from respiratory system failure associated with carbofuran exposure [5]. Complete recovery from an acute poisoning by carbofuran, with no long-term health effects, is possible if exposure ceases and the victim has time to regain their normal level of cholinesterase and to recover from symptoms [5]. The oral LD50 is 5 to 13 mg/kg in rats, 2 mg/kg in mice, and 19 mg/kg in dogs. The dermal LD50 is >1000 mg/kg in rabbits, [5]. The LC50 (4-hour) for inhalation of carbofuran is 0.043 to 0.053 mg/L in guinea pigs [10].

- **Chronic toxicity:** Rats given very high doses (5 mg/kg/day) for two years showed decreases in weight. Similar tests with mice gave the same results [5]. Prolonged or repeated exposure to carbofuran may cause the same effects as an acute exposure [5].
- **Reproductive effects:** Consuming high doses over long periods of time caused damage to testes in dogs, but carbofuran did not have any reproductive effects on rats or mice [5]. Available studies indicate carbofuran is unlikely to cause reproductive effects in humans at expected exposure levels.
- **Teratogenic effects:** Studies indicate carbofuran is not teratogenic. No significant teratogenic effects have been found in offspring of rats given carbofuran (3 mg/kg/day) on days 5 to 19 of gestation. No effects were found in offspring of mice given as much as 1 mg/kg/day throughout gestation. In rabbits, up to 1 mg/kg/day on days 6 to 18 of gestation was not teratogenic [5].
- **Mutagenic effects:** Weak or no mutagenic effects have been reported in animals and bacteria. Carbofuran is most likely nonmutagenic [5].
- **Carcinogenic effects:** Data from animal studies indicate that carbofuran does not pose a risk of cancer to humans [5].
- **Organ toxicity:** Carbofuran causes cholinesterase inhibition in both humans and animals, affecting nervous system function.
- **Fate in humans and animals:** Carbofuran is poorly absorbed through the skin [32]. It is metabolized in the liver and eventually excreted in the urine. The half-life in the body is from 6 to 12 hours. Less than 1% of a dose will be excreted in a mother's milk. It does not accumulate in tissue [5].

Ecological Effects:

- **Effects on birds:** Carbofuran is highly toxic to birds. One granule is sufficient to kill a small bird. Bird kills have occurred when birds ingested carbofuran granules, which resemble grain seeds in size and shape, or when predatory or scavenging birds have ingested small birds or mammals that have eaten carbofuran pellets [33]. Red-shouldered hawks have been poisoned after eating prey from carbofuran-treated fields [17]. The LD50 is 0.238 mg/kg in fulvous ducks, 0.48 to 0.51 mg/kg in mallard ducks, 12 mg/kg in bobwhite quail, and 4.15 mg/kg in pheasant [17]. The LD50 is 25 to 39 mg/kg in chickens consuming carbofuran as a powder [10]. The LC50 (96-hour) in Japanese quail is 746 ppm [34].
- **Effects on aquatic organisms:** Carbofuran is highly toxic to many fish. The LD50 (96-hour) is 0.38 mg/L in rainbow trout and 0.24 mg/L in bluegill sunfish [10]. The compound has a low potential to accumulate in aquatic organisms. The bioconcentration factor ranges from 10 in snails to over 100 in fish [14].
- **Effects on other organisms:** CArbofuran is toxic to bees except in the granular formulation [10].

Environmental Fate:

- **Breakdown in soil and groundwater:** Carbofuran is soluble in water and is moderately persistent in soil. Its half-life is 30 to 120 days. In soil, carbofuran is degraded by chemical hydrolysis and microbial processes. Hydrolysis occurs more rapidly in alkaline soils [14]. Carbofuran breaks down in sunlight. Carbofuran has a high potential for groundwater contamination [14]. Carbofuran is mobile to very mobile in sandy loam, silty clay, and silty loam soils; moderately mobile in silty clay loam soils; and only slightly mobile in muck soils. Small amounts of carbofuran have been detected (1 to 5 ppb) in water table aquifers beneath sandy soils in New York and Wisconsin [14].
- **Breakdown in water:** In water, carbofuran is subject to degradation by chemical hydrolysis under alkaline conditions. Photodegradation and aquatic microbes may also contribute to degradation. The hydrolysis half-lives of carbofuran in water at 25 C are 690, 8.2, and 1.0 weeks at pH values of 6.0, 7.0, and 8.0, respectively. Carbofuran does not volatilize from water, nor does it adsorb to sediment or suspended particles [14].
- **Breakdown in vegetation:** The half-life of carbofuran on crops is about 4 days when applied to roots, and longer than 4 days if applied to the leaves [8].

Physical Properties:

- **Appearance:** Carbofuran is an odorless, white crystalline solid. Heat breakdown can release toxic fumes. Fires, and the runoff from fire control, may produce irritating or poisonous gases. Closed spaces (storage, etc.) should be aired before entering.
- **Chemical Name:** 2,3-dihydro-2,2-dimethylbenzofuran-7-yl methylcarbamate [10]
- **CAS Number:** 1563-66-2
- **Molecular Weight:** 221.25
- **Water Solubility:** 320 mg/L @ 25 C [10]
- **Solubility in Other Solvents:** acetone v.s.; acetonitrile v.s.; benzene v.s.; cyclohexone v.s. (5)
- **Melting Point:** 153-154 C [10]
- **Vapor Pressure:** 2.7 mPa @ 33 C [10]
- **Partition Coefficient:** 1.2304-1.4150 [10]
- **Adsorption Coefficient:** 22 [13]

Exposure Guidelines:

- **ADI:** 0.01 mg/kg/day [10]
- **MCL:** 0.04 mg/L [19]
- **RfD:** 0.005 mg/kg/day [20]
- **PEL:** Not Available
- **HA**: Not Available
- **TLV**: 0.1 mg/m3 (8-hour) [31]

Basic Manufacturer:

FMC Corporation
Agricultural Chemicals Group
1735 Market Street
Philadelphia, PA 19103

- **Phone:** 215-299-6661 **Emergency:** 800-331-3148

***5.5- Extremely Hazardous Substance Chemical Profile on carbofuran (USEPA website)***

EPA CHEMICAL PROFILE
Date: October 31, 1985
Revision: November 30, 1987

CHEMICAL IDENTITY -- CARBOFURAN

CAS Registry Number: 1563-66-2
Synonyms: Carbamic Acid, Methyl-, 2,3-Dihydro-2,2-Dimethyl-7-Benzofuranyl Ester; 2,2-Dimethyl-2,2-Dihydrobenzofuranyl-7 N-Methylcarbamate; 2,3-Dihydro-2,2-Dimethyl-7-Benzofuranol-N-Methylcarbamate; 2,3-Dihydro-2,2-Dimethylbenzofuranyl Methylcarbamate; 2,3-Dihydro-2,2- Dimethylbenzofuranyl-7-N-Methylcarbamate; 7-Benzofuranol, 2,3-Dihydro- 2,2-Dimethyl-, Methylcarbamate; Bay 70143; Chinufur; Curaterr; D 1221; ENT 27,164; FMC 10242; Furadan; Furadan 3G; Furodan; NIA 10242; Niagara 10242; Niagara Nia-10242; OMS 864; Yaltox; 7-Benzofuranol, 2,3-Dihydro-2,2-Dimethyl-, Methylcarbamate

Chemical Formula: C12H15NO3

Molecular Weight: 221.28

SECTION I -- REGULATORY INFORMATION

CERCLA (SARA) 1986:
Toxicity Value Used for Listing Under Section 302: LC50 inhalation (guinea pig) 0.043 mg/liter/4 hours (*NIOSH/RTECS 1985)
TPQ: 10/10,000 (pounds)
RQ: 10 (pounds) Section 313 Listed (Yes or No): No

SECTION II -- PHYSICAL/CHEMICAL CHARACTERISTICS

Physical State: Solid
Boiling Point: Not Found
Specific Gravity (H2O=1): 1.18 at 20C (*Farm Chemicals Handbook 1984)
Vapor Pressure (mmHg): 0.00002 at 33C (*Farm Chemicals Handbook 1984)
Melting Point: 302-307F, 150-153C (*Merck 1983)
Vapor Density (AIR=1): Not Found
Evaporation Rate (Butyl acetate=1): Not Found
Solubility in Water: 700 ppm at 25C (*Merck 1976)
Appearance and Odor: White crystalline solid (*Merck 1976); odorless (*Farm Chemicals Handbook 1984)

SECTION III -- HEALTH HAZARD DATA

OSHA PEL: Not Found

ACGIH TLV: TWA 0.1 mg/m3 (*ACGIH 1983)
IDLH: Not Found
Other Limits Recommended: Not Found
Routes of Entry: Inhalation: Yes (*DOT 1984)
Skin: Yes (*DOT 1984)
Ingestion: Yes (*DOT 1984)

Health Hazards (Acute, Delayed, and Chronic): This material is extremely poisonous. May be fatal if swallowed, inhaled, or absorbed through skin. Contact may burn skin or eyes (*DOT 1984). Probable lethal oral dose to humans 5 to 50 mg/kg or 7 drops to 1 teaspoon for 150 lb. person (*Gosselin 1976).

Medical Conditions Generally Aggravated by Exposure: Not Found

SECTION IV -- FIRE AND EXPLOSION HAZARD DATA

Flash Point (Method Used): Not Found
Flammable Limits: LEL: Not Found
UEL: Not Found
Extinguishing Methods: Use dry chemical, carbon dioxide, water spray, or foam. Dike fire control water for later disposal, do not scatter the material (*DOT 1984).
Special Fire Fighting Procedures: Stay at maximum distance (*DOT 1984).
Unusual Fire and Explosion Hazards: May release nitrogen oxides (Sax 1984, p. 1152). Containers may explode in heat of fire (*DOT 1984).
NFPA Flammability Rating: Not Found

SECTION V -- REACTIVITY DATA

Stability: Unstable:
Stable: Yes (Under neutral or acid conditions (*Spencer 1982)
Conditions to Avoid: Not Found
Incompatibility (Materials to Avoid): Alkalies (*Merck 1976)

Hazardous Decomposition or Byproducts: Nitrogen oxides (Sax 1984, p. 1152)

Hazardous Polymerization: May Occur: Not Found May Not Occur: Not Found
Conditions to Avoid: Not Found

SECTION VI -- USE

This material is used as an insecticide on corn, alfalfa, tobacco and other field crops (*SRI).

SECTION VII -- PRECAUTIONS FOR SAFE HANDLING AND USE

(Steps to be Taken in Case Material is Released or Spilled)

In case of releases or spills, stay upwind; keep out of low areas. Ventilate closed spaces before entering them (*DOT 1984).

SECTION VIII -- PROTECTIVE EQUIPMENT FOR EMERGENCY SITUATIONS

For emergency situations, wear a positive pressure, pressure-demand, full facepiece self-contained breathing apparatus (SCBA) or pressure- demand supplied air respirator with escape SCBA and a fully-encapsulating, chemical resistant suit. See the introductory information section at the beginning of the profiles for additional information.

SECTION IX -- EMERGENCY TREATMENT INFORMATION

See Emergency First Aid Treatment Guide

# ANNEX VII – Information collected on the active ingredient thiram (CAS N.: 137-26-8)

7.1- JMPR Review on thiram – Excerpt from 1992 Report
7.2- Pesticide Data Sheet on thiram (INCHEM database)
7.3- International Chemical Safety Cards on thiram (INCHEM database)
7.4- EXTOXNET Pesticide information Profile on thiram (USEPA website)

**ANNEX VII – Information collected on the active ingredient thiram**

***7.1- JMPR Review on thiram – Excerpt from 1992 Report***

TOXICOLOGY

Thiram, a dimethyldithiocarbamate fungicide, was evaluated by the Joint Meeting several times between 1963 and 1987. A temporary ADI of 0-0.005 mg/kg bw, allocated in 1974, was extended in 1977 and 1980. The temporary ADI was withdrawn in 1985 because of the inadequacy of the total data base. The studies available to the 1987 Joint Meeting were not adequate for estimating an ADI. A complete data base on thiram has been generated since the previous evaluation, and was evaluated at the present Meeting.

Following oral administration to rats, thiram was well-absorbed (>83%) and eliminated via the expired air (41-48%), urine (25-40%), and faeces (2-5%). About 3% was recovered in various organs. The majority of the dose (84-90%) was eliminated within four days after dosing.

The metabolism of thiram was studied in rats. During the first five hours after administration a dose-dependent formation of carbon disulphide was demonstrated in the expired air. Metabolites detected in urine included polar oxidation products and conjugates.

The acute oral toxicity of thiram is low in mice and rats. The World Health Organization has classified thiram as slightly hazardous.

A 13-week dietary study in rats at levels of 0, 50, 500 or 1000 ppm resulted in changes in haematological and serum biochemical parameters and gastric irritation at 500 and 1000 ppm. The NOAEL was 50 ppm, equivalent to 2.5 mg/kg bw/day.

Dogs received thiram as a dietary admixture at levels of 0, 75, 250 or 500 ppm for 13 weeks or at levels of 0, 30, 90 or 250 ppm for 52 weeks. The NOAELs were 75 ppm (equal to 2.2 and 2.3 mg/kg bw/day in males and females respectively, for the 13-week study) and 30 ppm (equal to 0.84 mg/kg bw/day) in males and 90 ppm (equal to 2.5 mg/kg bw/day) in females in the 52-week study on the basis of changes in body-weight, increased absolute and relative liver weights and changes in haematological and serum biochemical parameters. In another study, dogs received thiram in gelatin capsules at doses of 0, 0.4, 4.0 or 40 mg/kg bw/day 7 days/week for 104 weeks. Nausea, vomiting and salivation, ophthalmological effects, convulsions, changes in haematological parameters, and renal changes were observed at 4 and 40 mg/kg bw/day. On the basis of the described effects, the NOAEL was 0.4 mg/kg bw/day. Since thiram was administered in capsules in this experiment and significantly less information was available on the study conditions than in those in the former two experiments with dietary administrations of thiram this NOAEL was not used as the basis for the estimation of an ADI.

In a 97-week oncogenicity study in mice using dietary concentrations of thiram of 0, 15, 150 and 300/600 ppm, the effects included dose-dependent decreases of food consumption and body-weight gain and changes in haematological parameters. Non-neoplastic findings included retinal atrophy, changes in the urinary bladder and in the skin, hyperkeratosis in the non-glandular stomach, and increased pigmentation in the spleen. Thiram was not carcinogenic in mice. The NOAEL for long-term toxicity in male and female mice was 15 ppm, equal to 3 mg/kg bw/day.

In a two-year toxicity study in rats at dietary concentrations of 0, 3, 30 or 300 ppm a NOAEL of 30 ppm, equal to 1.2 and 1.4 mg/kg bw/day in males and females respectively, was determined. It was based on lower red blood cell counts, haemoglobin levels and haematocrit levels and degenerative changes of the sciatic nerve accompanied by atrophy of the gastrocnemius muscle at 300 ppm. Thiram was not carcinogenic in rats.

In a second two-year long-term/carcinogenicity study in rats at dietary concentrations of 0, 30, 150 or 300 ppm, dose-dependent lower erythrocyte counts, haemoglobin levels and haematocrit values were observed. Based on these haematological changes a NOAEL of 30 ppm, equal to 1.5 and 1.8 mg/kg bw/day in males and females respectively, was determined.

In a 2-year carcinogenicity study in rats at dietary concentrations of 0, 500, or 1000 ppm (equal to 39 and 42 mg/kg bw/day in males and females respectively) there was no evidence of carcinogenicity. The Meeting concluded that thiram was not carcinogenic in rats.

In a two-generation reproduction study in rats at dietary concentrations of 0, 30, 60 or 180 ppm, no adverse effects on reproduction were observed. The NOAEL for reproductive effects was >180 ppm (equal to >8.9 and >14 mg/kg bw/day in males and females, respectively). The NOAEL for systemic toxicity was 30 ppm (equal to 1.5 and 2.3 mg/kg bw/day in males and females respectively). It was based upon reduction in body-weights and/or food consumption in both parental and offspring animals.

An oral teratogenicity study was performed in rats at gavage dose levels of 0, 7.5, 15 and 30 mg/kg bw/day. An NOAEL for maternal toxicity was not determined owing to a dose-dependent decrease in body weight gain and placental weight at all dose levels. Teratogenicity was not observed.

In an oral teratogenicity study in rabbits at gavage doses of 0, 1.0, 2.5 or 5.0 mg/kg bw/day, an NOAEL of 2.5 mg/kg bw/day for maternal toxicity was based on a dose-dependent reduction of body-weight gain. Teratogenicity was not observed.

An oral teratogenicity study was carried out in rabbits at gavage dose levels of 0, 1.0, 5.0 or 10 mg/kg bw/day. The NOAEL for maternal toxicity was higher than 10 mg/kg bw/day. Teratogenicity was not observed.

Thiram was mutagenic in the Ames test but not in mammalian cells *in vitro*. Since thiram was not mutagenic *in vivo*, the Meeting concluded that it did not present a genotoxic hazard for humans.

The central and peripheral nervous systems have been recognized as a possible targets for thiram toxicity. Neurotoxicity may be related to the thiram metabolite carbon disulphide.

An ADI was allocated, on the basis of the 1-year study in dogs and the 2-year studies in rats, using a 100-fold safety factor.

An addendum to the previous toxicological monographs on thiram and the dithiocarbamates was prepared.

TOXICOLOGICAL EVALUATION

Level causing no toxicological effect

| | |
|---|---|
| Mouse: | 15 ppm, equal to 3.0 mg/kg bw/day (97-week study) |
| Rat: | 30 ppm, equal to 1.2 mg/kg bw/day (two-year study)<br>30 ppm, equal to 1.5 mg/kg bw/day (two-generation reproduction study) |
| Rabbit: | 2.5 mg/kg bw/day (teratology study, maternal toxicity) |
| Dog: | 30 ppm, equal to 0.84 mg/kg bw/day (one-year study) |

Estimate of acceptable daily intake for humans

0-0.01 mg/kg bw.

Studies which will provide information valuable in the continued evaluation of the compound

1. Clarification of the potential for neurotoxicity of thiram.

2. Observations in humans.

***7.2- Pesticide Data Sheet on thiram (INCHEM database)***

**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 labelled rigid and leakproof 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 labelled leakproof 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 See Also:

*7.3- International Chemical Safety Cards on thiram (INCHEM database)*

| TYPES OF HAZARD /EXPOSURE | ACUTE HAZARDS/SYMPTOMS | PREVENTION | FIRST AID/FIRE FIGHTING |
|---|---|---|---|
| FIRE | Combustible, liquid formulations containing organic solvents may be flammable, gives off irritating or toxic fumes (or gases) in a fire. | NO open flames. | Powder, water spray, foam, carbon dioxide. |
| EXPLOSION | The explosion hazard will depend on the solvent used in the formulation or on the characteristics of the dust. | Prevent deposition of dust; closed system, dust explosion-proof electrical equipment and lighting. | |
| EXPOSURE | | AVOID ALL CONTACT! AVOID EXPOSURE OF (PREGNANT) WOMEN! | |
| INHALATION | Confusion, cough, dizziness, headache, sore throat. | Ventilation, local exhaust, or breathing protection. | Fresh air, rest, and refer for medical attention. |
| SKIN | Redness. | Protective gloves, protective clothing. | Remove contaminated clothes, and rinse and then wash skin with water and soap. |
| EYES | Redness, pain. | Safety spectacles or eye protection in combination with breathing protection. | First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then take to a doctor. |
| INGESTION | (further see Inhalation). | Do not eat, drink, or smoke during work. | Rinse mouth, and refer for medical attention. |

| SPILLAGE DISPOSAL | STORAGE | PACKAGING & LABELLING |
|---|---|---|
| Do NOT wash away into sewer, sweep spilled substance into containers, carefully collect remainder, then remove to safe place (extra personal protection: self-contained breathing apparatus). | Separated from acids, strong oxidizers, food and feedstuffs, dry, keep in a well-ventilated room. | Do not transport with food and feedstuffs.<br><br>Xn symbol<br>R: 20/22-36/37-40-43<br>S: 36/37<br><br>UN Hazard Class: 6.1<br>UN Packing Group: III |

| | | | |
|---|---|---|---|
| IMPORTANT DATA | **PHYSICAL STATE; APPEARANCE:**<br>COLOURLESS CRYSTALS. | **ROUTES OF EXPOSURE:**<br>The substance can be absorbed into the body by inhalation of its aerosol and by ingestion. | |
| | **PHYSICAL DANGERS:**<br>Dust explosion possible if in powder or granular form, mixed with air. | **INHALATION RISK:**<br>Evaporation at 20°C is negligible; a harmful concentration of airborne particles can, however, be reached quickly by spraying or dispersing. | |
| | **CHEMICAL DANGERS:**<br>The substance decomposes on heating and on burning producing toxic fumes (nitrogen, sulfur oxides). Reacts with strong oxidants, acids and oxidizable materials. | **EFFECTS OF SHORT-TERM EXPOSURE:**<br>The substance irritates the eyes, the skin and the respiratory tract. | |
| | **OCCUPATIONAL EXPOSURE LIMITS (OELs):**<br>TLV: ppm; 1 mg/m3 (ACGIH 1991-1992). PDK: 0.5 mg/m3 P (USSR 1991). | **EFFECTS OF LONG-TERM OR REPEATED EXPOSURE:**<br>Repeated or prolonged contact may cause skin sensitization. The substance may have effects on the thyroid, liver. Animal tests show that this substance possibly causes toxic effects upon human reproduction. | |
| PHYSICAL PROPERTIES | Boiling point at 2.6 kPa: | | 129°C |
| | Melting point: | | 155-156°C |

| | | |
|---|---|---|
| | Relative density (water = 1): | 1.29 |
| | Solubility in water: | none |
| | Vapour pressure, Pa at 20°C: | <0.001 |
| | Flash point: | 148.9°C (o.c.)°C |
| | Octanol/water partition coefficient as log Pow: | 1.82 |
| ENVIRONMENTAL DATA | This substance may be hazardous to the environment; special attention should be given to fish and birds. | |

| **NOTES** |
|---|
| Use of alcoholic beverages enhances the harmful effect, carrier solvents used in commercial formulations may change physical and toxicological properties, do NOT take working clothes home, arasan, Tersan, Fernasan, Pomarsol, Thiosan, Hermal, Fungitex, Vulkacit-Thiuram, Ekagom-TB, Thiurad, Robac TMTD, Tuex are trade names. |
| Transport Emergency Card: TEC (R)-61G47c |

| **ADDITIONAL INFORMATION** |
|---|

***7.4- EXTOXNET Pesticide information Profile on thiram (USEPA website)***

**E X T O X N E T**
**Extension Toxicology Network**
**Pesticide Information Profiles**

A Pesticide Information Project of Cooperative Extension Offices of Cornell University, Oregon State University, the University of Idaho, and the University of California at Davis and the Institute for Environmental Toxicology, Michigan State University. Major support and funding was provided by the USDA/Extension Service/National Agricultural Pesticide Impact Assessment Program.
EXTOXNET primary files maintained and archived at Oregon State University
Revised June 1996

# Thiram

Trade and Other Names**:** Common names include thiram (U.S.), thiuram (Japan), and TMTD (former U.S.S.R.), TMT, and TMTDS. Trade names include AAtack, Arasan, Aules, Fermide 850, Fernasan, FMC 2070, Hexathir, Mercuram, Micropearls, Nomersan, Pomarsol, Puralin, Rezifilm, Rhodiasan Express, Spotrete, Tersan, Thiosan, Thiotex, Thiramad, Thirame, Thiuramin, Thirasan, Tirampa, Tiuramyl, TMTC, TMTD 50 Borches, Trametan, Tuads, and Tulisan.

Regulatory Status**:** Thiram is registered as a General Use Pesticide (GUP) by the U.S. Environmental Protection Agency (EPA). It is classified as toxicity class III - slightly toxic. Pesticide products containing thiram bear the Signal Word CAUTION on the product label.

Chemical Class: dimethyl dithiocarbamate

Introduction**:** Thiram is a dimethyl dithiocarbamate compound used as a fungicide to prevent crop damage in the field and to protect harvested crops from deterioration in storage or transport. Thiram is also used as a seed protectant and to protect fruit, vegetable, ornamental, and turf crops from a variety of fungal diseases. In addition, it is used as an animal repellent to protect fruit trees and ornamentals from damage by rabbits, rodents, and deer. Thiram is available as dust, flowable, wettable powder, water dispersible granules, and water suspension formulations, and in mixtures with other fungicides. Thiram has been used in the treatment of human scabies, as a sunscreen, and as a bactericide applied directly to the skin or incorporated into soap.

Formulation: Thiram is available as dust, flowable, wettable powder, water dispersible granules, and water suspension formulations, and in mixtures with other fungicides.

Toxicological Effects:

- **Acute toxicity:** Thiram is slightly toxic by ingestion and inhalation, but it is moderately toxic by dermal absorption. Acute exposure in humans may cause headaches, dizziness, fatigue, nausea, diarrhea, and other gastrointestinal complaints. In rats and mice, large doses of thiram produced muscle incoordination, hyperactivity followed by inactivity, loss of muscular tone, labored breathing, and convulsions. Most animals died within 2 to 7 days [4]. Thiram is irritating to the eyes, skin, and respiratory tract. It is a skin sensitizer. Symptoms of acute inhalation exposure to thiram include itching, scratchy throat, hoarseness, sneezing, coughing, inflammation

of the nose or throat, bronchitis, dizzines, headache, fatigue, nausea, diarrhea, and other gastrointestinal complaints. Persons with chronic respiratory or skin disease are at increased risk from exposure to thiram [4]. Ingestion of thiram and alcohol together may cause stomach pains, nausea, vomiting, headache, slight fever, and possible dermatitis. Workers exposed to thiram during application or mixing operations within 24 hours of moderate alcohol consumption have been hospitalized with symptoms. The 4-hour inhalation LC50 for thiram is greater than 500 mg/L in rats. Reported oral LD50 values for thiram are 620 to over 1900 mg/kg in rats; 1500 to 2000 mg/kg in mice; and 210 mg/kg in rabbits [1,3]. The dermal LD50 is greater than 1000 mg/kg in rabbits [4] and in rats [1,3].

- **Chronic toxicity:** Symptoms of chronic exposure to thiram in humans include drowsiness, confusion, loss of sex drive, incoordination, slurred speech, and weakness, in addition to those due to acute exposure. Repeated or prolonged exposure to thiram can also cause allergic reactions such as dermatitis, watery eyes, sensitivity to light, and conjuntivitis [1]. Except for the occurrence of allergic reactions, harmful chronic effects from thiram have been observed in test animals only at very high doses. In one study, a dietary dose of 125 mg/kg/day thiram was fatal to all rats within 17 weeks. Oral doses of about 49 mg/kg/day to rats for 2 years produced weakness, muscle incoordination, and paralysis of the hind legs. Rats fed 52 to 67 mg/kg/day for 80 weeks exhibited hair loss, and paralysis and atrophy of the hind legs. Symptoms of muscle incoordination and paralysis from thiram poisoning have been shown to be associated with degeneration of nerves in the lower lumbar and pelvic regions. Day-old white leghorn chicks fed 30 and 60 ppm for 6 weeks exhibited bone malformations [1]. At doses of about 10% of the LD50 for 15 days, thiram reduced blood platelet and white blood cell counts, suppressed blood formation, and slowed blood coagulation in rabbits [1].
- **Reproductive effects:** Very high oral doses of approximately 1200 mg/kg/day thiram to mice on days 6 to 17 of pregnancy caused resorption of embryos and retarded fetal development. In another study, doses of 132 mg/kg/day for 13 weeks produced infertility in male mice, while doses of 96 mg/kg/day for 14 days delayed the estrous cycle in females [1]. The feeding of 50 mg/kg/day thiram from day 16 of pregnancy to 21 days after birth caused reduced growth and survival of the pups. Pups that were transferred to untreated dams at birth remained healthy, while pups transferred from untreated to treated dams showed toxic effects [1]. These data suggest that reproductive effects occur at high doses not likely to be experienced by humans.
- **Teratogenic effects:** Cleft palate, wavy ribs, and curved long leg bones were observed in the offspring of mice that ingested very high thiram doses of 1200 mg/kg/day on days 6 to 17 of pregnancy. Maternal doses of 125 mg/kg/day thiram were teratogenic in hamsters, causing incomplete formation of the skull and spine, fused ribs, abnormalities of the legs, heart, great vessels, and kidneys [1]. Developmental toxicity was observed in a three-generation study of rats fed 5.0 mg/kg/day [1,4]. These data suggest that high doses are required to cause teratatogenic effects.
- **Mutagenic effects:** Thiram has been found to be mutagenic in some test organisms but not in others [1]. Thus, the evidence is inconclusive.
- **Carcinogenic effects:** When administered to mice at the highest dose possible, thiram was not carcinogenic. Dietary levels as high as 125 mg/kg/day for 2 years did not cause tumors in rats [1]. These data indicate that thiram is not carcinogenic.
- **Organ toxicity:** Studies have shown evidence of damage to the liver by thiram in the form of decreased liver enzyme activity and increased liver weight [1]. Thiram may also cause damage to the nervous system, blood, and kidneys [4].

- **Fate in humans and animals:** In the body, carbon disulfide is formed from the breakdown of thiram and does contribute to the toxicity of thiram to the liver [1,3]. Thiram is not a member of the ethylene(bis)dithiocarbamate (EBDC) chemical family, and thus it should not generate ethylene thiourea (ETU) [1].

Ecological Effects:

- **Effects on birds:** Thiram is practically nontoxic to birds. The reported dietary LC50 of thiram in Japanese quail is greater that 5000 ppm [36]. Reported dietary LC50 values in pheasants and mallard ducks are 2800 ppm and 673 ppm, respectively [14]. The LD50 for the compound in red-winged blackbirds is greater than 100 mg/kg [3].
- **Effects on aquatic organisms:** Thiram is highly toxic to fish [4]. The LC50 for the compound is 0.23 mg/L in bluegill sunfish, 0.13 mg/L in trout, and 4 mg/L in carp [17]. Thiram is not expected to bioconcentrate in aquatic organisms [19].
- **Effects on other organisms:** Thiram is nontoxic to bees [3].

Environmental Fate:

- **Breakdown in soil and groundwater:** Thiram is of low to moderate persistence. It is nearly immobile in clay soils or in soils high in organic matter. Because it is only slightly soluble in water (30 mg/L) and has a strong tendency to adsorb to soil particles, thiram is not expected to contaminate groundwater. The soil half-life for thiram is reported as 15 days [20]. Thiram degrades more rapidly in acidic soils and in soils high in organic matter. In a humus sandy soil, at pH 3.5, thiram decomposed after 4 to 5 weeks, while at pH 7.0, thiram decomposed after 14 to 15 weeks. Thiram persisted for over 2 months in sandy soils, but disappeared within 1 week from a compost soil. The major metabolites of thiram in the soil are copper dimethyldithiocarbamate, dithiocarbamate, dimethylamine, and carbon disulfide [19]. In soil, thiram will be degraded by microbial action or by hydrolysis under acidic conditions. Thiram will not volatilize from wet or dry soil surfaces [19].
- **Breakdown in water:** In water, thiram is rapidly broken down by hydrolysis and photodegradation, especially under acidic conditions. Thiram may adsorb to suspended particles or to sediment [19].
- **Breakdown in vegetation:** No data are currently available.

Physical Properties:

- **Appearance:** Thiram is a white to yellow crystalline powder with a characterisitc odor [3].
- **Chemical Name:** tetramethylthiuram disulfide [3]
- **CAS Number:** 137-26-8
- **Molecular Weight:** 240.44
- **Water Solubility:** 30 mg/L at 25 C [3]
- **Solubility in Other Solvents:** s.s in ethanol; s. in acetone and chloroform [3]
- **Melting Point:** 146 C [3]
- **Vapor Pressure:** Negligible at room temperature [3]
- **Partition Coefficient:** Not Available
- **Adsorption Coefficient:** 670 [11]

Exposure Guidelines:

- **ADI:** 0.01 mg/kg/day [33]
- **MCL:** Not Available
- **RfD:** 0.005 mg/kg/day [27]
- **PEL:** 5 mg/m3 (8-hour) [28]
- **HA:** Not Available

- **TLV**: Not Available

Basic Manufacturer:

ELF Atochem North America, Inc.
2000 Market Street
Philadelphia, PA 19103-3222

- **Phone:** 215-419-7219
- **Emergency:** 800-523-0900