Annexure- 3.1.1

CONFIDENTIAL

REPORT OF THE EXPERT GROUP

Under the Chairmanship of Dr. C.D. Mayee

For Pesticides Reviewed for their continued use or otherwise in the country.

Part II

Submitted to
The Registration Committee

MINISTRY OF AGRICULTURE

DEPARTMENT OF AGRICULTURE AND COOPERATION

2006

INDEX

EXECUTIVE SUMMARY

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The Registration Committee on the directives of the Inter-ministerial Committee constituted a group under the Chairmanship of Dr. C.D. Mayee, Chairman, Agricultural Scientists Recruitment Board (ASRB), Indian Council of Agricultural Research, Krishi Anusandhan Bhawan, Pusa, New Delhi to review toxicity, persistence , safety in use and substitute available of 36 pesticides and monocrotophos (List at **Annexure I**)and make recommendations for their continued use or otherwise in the country. The group undertook the review and has made the following specific recommendations w.r.t. pesticides reviewed in the second phase.

1. Carbosulfan

Use of Carbosulfan be continued.

2. Chlorothalonil

1. Use of Chlorothalonil should be continued.
2. Precautions with reference to skin irritation & contact dermatitis need to be categorically indicated on labels and Leaflets.
3. Maximum HCB & DCB contents should not exceed 0.004 & 0.003% respectively of Chlorothalonil content found in technical material.

3. Deltamethrin (Decamethrin)

1. Use of Deltamethrin be continued.
2. The formulation recommended for use in grain storage i.e Deltamethrin 2.5% WP is reported to be irritant and causing mild allergic manifestations viz. itching, sneezing, burning sensation of nose tips & eyes, redness in eyes, throat irritation, body ache etc, therefore, workers should be provided with and instructed to use necessary protective clothings / measures.

4. Diazinon

Considering the environmental toxicity of the product, it has been recommended to ban its use in Agriculture, however its use in household be continued.

5. Dinocap

Use of Dinocap be continued.

6. Ethofenprox (Etofenprox)

1. Use of Ethofenprox be continued.

2. The label and leaflet should bear the safety precaution that it should not be used in the areas where pisiculture/ aquaculture is practiced alongwith rice cultivation.

7. Fenthion

1. Use in Agriculture be withdrawn except for locust control.
2. Use in household and public health be continued.
3. A multilocation study (minimum 3 locations) be carried out as per the protocol approved by the Registration Committee in the workers of the manufacturing unit by the basic manufactures of Fenthion under the supervision of National Institute of Occupational Health(NIOH), Indian Council of Medical Research(ICMR).

8. Metaldehyde

Use of Metaldehyde be continued.

9. Metoxuron

Use should be withdrawn as the concerns raised were not addressed by the manufacturers .

10. Trifluralin

Use of Trifluralin be continued

11. Thiophanate-Methyl

1. Use of Thiophanate methyl be continued.
2. Thyroid functions of the workers be monitored for two years in manufacturing units and submit data to registration Secretariat for perusal.
3. A multilocation study (minimum 3 locations) be carried out as per the protocol approved by the Registration Committee in the workers of the manufacturing unit by the basic manufactures of Thiophanate-Methyl under the supervision of National Institute of Occupational Health(NIOH), Indian Council of Medical Research(ICMR).

PREAMBLE

PREAMBLE:

Background regarding the composition of the expert group

In pursuance to the order of the Supreme Court in its judgment in the case of the writ petition No. 1094 of 1988 a Committee [Interministerial Committee (IMC)] has been constituted with the Secretary, Department of Agriculture & Cooperation as Chairman and Secretary, Department of Chemicals & Petrochemicals , Secretary, Department of health and Secretary , Ministry of environment and forest as members to review the use of Insecticides and Chemicals found Hazardous to health and take suitable remedial measures in this regard. In the 25th meeting of IMC a list of pesticides which have been banned/ restricted in other countries but being used in India and the statement containing the review status of those pesticides was put up for deliberation. The Committee decided that the Registration Committee should take up the review of the remaining pesticides within a stipulated time frame .Based on the decision of Inter Ministerial Committee, the Government of India, Ministry of Agriculture (Department of Agriculture & Cooperation) decided to undertake review of 36 pesticides (decision in the 26th IMC meeting)and monocrotophos through Registration Committee (RC) to consider their continued use or otherwise in the country. For the purpose, a Group was constituted by the RC in its 252nd – 253rd meeting under the Chairmanship of Dr. C.D. Mayee, Chairman, ASRB, Indian Council of Agricultural Research. .The terms of reference for the group were laid down in the 254th meeting (copy at Annexure II)The constitution of the group is as under :

1. Dr. C.D. Mayee, — Chairman
   Chairman ASRB,
   Indian Council of Agricultural Research Institute ,
   Krishi Anusanshan bhavan-1 ,
   PUSA, New Delhi

2. Dr P.S. Chandurkar — Member
   Plant Protection Adviser
   to the Govt. of India,
   Dte. of PPQ&S, Faridabad

3. Shri P.N. Maji, — Member
   Additional Industrial Advisor,
   Representative from Deptt. of Chemicals
   & Petro Chemicals, New Delhi.

4. Dr. O.P. Dubey — Member
   ADG(OP),
   Indian Council of Agricultural research
   Krishi Bhavan New Delhi

5. Dr. S. K. Handa — Member
   WHO Consultant
   Room No 526 , Wing A
   Representative from PFA Div.
   Min. Of Health & Family Welfare,
   New Delhi

6. Dr. H.N. Saiyed — Member
Director,National Institute of Occupational Health(NIOH,)
Indian Council of Medical research
Ahmedabad- 380016

7. Dr. Y.K. Gupta — Member
Professor & Head
Department of pharmacology
All India Institute of Medical Sciences
Ansari Nagar, New Delhi-110029

8. Dr. (Mrs.) Chanda Chaudhary — Member
Addl. Director HSM Division,
Ministry of Environment & Forests
CGO Complex, Lodi road, New Delhi

9. Dr. B.S. Parmer — Member
Joint. Director (Research),
IARI, Pusa, New Delhi.

10. Dr. R.A. Tripathi — Member
Prof.& Head, Div. Member of
Entomology, CS Azad Uni. of
Agri.& Tech, Kanpur

11. Dr. Y.S. Ahlawat — Member
Division . of Plant Pathology,
IARI, New Delhi-12

12. Dr. L.S. Barar — Member
Prof.& Head, Deptt. of Agronomy,
PAU, Ludhiana

13. Dr. (Mrs.) Sandhya Kulshrestha, — Member Secretary
Secretary CIB & RC
N. H. IV, Faridabad

The group Co-opted the following members :-

1. Dr. T. P. Rajendran — Co-opted Member
ADG (PP)
Indian Council of Agricultural research
Krishi Bhavan New Delhi,

2. Dr. A.K. Majumdar, — Co-opted Member
Director (IH),
Director (IH),
Central labour Institute, Sion, Mumbai 400 022.

3.	Dr. T.S Thind , Professor Plant Pathology, Deptt. of Plant Pathology, PAU, Ludhiana-141004 (Punjab)	Co-opted Member
4.	Dr. Keshav Kranti, Senior Scientist, Entomology, CICR, Post Bag No.2, Nagpur-440010 (MS)	Co-opted Member
5.	Dr. N.T. Yaduraju, National Coordinator, National Agricultural Innovation Project ICAR, Krishi Anusandhan Bhawan –II Pusa Campus, New Delhi	Co-opted Member
6.	Dr. K.K. Sharma, Project Coordinator, AICRP on Pesticide Residue, LBS Building, IARI, New Delhi-110012	Co-opted Member

MODALITIES FOR THE FUNCTIONING OF THE GROUP AND PREPARATION OF THE REPORT

MODALITIES FOR THE FUNCTIONING OF THE GROUP AND PREPARATION OF THE REPORT

The list of pesticides reviewed in second phase is as under :-

1. Carbosulfan
2. Chlorothalonil
3. Deltamethrin (Decamethrin)
4. Diazinon
5. Dinocap
6. Ethofenprox (Etofenprox)
7. Fenthion
8. Metaldehyde
9. Metoxuron
10. Trifluralin
11. Thiophanate-Methyl

The group followed the same modalities i.e followed for review of pesticides in the first phase. The group met three more times i.e 6th, 7th & 8th meeting of the committee which were held on 29th May, 2006, 31st July, 2006 & 29th September, 2006 to discuss the pesticides under review in the second phase. The Group reviewed the literature and prepared the base papers on each of the pesticides under review. The base paper were deliberated. After a detailed discussion with the industry and among the members and based on the scientific information, the Group decided to have certain general recommendations apart from specific recommendations. The group decided to give the general recommendation in the final review report .

PRODUCT SPECIFIC RECOMMENDATIONS

1.4 RECOMMENDATIONS:

Use of Carbosulfan be continued.

2. Chlorothalonil

Chlorothalonil is unlikely to present acute hazard in the normal use (U) as per WHO recommended Classification of Pesticides by Hazard 2004.

2.1 THE BAN/RESTRICTION STATUS INTERNATIONALLY

It is banned in Sweden being carcinogenic. No uses are allowed.

2 .2 THE PRESENT STATUS OF THE PESTICIDE USE IN INDIA.

2.2 (a) PESTICIDE CONSUMPTION IN INDIA

35 MT Technical grade (1999-2000)
(Source States / UT's)

2.2 (b) FORMULATIONS REGISTERED AND THEIR LABEL CLAIMS.

Chlorothalonil 75 WP- Ground nut, Potato, Apple, Grapes & Chilies

2.3 .MAJOR CONCERNS OF THE COMMITTEE REGARDING CHEMISTRY, TOXICITY, RESIDUE PERSISTENCE AND RESISTENCE:

The group noted that Chlorothalonil causes severe eye and skin irritation and contact dermatitis and probably has not been popular due to this. These symptoms are more severe and of concern in the hot and humid climate of India. It is highly toxic to fish and aquatic fauna. It is banned in Sweden being carcinogenic.

The group critically analyzed the information submitted by the industry (copy of the presentation made by the industry at **Annexure – III B)** . Considering the facts the group recommended the following:

2.4 RECOMMENDATIONS:

1. Use of Chlorothalonil should be continued.
2. Precautions with reference to skin irritation & contact dermatitis need to be categorically indicated on labels and Leaflets.
3. Maximum HCB & DCB contents should not exceed 0.004 & 0.003% respectively of Chlorothalonil content found in technical material.

3. Deltamethrin (Decamethrin)

Deltamethrin is moderately hazardous (Class II) insecticide as per WHO recommended Classification of Pesticides by Hazard 2004.

3.1 THE BAN/RESTRICTION STATUS INTERNATIONALLY

Deltamethrin is banned in Denmark due to its being toxic to the aquatic organisms. The products are therefore assessed to be seriously damaging to the environment.

3.2 THE PRESENT STATUS OF THE PESTICIDE USE IN INDIA.

3.2 a PESTICIDE CONSUMPTION IN INDIA

83 MT Technical grade (2003- 04)
(Source States / UT's)

3.2 (b) FORMULATIONS REGISTERED AND THEIR LABEL CLAIMS:-

Deltamethrin 11% EC - Cotton
Deltamethrin 1.8% EC - Rice and Cotton
Deltamethrin 1.25% ULV - For adult mosquitoes in public health
Deltamethrin 2.5% FLOW – For adult mosquito by impregnation of polyester, nylon and cotton bednet, housefly, cockroach
Deltamethrin 25% Tablet - For adult mosquito by impregnation of polyester, nylon and cotton bednet - Rice and cotton
Deltamethrin 0.5% Chalk - For the control of cockroaches in houses.
Delamethrin 0.5% Tablet bait- Cockroach,
Deltamethrin 1% paint – Cockroach
Deltamethrin 2.8% EC – Cotton, Tea, Okra, Ground nut, Mango, Chili, Chick pea, Brinjal & Red gram
Deltamethrin 2.5% WP – Mosquito control under public health, wheat, Rice

3.3 MAJOR CONCERNS OF THE COMMITTEE REGARDING CHEMISTRY, TOXICITY, RESIDUE PERSISTENCE AND RESISTENCE.

The group noted the Cutaneous and mucous membrane irritation and paraesthesiae reported frequently after Deltamethrin exposure. The Information on health survey carried out among spraymen exposed to 2.5% *deltamethrin* emulsifiable concentrate in cotton fields in China was also noted. In this survey, the subjects were exposed to *deltamethrin* at concentrations of 0.022 - 24.070 $\mu g/m^3$ in the air of the respiratory zone and 0.013 - 0.347 $\mu g/cm^2$ of skin contact. One half of the 44 sprayers complained of itching and burning sensations on their faces. A few military red papules also appeared on the face of one of them. (Wang et al., 1988). The Central Warehousing Corporation, Delhi and Food Corporation of India, Delhi were asked

regarding the quantum and purpose of use of the product, methodology of handling, and any adverse effect observed in workers. The Central Warehousing Corporation have informed that the Complaints of itching to the labour force carrying *Deltamethrin* treated bags have been received from their Delhi, Mumbai & Bhopal Region ; Itching & redness from Chandigarh region; Throat irritation, itching and body ache from Hyderabad region; Sneezing, Redness in eyes, irritation, burning sensation on nose tips from Lucknow and itching, redness, burning sensation in eyes from Kolkata region. The food corporation of India has informed that ever since its use no complaints with regard to itching and redness has been reported from any corner. Its toxicity to aquatic organisms was also considered.

The group critically analyzed the information submitted by the industry(copy of the presentation made by the industry at **Annexure – III C)** . Considering the facts the group recommended the following:

3.4 RECOMMENDATIONS:

1. Use of Deltamethrin be continued.
2. The formulation recommended for use in grain storage i.e Deltamethrin 2.5% WP is reported to be irritant and causing mild allergic manifestations viz. itching, sneezing, burning sensation of nose tips & eyes, redness in eyes, throat irritation, body ache etc, therefore, workers should be provided with and instructed to use necessary protective clothings / measures.

4. Diazinon

Diazinon is moderately hazardous (Class II) insecticide as per WHO recommended Classification of Pesticides by Hazard 2004.

4 .1 THE BAN/RESTRICTION STATUS INTERNATIONALLY

It is banned in Denmark due to being persistent in soil and poison aquatic organism, wild birds and mammals. Caused ground water pollution. It is banned in Korea due to high acute toxicity.

4.2 THE PRESENT STATUS OF THE PESTICIDE USE IN INDIA

4.2 (a) PESTICIDE CONSUMPTION IN INDIA

40 MT Technical grade (2003- 04)
(Source States / UT's)

4.2 (b) FORMULATIONS REGISTERED AND THEIR LABEL CLAIMS:-

Diazinon 20% EC - Cauliflower
Diazinon 10% GR - Paddy and sorghum
Diazinon 5% GR - Paddy and sorghum
Diazinon 25% microencapsulation- housefly, cockroach and mosquito.
Diazinon 2% RTU spray- housefly, cockroach and mosquito
Diazinon 0.5% + Pyrethrin 0.1% spray- mosquito

4.3 MAJOR CONCERNS OF THE COMMITTEE REGARDING CHEMISTRY, TOXICITY, RESIDUE PERSISTENCE AND RESISTENCE.

The group noted that it is banned in Denmark due to being persistent in soil and poison aquatic organism, wild birds and mammals. Caused ground water pollution. It is banned in Korea due to high acute toxicity. Its high toxicity to bees, Neurotoxicity due to its metabolite Diazoxon and Teratogenic potential were also noted.
The group critically analyzed the information submitted by the industry (copy of the presentation made by the industry at **Annexure- III D)** . Considering the facts the group recommended the following:

4.4 RECOMMENDATIONS:

Considering the environmental toxicity of the product, it has been recommended to ban its use in Agriculture, however its use in household be continued.

5. Dinocap

Dinocap is slightly hazardous (Class-III) fungicide. as per WHO recommended Classification of Pesticides by Hazard 2004.

5.1 THE BAN/RESTRICTION STATUS INTERNATIONALLY

Dinocap is banned in Argentina due to risk to human health and environment. Risk of teratogenicity in mice and rats. It is banned in Sweden due to teratogenicity in mice and rabbits.

5.2 THE PRESENT STATUS OF THE PESTICIDE USE IN INDIA

5.2 (a) PESTICIDE CONSUMPTION IN INDIA

13 MT Technical grade (2003- 04)
(Source States / UT's)

5.2 (b) FORMULATIONS REGISTERED AND THEIR LABEL CLAIMS:-

Dinocap 48% EC - Grapes, peaches, apples, ber, mango, okra, chillies, cowpea, cluster bean & French beans, peas, pumpkin, melon, kakri, fenugreek, wheat, cumin, poppy and rose.

5.3 .MAJOR CONCERNS OF THE COMMITTEE REGARDING CHEMISTRY, TOXICITY, RESIDUE PERSISTENCE AND RESISTENCE.

The group noted that Dinocap is banned in Argentina due to risk to human health and environment. Risk of teratogenicity in mice and rats. It is banned in Sweden due to

Fenthion is banned in ANG because of health and environmental reasons.

7.2 THE PRESENT STATUS OF THE PESTICIDE USE IN INDIA

7.2 (a) PESTICIDE CONSUMPTION IN INDIA

62 MT Technical grade (2003- 04)
(Source States / UT's)

7.2 (b) FORMULATIONS REGISTERED AND THEIR LABEL CLAIMS:-

Fenthion 82.5% EC - Paddy, wheat, cucurbits, bhindi, onion and chillies
Fenthion 2% GR - For the control of mosquito larvae
Fenthion 2% spray - As an household insecticide for the control of cockroaches and bedbugs
Fenthion 5% GR - Rice

7.3 MAJOR CONCERNS OF THE COMMITTEE REGARDING CHEMISTRY, TOXICITY, RESIDUE PERSISTENCE AND RESISTENCE.

The group noted the Reports of effect on neuromuscular function during exposure, reported numbness and tingling in Nigerian workers who did not use skin protection. It has high toxicity to fish and is reported to be Carcinogenic in male mice.

The group critically analyzed the information submitted by the industry(copy of the presentation made by the industry at **Annexure- III G)** . Considering the facts the group recommended the following:

7.4 RECOMMENDATIONS:

1. Use in Agriculture be withdrawn except for locust control.
2. Use in household and public health be continued.
3. A multilocation study (minimum 3 locations) be carried out as per the protocol approved by the Registration Committee in the workers of the manufacturing unit by the basic manufactures of Fenthion under the supervision of National Institute of Occupational Health(NIOH), Indian Council of Medical Research(ICMR).

8. Metaldehyde

Metaldehyde is moderately hazardous (Class II) pesticide as per WHO recommended Classification of Pesticides by Hazard 2004.

8.1 THE BAN/RESTRICTION STATUS INTERNATIONALLY

It is restricted in Kuwait being harmful to human health and environment. Uses allowed only under strict supervision of trained personnel.

8.2 THE PRESENT STATUS OF THE PESTICIDE USE IN INDIA

8.2 (a) PESTICIDE CONSUMPTION IN INDIA

42 MT Technical grade (1999-2000)
(Source States / UT's)

8.2 (b) FORMULATIONS REGISTERED AND THEIR LABEL CLAIMS:-

It is used as mollusicide.

8.3 MAJOR CONCERNS OF THE COMMITTEE REGARDING CHEMISTRY, TOXICITY, RESIDUE PERSISTENCE AND RESISTENCE.

The group noted that Metaldehyde is moderately hazardous (Class II) pesticide as per WHO recommended Classification of Pesticides by Hazard 2004. It is restricted in Kuwait being harmful to human health and environment. Uses allowed only under strict supervision of trained personnel. Considering all the information and the data available the group noted that there are no safety concerns with Metaldehyde and therefore the group recommended the following:-

8.4 RECOMMENDATIONS:

Use of Metaldehyde be continued.

9. Metoxuron

Metoxuron is unlikely to present acute hazard in normal use as per WHO recommended Classification of Pesticides by Hazard 2004.

9.1 THE BAN/RESTRICTION STATUS INTERNATIONALLY

It is banned in Sweden being suspected carcinogen.

9.2 THE PRESENT STATUS OF THE PESTICIDE USE IN INDIA

9.2 (a) PESTICIDE CONSUMPTION IN INDIA

10 MT Technical grade (2003- 04)
(Source States / UT's)

9.2 (b) FORMULATIONS REGISTERED AND THEIR LABEL CLAIMS:-

Metoxuron 80% WP- Wheat, Lentil & Ragi

9.3 .MAJOR CONCERNS OF THE COMMITTEE REGARDING CHEMISTRY, TOXICITY, RESIDUE PERSISTENCE AND RESISTENCE.

The group noted that it is banned in Sweden being suspected carcinogen. The usage of the product is almost non existent.
No industry come forward to address the concerns. A letter has been received from M/s Syngenta informing that they would like to withdraw the registration because of commercial reasons (copy at **Annexure – III H**)

9. 4 RECOMEN DATIONS:

Use should be withdrawn as the concerns raised were not addressed by the Manufacturers.

10. Trifluralin

Trifluralin is unlikely to present acute hazard in normal use as per WHO recommended Classification of Pesticides by Hazard 2004.

10.1 THE BAN/ RESTRICTION STATUS INTERNATIONALLY

It is banned in Denmark due to its unacceptably persistence in soil and the products are therefore assessed to be harmful to the environment. It is banned in Norway due to persistence in soil and toxicity for aquatic organisms. It is banned in Sweden due to persistence. It is restricted in Korea due to health risk and environmental impact. Mutagenic and Carcinogenic effects. The amount of NDPA (N-Nitros-dipropylamine) contamination in technical product must not exceed 0.5 ppm.

10.2 THE PRESENT STATUS OF THE PESTICIDE USE IN INDIA

10.2 (a) PESTICIDE CONSUMPTION IN INDIA

10 MT Technical grade (2003- 04)
(Source States / UT's)

10.2 (b) FORMULATIONS REGISTERED AND THEIR LABEL CLAIMS:-

Trifluralin 48% EC- Cotton, Soyabean

10.3 MAJOR CONCERNS OF THE COMMITTEE REGARDING CHEMISTRY, TOXICITY, RESIDUE PERSISTENCE AND RESISTENCE.

The group noted that It is banned in Denmark due to its unacceptably persistence in soil and the products are therefore assessed to be harmful to the environment. It is banned in Norway due to persistence in soil and toxicity for aquatic organisms. It is banned in Sweden due to persistence. It is restricted in Korea due to health risk and

environmental impact. Mutagenic and Carcinogenic effects. The amount of NDPA (N-Nitros-dipropylamine) contamination in technical product must not exceed 0.5 ppm. The group critically analyzed the information submitted by the industry(copy of the presentation made by the industry at **Annexure- III – I)** . Considering the facts the group recommended the following:

10.4 RECOMMENDATIONS:

Use of Trifluralin be continued.

11. Thiophanate methyl

Thiophanate methyl is unlikely to present acute hazard in normal use as per WHO recommended Classification of Pesticides by Hazard 2004.

11.1 THE BAN/ RESTRICTION STATUS INTERNATIONALLY

It is banned in Denmark due to unacceptable persistence in soil and toxic for earthworms. It is severely restricted in Sweden due to chemical relationship with Benomyl and Carbendazim. Uses allowed only against fungi or winter cereals and ornamentals (one treatment only per crop with Thiophanate methyl or Carbendazim).

11.2 THE PRESENT STATUS OF THE PESTICIDE USE IN INDIA

11.2 (a) PESTICIDE CONSUMPTION IN INDIA

15MT Technical grade (2003- 04)

(Source States / UT's)

11.2 (b) FORMULATIONS REGISTERED AND THEIR LABEL CLAIMS:-

Thiophanate methyl 70%WP:- Papaya, Apple, Wheat, Tomato, Bottle gourd, Cucurbits & Pigeon pea

11.3 MAJOR CONCERNS OF THE COMMITTEE REGARDING CHEMISTRY, TOXICITY, RESIDUE PERSISTENCE AND RESISTENCE.

The group noted that it is banned in Denmark due to unacceptable persistence in soil and toxicity for earthworms. It is severely restricted in Sweden due to chemical relationship with Benomyl and Carbendazim. Uses allowed only against fungi or winter cereals and ornamentals (one treatment only per crop with Thiophanate methyl or Carbendazim). Its potential to cause Neurotoxicity, Carcinogenicity and effect on thyroid function were also noted. Thiophanate methyl causes depression of T_4 and T_3 levels and increase of TSH levels as propylthiouracil (PTU, inhibitor of thyroid hormones synthesis). It also induced microsomal UDP- glucuronosyltransferase, which is considered to play an important role in T_4 excretion by the liver and subsequent slight thyroid hypertrophy. Also inhibition of thyroid peroxidase could be a main cause of thyroid hypertrophy in rats. The group critically analyzed the information submitted by the industry(copy of the presentation made by the industry at **Annexure – !!! J)** . Considering the facts the group recommended the following:

11.4 RECOMMENDATIONS:

1. Use of Thiophanate methyl be continued.

2. A multilocation study (minimum 3 locations) be carried out as per the protocol approved by the Registration Committee in the workers of the manufacturing unit by the basic manufactures of Thiophanate-Methyl under the supervision of National Institute of Occupational Health(NIOH), Indian Council of Medical Research(ICMR).

Annexure - I

Review of various pesticides which are banned/ restricted in other countries but are being used in India

S.No.	Name of Pesticides	S.No.	Name of Pesticides
1	Monocrotophos	20	Dinocap
2	Mancozeb	21	Ethofenprox (Etofenprox)
3	Quinalphos	22	Metoxuron
4	Butachlor	23	Trifluralin
5	Diclorvos (DDVP)	24	Chlorofenvinphos
6	Acephate	25	Fenpropathrin
7	Fenitrothion	26	Iprodione
8	Carbendazim	27	Benfuracarb
9	Atrazine	28	Bifenthrin
10	Pendimethalin	29	Dazomet
11	Deltamethrin (Decamethrin)	30	Diflubenzuron
12	Fenthion	31	Kasugamycin
13	Simazine	32	Linuron
14	Metaldehyde	33	Mepiquate Chloride
15	Diazinon	34	Propergite
16	Carbosulfan	35	Propineb
17	Chlorothalonil	36	Thiodicarb
18	Dalapon	37	Trichlorofon
19	Thiophanate-Methyl		

Annexure -I

Review of various pesticides which are banned/ restricted in other countries but are being used in India

S.No.	Name of Pesticides	S.No.	Name of Pesticides
1	Monocrotophos	20	Dinocap
2	Mancozeb	21	Ethofenprox (Etofenprox)
3	Quinalphos	22	Metoxuron
4	Butachlor	23	Trifluralin
5	Diclorvos (DDVP)	24	Chlorofenvinphos
6	Acephate	25	Fenpropathrin
7	Fenitrothion	26	Iprodione
8	Carbendazim	27	Benfuracarb
9	Atrazine	28	Bifenthrin
10	Pendimethalin	29	Dazomet
11	Deltamethrin (Decamethrin)	30	Diflubenzuron
12	Fenthion	31	Kasugamycin
13	Simazine	32	Linuron
14	Metaldehyde	33	Mepiquate Chloride
15	Diazinon	34	Propergite
16	Carbosulfan	35	Propineb
17	Chlorothalonil	36	Thiodicarb
18	Dalapon	37	Trichlorofon
19	Thiophanate-Methyl		

ANNEXURE-II

The terms of reference of the Expert Group ;

I. To review toxicity, persistence , safety in use and substitute available of 37 pesticides (List at APPENDIX-I) and make recommendations for their continued use or restricted use or phasing out in the country .

II. The review may be done in phased manner. In the first phase those pesticides whose consumption is more than 100 MT per annum, may be reviewed .In the next phase pesticide whose consumption is between 99- 11 M.T. and in the third phase whose consumption is less than 10 M.T or data not available may be reviewed .[As per the pesticide consumption information 2003-2004 , the pesticide to be reviewed in different phases are indicated in the enclosed list at APPENDIX-II]

III. The Expert group can co-opt any Member for conducting the business.

IV. The group may evolve its own procedure and methodology of functioning and call for any relevant data from any department of the Central / State Government / Private Organization/persons etc.

V. The TA/DA of the Members of the Expert Group will be met by the Organizations from where their pay is being drawn .

VI. The expert group may give the report within six months for the pesticide to be reviewed in the first phase , In the next 6 months for pesticides to be reviewed in the second phase and further 6 months in the third phase .

S.No.	Name of the Pesticide	Consumption (M.T) Tech. Grade year 2003-04	
1	Monocrotophos	3115 *	
2	Mancozeb	2615 *	
3	Quinalphos	1650 *	
4	Butachlor	1520 *	
5	Diclorvos (DDVP)	818 *	
6	Acephate	440 *	
7	Fenitrothion	412 *	
8	Carbendazim	400 *	
9	Atrazine	315 *	
10	Pendimethalin	140 *	
11	Deltamethrin (Decamethrin)	83 **	
12	Fenthion	62 **	
13	Simazine	45 **	
14	Metaldehyde	42 **	
5	Diazinon	40 **	1999-2000
16	Carbosulfan	35 **	
17	Chlorothalonil	35 **	
18	Dalapon	17 **	1999-2000
19	Thiophanate-Methyl	15 **	
20	Dinocap	13 **	
21	Ethofenprox (Etofenprox)	11 **	
22	Metoxuron	10 **	
23	Trifluralin	10 **	
24	Chlorofenvinphos	8***	
25	Fenpropathrin	0 ***	
26	Iprodione	0 ***	
27	Benfuracarb	Data Not Available ***	
28	Bifenthrin	Data Not Available ***	
29	Dazomet	Data Not Available ***	
30	Diflubenzuron	Data Not Available ***	
31	Kasugamycin	Data Not Available ***	
32	Linuron	Data Not Available ***	
33	Mepiquate Chloride	Data Not Available ***	
34	Propergite	Data Not Available ***	
35	Propineb	Data Not Available ***	
36	Thiodicarb	Data Not Available ***	
37	Trichlorofon	Data Not Available ***	

* Proposed to be reviewed in the first phase
** Proposed to be reviewed in the second phase
*** Proposed to be reviewed in the third phase

CONSUMPTION OF INDIGENOUS PESTICIDES IN AGRICULTURE FOR THE LAST FIVE YEARS (1999-2000 TO 2003-2004)

M.T. (Tech. Grade)

S. No.	Pesticides	Group	1999-2000	2000-01	2001-02	2002-03	2003-04
1.	Acephate	i	697	674	750	782	440
2.	Cypermethrin	i	957	1033	1300	1315	32
3.	Dichlorvos	i	971	1021	1070	1250	818
4.	Dimethoate	i	1505	1277	1500	2009	625
5.	Endosulphan	i	3170	2820	3985	2000	2900
6.	Ethion	i	239	385	415	410	315
7.	Fenitrothion	i	239	385	415	410	412
8.	Fenthion	i	34	38	60	79	62
9.	Fenvalerate	i	695	1085	2100	1192	975
10.	Lindane	i	607	683	700	615	—
11.	Metal Dehyde	i	42	48	32	40	07
12.	Malathion	i	2635	2486	2600	2384	3015
13.	Methyl Parathion	i	2705	2639	3008	3023	3200
14.	Monocrotophos	i	3496	2680	2815	3205	3115
15.	Neem based insecticides	i	739	551	736	632	824
16.	Oxydemeton methyl	i	432	384	512	382	213
17.	Paradichloro-benzene	i	0	0	0	0	1
18.	Phorate	i	2006	2133	2215	2316	3010
19.	Phosalone	i	224	185	218	275	145
20.	Phosphamidon	i	1748	1023	1100	1020	1430
21.	Pyrethrum	i	10	10	13	10	11
22.	Quinalphos	i	1906	1858	2181	2318	1650
23.	Sevidol	i	0	0	0	0	0
24.	Temephos	i	0	0	0	0	1
25.	Triazophos	i	107	118	114	108	115
26.	Aureofungin	f	10	6	8	5	12
27.	Captafol/Difolaton	f	144	227	419	344	15
28.	Captan	f	218	156	170	256	200
29.	Carbendazim	f	514	464	625	359	400
30.	Copper Oxychloride	f	1081	955	1122	1213	1030
31.	Copper Sulphate	f	592	692	1042	1128	514
32.	Cuprous Oxide	f	2	0	5	2	5
33.	Ethyl Mercury Chloride	f	0	0	0	0	0
34.	Ferbam	f	15	10	25	9	12
35.	Lime Sulphur	f	16	22	32	45	20
36.	Mancozeb	f	2200	1939	2577	2800	2615
37.	MEMC	f	85	87	71	81	22
38.	Organo Mercurials	f	0	0	0	0	0
39.	Nickel Chloride	f	21	40	55	60	0
40.	Paris Green	f	0	0	0	0	0
41.	PMA	f	0	0	0	0	0
42.	Streptocycline	f	26	31	39	47	20
43.	Sulphur	f	1989	2083	2332	3185	3010

44.	Thiram	f	405	403	419	402	302
45.	Zineb	f	215	213	318	418	205
46.	Ziram	f	194	192	277	385	100
47.	Alachlor	h	153	123	142	150	95
48.	Anilophos	h	380	402	535	716	200
49.	Butachlor	h	2332	2161	2019	2480	1520
50.	Dalapon	h	11	51	72	85	17
51.	2,4-D	h	680	678	612	680	612
52.	Diuron	h	11	5	12	11	10
53.	Fluchloralin	h	105	149	155	213	115
54.	Glyphosate	h	178	154	180	178	162
55.	Isoproturon	h	2649	2742	2512	2618	2208
56.	Paraquat Dichloride	h	113	165	110	156	70
57.	Propanil	h	0	0	0	0	30
58.	TCA	h	0	0	0	0	15
59.	Aluminium Phosphide	r	250	265	234	250	142
60.	Barium Carbonate	r	0	0	0	0	0
61.	EDCT Mixture	r	0	0	0	0	0
62.	EDB	r	22	18	18	23	0
63.	Methyl bromide	r	5	2	4	7	7
64.	Warfarin	r	4	4	6	10	1
65.	MB+FDB	r	0	0	0	0	0
66.	Zinc Phosphide	r	207	223	220	359	215
67.	Alpha napthyl acetic acid	pg	41	27	18	19	25
68.	Chlormequat chloride	pg	4	5	12	4	10
69.	Others		734	604	0	0	0
	TOTAL:	Indegen-ious	41101	38796	43300	45130	37352

ource: States/UTs

ote: i - Insecticide
f - Fungicide
h - Weedicide
r - Rodenticide
fm - Fumigants
pg - Plant growth regulator
mp - Misc. pesticides

CONSUMPTION OF IMPORTED PESTICIDES DURING THE LAST FIVE YEARS (1999-2000 TO 2003-2004)

S. No.	Pesticides	Group	1999-2000	2000-01	2001-02	M.T. (Tech. Grade) 2002-03	2003-04
1.	Aldicarb	i	0	0	0	0	0
2.	Allethrin	i	20	11	5	8	9
3.	Alpha cypermethrin	i	30	27	7	10	12
4.	Bacillus thuringiensis	i	135	132	166	143	157
5.	Carbaryl	i	611	543	155	219	273
6.	Carbofuran	i	589	786	419	308	500
7.	Carbosulfan	i	133	29	17	20	35
8.	Cartap hydrochloride	i	56	63	34	26	29
9.	Cyfluthrin	i	0	0	0	0	5
10.	Chlorfenvinphos	i	4	18	71	6	8
11.	Chlorpyriphos	i	912	929	718	825	1161
12.	Cyphenothrin	i	0	0	0	0	8
13.	Deltamethrin	i	166	136	106	96	33
14.	Diazinon	i	62	63	31	35	40
15.	Dicofol	i	357	110	73	56	52
16.	Ethofenprox	i	11	10	2	5	11
17.	Formothion	i	57	35	10	3	8
18.	Febabucarb (BPMC)	i	11	27	8	9	6
19.	Fenpropathrin	i	1	0	0	0	0
20.	Fipronil	i	11	40	10	7	13
21.	Fluvalinate	i	9	10	6	5	7
22.	Lamdocyahalothrin	i	16	83	35	41	28
23.	Methomyl	i	55	66	41	38	10
24.	Permethrin	i	12	4	2	4	3
25.	Phenthoate	i	84	52	38	57	35
26.	Propoxur	i	1	2	1	1	0
27.	Propstemphos	i	0	0	0	0	0
28.	Profenofos	i	85	82	60	39	45
29.	Thiometon	i	3	2	1	1	1
30.	Bencmyl	f	21	31	10	12	13
31.	Bitertanol	f	2	1	1	2	3
32.	Carboxin	f	23	29	14	12	10
33.	Chlorthalonil	f	35	27	16	27	15
34.	Dodin	f	33	35	2	1	6
35.	Dithianon	f	0	12	6	8	0
36.	Dinocap	f	14	17	12	19	13
37.	Ediphenphos	f	57	37	22	25	20
38.	Fosetyl-Al	f	35	53	14	17	18
39.	Hexaconazole	f	26	37	9	7	14
40	Iprodione	f	1	0	0	0	0
41.	Isoprothiolane	f	4	16	11	6	7
42.	Kitazin	f	78	69	63	68	70
43.	Kasugamycin	f	0	17	3	8	10

2149

44.	Metalaxyl	f	28	32	25	21	6
45.	Penconazole	f	1	1	1	0	0
46.	Propiconazole	f	26	16	7	6	9
47.	Tridemorph	f	269	250	115	125	120
48.	Thiophenate methyl	f	31	40	20	19	15
49.	Triademefon	f	9	18	13	11	1
50.	Tricyclazole	f	13	16	6	15	11
51.	Validamycine	f	2	1	2	1	3
52.	Atrazine	h	340	330	390	325	315
53.	Benthiocarb	h	93	112	147	140	135
54.	Methabenzthiazuron	h	3	0	0	0	8
55.	Metoxuron	h	25	25	42	38	10
56.	Metribuzin	h	2	0	0	0	0
57.	Metalachlor	h	0	0	0	0	2
58.	Oxadiazon	h	2	4	8	8	3
59.	Oxadiargyl	h	0	2	3	5	2
60.	Oxyfluorfen	h	6	3	5	2	6
61.	Pendimethalin	h	161	126	130	149	140
62.	Partilachlor	h	31	12	15	12	13
63.	Simazine	h	84	42	55	64	45
64.	Triliats	h	0	0	0	0	1
65.	Trifluralin	h	8	13	7	11	10
66.	Bromodiolone	r	74	47	79	83	50
67.	Ethepon	pg	7	5	3	1	0
68.	Giberallic Acid	pg	10	13	12	10	15
69.	Meleic hydrazide	pg	6	0	0	0	0
70.	DD Mixture	n	0	0	0	0	0
71.	Others	n	101	9	0	0	0
	TOTAL:	Imported	5094	4788	3220	3220	3663
		Indegen-ious	41101	38796	43800	45130	37352
	Grand Total:		46195	43584	47020	48350	41020

Source: States/UTs

Note: i - Insecticide
f - Fungicide
h - Weedicide
r - Rodenticide
fm - Fumigants
pg - Plant growth regulator
mp - Misc. pesticides

FMC

CARBOSULFAN Review

July 31, 2006

Carbosulfan

- Discovered at University of California in mid 1970's
- First commercialization by FMC Corporation, USA in 1980
- Registered for use in more than 80 countries

Carbosulfan Toxicology

Carbosulfan is not mutagenic

It is not a developmental toxin

It is not a reproductive toxin- it does not affect subsequent generations

Carbosulfan is unlikely to cause any chronic effects

Any neurotoxic effects of Carbsulfan is rapidly reversible and non-cumulative

Carbosulfan Toxicology

- Acute oral LD_{50} (rat) – 105 mg/kg
- Acute dermal LD_{50} (rabbit) – 1520mg/kg
- Acute inhalation LC_{50} (rat) – 1.06mg/l/1hr
- Skin irritation (rabbit) – Moderately irritating
- Eye irritation (guinea pig) – Sensitizing

Carbosulfan

Biological Characteristics

- Systemic, broad-spectrum carbamate insecticide.
- Controls a number of economically important soil and foliar insect pests
- Insecticide with acaricidal and nematicidal properties
- Formulations – EC, granules and seed dressers

Carbosulfan - Bio Characteristics contd..

- Carbosulfan acts on insects by contact and ingestion
- It has a low vapour pressure
- Carbosulfan affects the insect nervous system

Carbosulfan Registration in India

Product	Year of Registration	Label claim Approved Crops
Carbosulfan Technical	1997	NA
Carbosulfan 25%EC	1997	Rice and chillies
Carbosulfan 25%DS	1997	Seed treatment - Cotton
Carbosulfan 6%G	2002	Rice

Cabosulfan 25%EC Pending label expansion: Cumin, Brinjal and Cotton

MRL Status: Residue/tox. data submitted in the proforma for Rice, chillies and cotton in April 2006

Carbosulfan - Comment i:

Higher potential of Carbosulfan to cause genetic alterations than cypermethrin in mice and also that it poses a mutagenic risk to human beings

Response:

The genotoxicity (mutagenicity) of carbosulfan has been investigated in a number of *in vitro* and *in vivo* genotoxicity studies, including a number of mouse studies.

The collective carbosulfan mutagenicity database, including a recent carbosulfan mouse *in vivo* chromosomal aberration study conducted for Europe (FMC Report A2004-5853), clearly shows that carbosulfan has negligible mutagenic potential.

Carbosulfan - Comment i contd..

Carbosulfan - Comment ii:

Carbosulfan is metabolized by hydrolysis to the 7-phenol or to carbofuran and dibutylamine, and is subsequently further metabolized via hydrolysis, oxidation and conjugation to a variety of metabolites. Metabolites of the dibutylamino moiety may enter the carbon pool and be incorporated into natural constituents of the body.

Response:

Carbosulfan is indeed rapidly metabolized by hydrolysis to the 7-phenol or to carbofuran and dibutylamine, and is subsequently further metabolized via hydrolysis, oxidation and conjugation

contd..

Carbosulfan – Comment : Contd..

The negative results (no increased tumors) from the carbosulfan mouse and rat carcinogenicity studies plus the negligible mutagenic potential from the carbosulfan mutagenicity studies indicate that carbosulfan poses a negligible mutagenic risk to human beings.

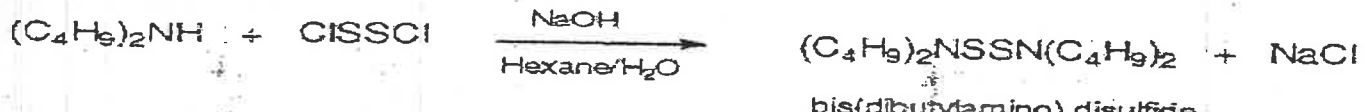
Carbosulfan - Comment iii:

Broad outline for process of manufacture along with the raw materials used

Response:

Carbosulfan

Step 1



bis(dibutylamino) disulfide

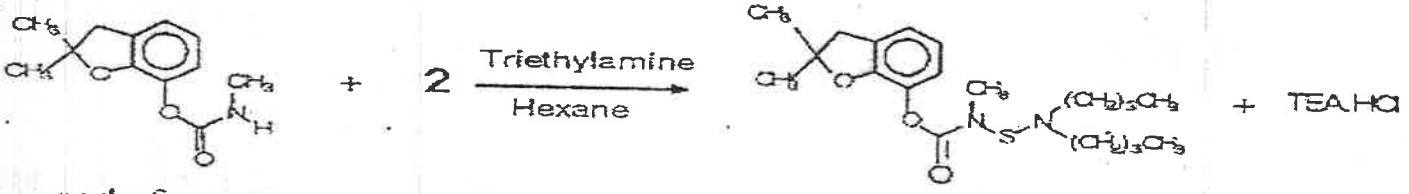
1

Step 2

(dibutylamino)sulfenyl chloride

2

Step 3



carbofuran

carbosulfan

Carbosulfan - Comment ii contd..

The majority of 7-phenol and carbofuran metabolites are eliminated within 24-96 hrs in urine; excretion in the faeces is lower than in urine

Dibutylamine is naturally occurring in the environment as a result of natural catalysis of proteins, and occurs naturally in our foods.

Dibutylamine is primarily eliminated intact rapidly in urine, but also undergoes metabolism to natural constituents prior to metabolism and elimination as carbon dioxide.

Carbosulfan - Comment iv:

Whether this molecule was deregistered/banned any time in Malaysia and its status of registration from 2000-2002. It may also be explained that why the import and the use have been prohibited for agriculture in Panama as per the United Nation list of products whose consumption and / or sale have been banned, withdrawn, severely restricted or not approved by the governments...

Response:

- Carbosulfan was not deregistered/banned at any time in Malaysia
- In 2000-2002, it was undergoing registration renewal in brinjal, chili, chrysanthemum, cucumber, longbean and watermelon and got approved in 2002

contd..

Carbosulfan – Comment iv Contd..

In the same period, its label expansion on rice was applied for and approved in 2003

The cited United Nation list of products needs to be corrected as carbosulfan is registered in Panama as well as Malaysia

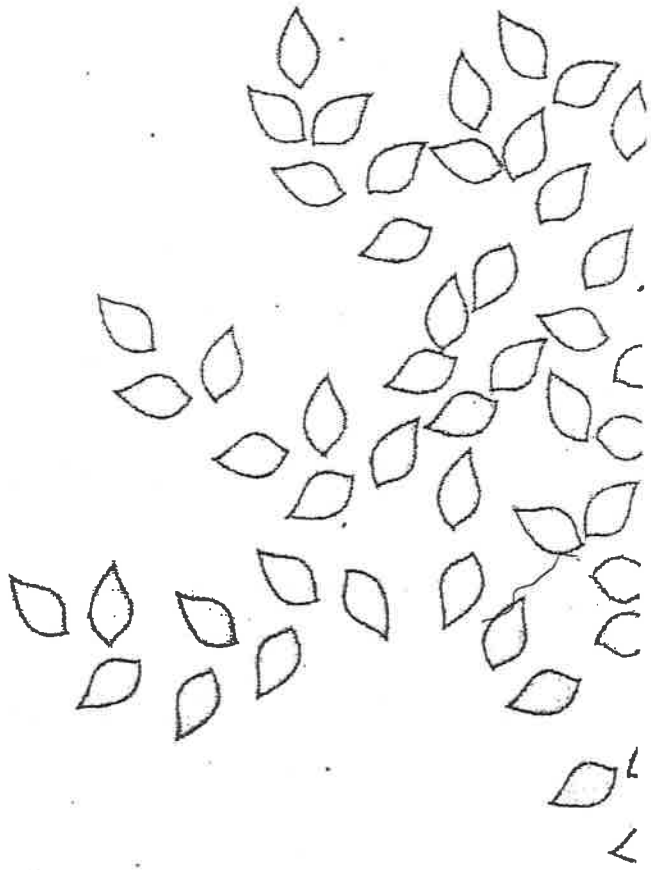
Legalized copies of the registration certificates from both countries were already submitted to the committee

CHLOROTHALONIL: Review In INDIA

S.K.Khosla

31.7.2006

syngenta



Chlorothalonil – Fungicide of Choice

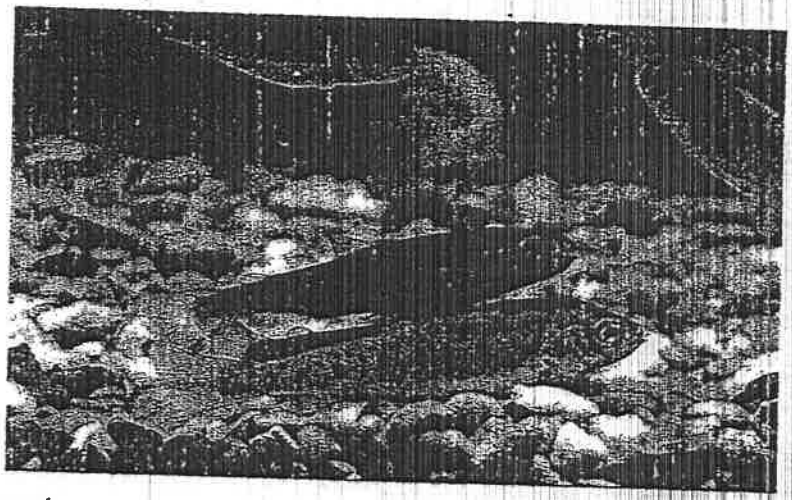
- Unique Multisite Mode of action as fungicide but also has mildewicide , bactericide & microbiocide properties – Non systemic Foliar fungicide with Protective Action. Not Known to have developed resistance to any fungi till date globally.
- Controls Many fungal diseases - Broad spectrum of activity - in a wide range of crops including Fruits, Vegetables, Oilseeds, Plantations etc.Has full global tolerances notified under Codex for 39 crops.
- Application Rates for food crops are 0.75 to 1.5 Kg / Ha
- In India approved for use in Apple, Chilli, Grapes, Groundnut & Potato for Scab, Early & Late Blight, Rusts,Anthraconose, downy mildew & Fruit rot.
- Highly recommended by the NRC for Oilseeds in control of Tikka leaf spot & rust in groundnut to boost the Oilseeds production in the country. There is no other fungicide providing such a dual benefit.
- NRC on Banana , trichy recommends its use for Sigatoka Leafspot disease as an alternate fungicide
- Chlorothalonil also provides excellent control of leafspots specially caused by Alternaria, Cercospora in vegetable crops

Chlorothalonil – Fungicide of Choice

- NRC of Grapes & APEDA recommends the use of chlorothalonil for effective control of Anthraconose and Downy Mildew. It is also recommended for rotation with other chemicals to prevent resistance.
- National Project on Pulses improvement has recommended its use in root wilt disease
- National Center for Horticulture has highly recommended the use of CLTH for control of Purple blotch of onion
- State Agricultural Universities have recommended the use of chlorothalonil in their package of Practices for all the above crops and also many more
- FRAC – Chlorothlonil a multisite fungicides greatly reduces the probability of resistance development

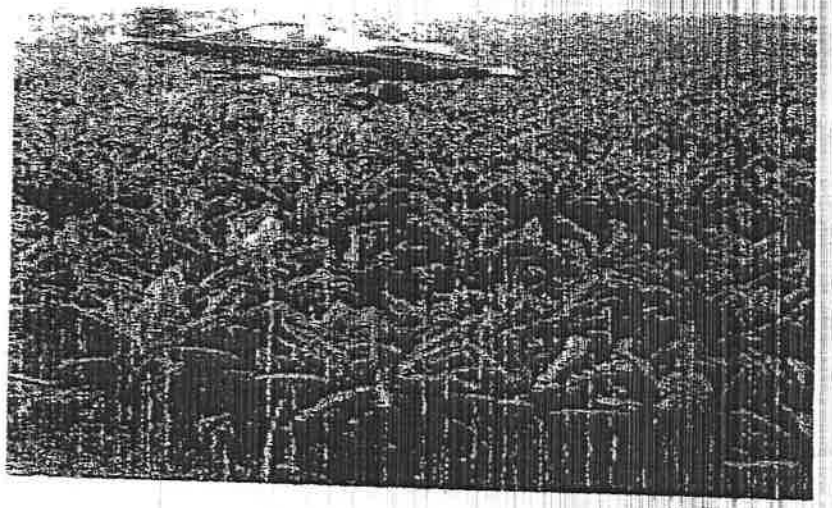
Chlorothalonil is highly toxic to aquatic organisms, BUT KAVACH has low risk to aquatic organisms when used as directed

Fish



Laboratory data -initial risk assessment
Fish 96 h LC50 values ~ 10 – 100 ug/l
Unacceptable risk at modelled
environmental concentrations

Refined assessment
Dissipation in water is rapid (DT50 < 8 hours)
Toxicity is reduced in water/sediment systems
Low inter-species sensitivity
Field study by Environment Canada – no effects on trout from direct applications (3 x 750 g ai/ha)
Low risk at Predicted Environmental Concentration from use in both EU and US



India
Low risk to fish in India as the product is
Approved for crops like Apple, chilli,
Grapes, Groundnut & Potato wherein
No interbreeding of fish takes place. We do
Not recommend its use in rice fields.

Demonstrating Acceptability of Risk in Indian Diet

Label claim	MRL Approved & Proposed	Terminal residues after waiting period (ppm)	Diet (g/day) (F)	TMDI (MRL x F) mg/day	Cummulative TMDI (mg/day)	ADI (mg/day/kg b.w)	ADI of a 50kg person mg/kg/bw	%ADI over TMDI
Potato	0.1	< 0.1	85	0.0085	0.1	0.015	0.75	13.33
Groundnut	0.1	< 0.1	20	0.002				
Apple	1	< 0.06	82	0.082				
Chilli	2	< 0.9	2	0.004				
Grape	1	< 0.1	6	0.006				
				0.1025				

ADI (EU) = 0.015 mg/kg/d Hence ADI for a 50kg person shall be 0.75mg/day

TMDI – India (50kg human being - worse case – all crops Potato, Groundnut, apple, chilli & Grapes consumed by the concerned person) = 0.1 mg/person/d = 13.33% of ADI

- Acceptable levels of risk indicate that product is safe to use

Chlorothalonil: Demonstrating Acceptability of Risk

USA – Q*-based risk cancer assessment (assumes that no threshold exists for the induction of tumours)

- US EPA considers that cancer risk assessments are acceptable for all exposed populations

Conclusion: Long-term consumer exposure to chlorothalonil is very low and does not pose a carcinogenic risk to humans

AOEL = 0.009 mg/kg/d

- Operator risk assessments indicate acceptability of risk across product portfolio. Operator Risks could be mitigated and reduced by having a close loading & mixing operaton.

Conclusion: Short-term exposure to chlorothalonil does not pose a risk to workers

Chlorothalonil: Chronic Toxicity & Carcinogenicity

- Increased incidence of kidney tumours in rats & mice. Basis for R40 hazard classification (Limited evidence of a carcinogenic effect)
  - Non-genotoxic mode of action
  - Threshold based (NOELS have been established)
  - Tumours occur as a secondary consequence of target organ toxicity

- Increased incidence of forestomach tumours in rats & mice
  - Not considered to be relevant to human health (humans do not have a forestomach)

Chlorothalonil - Hazard End-Points

Hazard End-Point	NOAEL – No adverse effect level	SF – Safety factor	Reference Dose
ARfD	1.5 mg/kg/d Kidney toxicity (7 Day Rat)	100	**0.015 mg/kg/d** **New study** **0.6 mg/kg/d**
AOEL	2.7 mg/kg/d (2 Year Rat)	100 (32% oral absorption in rats)	**0.009 mg/kg/d**
ADI	1.5 mg/kg/d Kidney toxicity (90 Day Rat)	100	**0.015 mg/kg/d**

Chlorothalonil: Sub-Chronic Toxicity

- Target organs in rodents: Kidney & forestomach
- Effects in kidney observed at 3.0 mg/kg/d and above
- Key No Effect Level = 1.5 mg/kg/d (rat 90 day study)

- No evidence of systemic toxicity following dermal application of 600 mg/kg/d for 21 days – low dermal toxicity

Acute Toxicity of Active Ingredient and Solo Kavach 75%WP Formulation

End-Point	Active Ingredient	Kavach 75WP Formulation
	Toxicity	Toxicity
Oral	>5000 mg/kg	4200 mg/kg
Dermal	>5000 mg/kg	>20, 000 mg/kg
Inhalation	0.1 mg/l	>1.96 mg/l
Eye Irritation	Severe irritant	Mild Irritant
Skin Irritation	Non-irritant	Non-irritant
Skin Sensitisation	Sensitiser	Sensitiser

Chlorothalonil: Reproductive & Developmental Toxicity

- No evidence of an effect on reproductive performance

- No evidence of an effect on development

Chlorothalonil is not a reproductive toxicant

Hexachlorobenzene - Impurity

- Chlorothalonil when originally registered globally was with a content of 500PPM of HCB way back in 1980's & Min AI of 96 percent purity
- However these specifications were first modified by FAO 1998 with HCB impurity limit of 300ppm & Min AI of 98.5 percent purity
- Chlorothalonil current specifications under FAO in February 2005 has further reduced the limit of HCB to 40ppm and introduced a limit of 30ppm for Decachlorobiphenyl (DCB)
- Hexachlorobenzene(HCB) and Decachlorobiphenyl (DCB) are both persistant organic pollutants (POP's) – the new limits on impurities were introduced as a consequence of the requirement of Stockholm convention to restrict the release of persistant organic pollutants into the environment

Hexachlorobenzene - Impurity

- New Technology has made it possible today to reduce HCB content in the Chlorothalonil Technical & meet FAO February 2005 specifications of Min AI of 98.5 percent & Max. HCB content to 40PPM & 30PPM of DCB.

- SDS Biotech , Japan the approved source of import & Syngenta US, manufacture CLTH with HCB content of 10ppm – what is being imported into the country.

- HCB content is quantified by GCMS and measured at the time of production and no batch is released without this measurement.

- ADI of HCB allocated by FAO/WHO is 0.0006mg/kg, while the ADI of CLTH is 0.015mg/kg indicating an appox. Long term toxicity ratio of 25:1. Thus at 40PPM limit HCB is not expected to contribute to the overall toxicological hazard of chlorothalonil

Conclusion

- In 1994, WHO JMPR concluded that the risk arising from exposure to chlorothalonil should be determined assuming that a threshold exists for the occurrence of cancer in animal studies.

- EPA in its RED – April 1999 for chlorothalonil concluded that the level of chlorothalonil to which people are exposed in diet is extremely low and falls well below those levels that have been shown not to cause cancer in animals, indicating that the carcinogenic risk to humans is negligible. Therefore, on the basis of dietary risk assessment, there are no concerns regarding the carcinogenic potential of chlorothalonil in humans.

- In 2005 chlorothalonil achieved Annex 1 inclusion in the EU, which can only be given when safe uses exist.

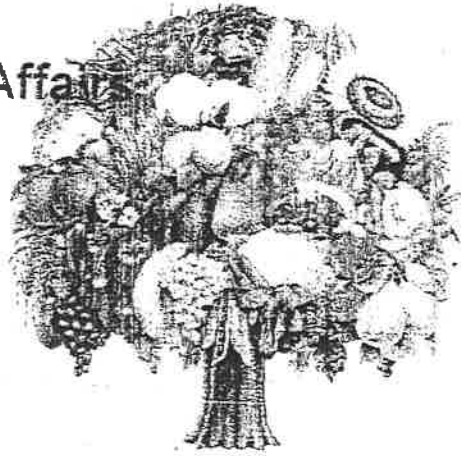
Bayer CropScience

Deltamethrin - General Overview

By : Mr. Kishor Nahar

Head – Registration & Regulatory Affairs

Bayer CropScience, India



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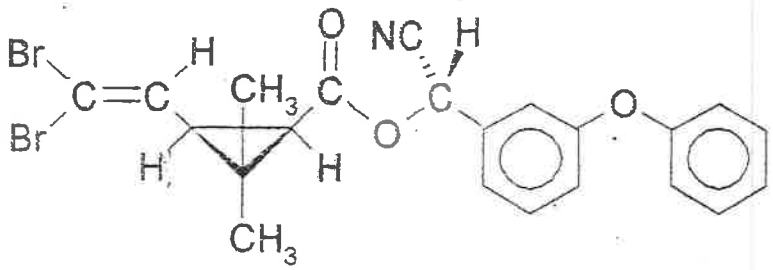

Deltamethrin (one pure isomer)

- Deltamethrin belongs to the class of pyrethroids and is a chemical derivative of the natural compound Pyrethrin I, obtained from *Chrysanthemum cinerafolis.*

- Deltamethrin shows broad spectrum insecticidal activity (against Lepidoptera, Homoptera, Heteroptera etc.)

- Deltamethrin has been on the market worldwide for more than 20 years and is therefore one of the best-studied pesticides in the world.

General Overview

- Deltamethrin is the second - largest insecticide in Bayer CropScience's portfolio

- Deltamethrin products are used at low dose rates; the active substance is non-systemic and has a low toxicity; which leads directly to advantages such as an excellent food chain profile and low environmental burden.

- Deltamethrin is used in following Key Segments in India and Worldwide;
  - Crop Protection (**Deltamethrin 2.8 EC, 11 EC, and 1.8 EC)**
  - Public Health, Storage and House hold (**Deltamethrin 2.5 WP, 2.5 SC, Tablet and ULV**), and
  - Animal Health market

History of the Ban on Outdoor Use in Denmark

Concern (as mentioned in UN list) 2002 : "Toxicity to aquatic organisms. The products are therefore assessed to be seriously damaging to the environment."

Remarks (as mentioned in UN list) 2002 : "All authorization for products, containing Deltamethrin as an active substance have been withdrawn from the market in 1997 and further use has been banned for outdoor use from 1998. Indoor uses are still allowed."

History of the Ban on Outdoor Use in Denmark

- Deltamethrin was banned in Denmark for **outdoor use** in 1998, after the Danish authorities had imposed an additional safety factor of 10 in the aquatic risk assessment, above and beyond the EU and US EPA standard.

- Following Annex I listing of Deltamethrin a.i. in Europe in 2003, the additional safety factor has been removed from the Danish aquatic risk assessment.

- Preparation of the retrieval of the registration for outdoor use of a Deltamethrin 2.5 EC formulation in Denmark is ongoing.

- The **indoor use** of Deltamethrin based products was never banned in Denmark (Deltamethrin 2.5% SC and Deltamethrin 0.05% Dust for House hold pest control).

The following concerns raised by the Pesticide Review Committee would be addressed by our experts :

- Cutaneous, Mucous membrane irritation and Paresthesia upon exposure.
- Information on health survey of spraymen using Deltamethrin 2.5% EC in cotton fields **in China.**
- Toxicity to aquatic organisms.

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Deltamethrin - Concerns

1) Cutaneous, Mucous membrane irritation and Paresthesia upon exposure.

2) Health survey of spraymen using Deltamethrin 2.5% EC in cotton fields in China

By : Dr. (Ms.) Kerstin Henninger
Regulatory Toxicologist
Bayer CropScience, Germany

Skin Irritation

Primary skin irritation, also called irritant dermatitis, is a localized reversible dermal response resulting from a single application of, or exposure to, a chemical without the involvement of the immune system.

- Symptoms: redness (erythema), eschar formation, edema, vesiculation, corrosion.
- Standard protocol for investigating dermal irritation consists of applying the a.i. to the shaved back of rabbits.
- Deltamethrin Technical is non -irritant to skin.
- The Deltamethrin Formulations viz; EC, WP and SC which are widely used are classified in India as non - irritant to slightly irritant to skin.

Irritation to Mucous Membrane

- Mucous membranes are more sensitive to irritation than skin.
- Irritation to mucous membranes is tested in the experimental setting of eye irritation.
- Deltamethrin Technical is not classified as irritant to the eye.
- Deltamethrin Formulations viz; EC, WP and SC are classified in India as slightly irritant to eyes.

Paresthesia is different from skin irritation

Paresthesia is defined as an abnormal sensation of the skin, such as numbness, tingling, pricking, burning, or creeping on the skin that has no objective cause. These skin sensations resulting from exposure typically occur without erythema, edema, vesiculation or any other sign of dermal irritation.

- Paresthesia is a well-known general property of **pyrethroids**;
- Paresthesia is the most frequently reported symptom of inadvertent human occupational exposure after handling of pyrethroids in the field and in manufacture;
- Paresthesia is concentration-dependent but not dose-dependent;
- Paresthesia occurs within a few minutes and may last up to 24 hours before **resolving spontaneously**;

Mode of action underlying paresthesia

- Pyrethroids interact with the voltage-dependent sodium channels of the nerve cell membrane.
- As a result during depolarization the sodium channels stay open for a longer period of time than usual leading to repetitive nerve activity (repetitive firing) particularly in the sensory nervous system.
- The skin sensations induced by dermal exposure to **pyrethroids** are thought to be a result of repetitive firing of sensory nerve endings.
- **The effect is reversible due to elimination of the compound.**

Paresthesia is not an adverse effect

- Paresthesia is a subjective feeling with great variations and susceptibility between individuals;
- The face is the most common area affected although other body areas with mucous membranes can be involved and more particularly those with a high density of nerve endings;
- Upper respiratory tract (URT) sensory irritation inducing rhinitis, sneezing and coughing is also occasionally observed, mainly in unprotected workers spraying **pyrethroids** or in occupational settings;

Paresthesia is not a systemic effect;
It is a local and quickly reversible effect.

Paresthesia is not an adverse effect as such.
It is rather a signal for exposure and hence steps to reduce exposure can be taken.

Incidence of dermatitis among farmers exposed to deltamethrin in the cotton field, Wang Shujie et al.

Spraymen exposed to 2.5% deltamethrin emulsifiable concentrate in cotton fields in China:

"The subjects were exposed to deltamethrin at concentrations of 0.022 – 24.070 µg/m³ in the air of the respiratory zone and 0.013 – 0.347 µg/m³ of skin contact. One half of the 44 sprayers complained of itching and burning sensations on their faces. A few miliary red papules also appeared on the face of one of them."

- The active ingredient deltamethrin has been demonstrated to be non-irritant to the skin;
- The formulation used in this study contained xylene which is a known skin irritant
  - *"Potential that xylene was the cause of the symptoms described."* (Wang Shujie *et al.*, 1988)
- The workers in this survey were not using any personal protective equipment as advised on the label;
- It is possible that itching and burning sensation on the face reported was not only the irritation to skin but also due to paresthesia.

- **Deltamethrin Formulations registered in India do not contain xylene as solvent.**
- **To the best of our knowledge, despite many years of use there are no incidents reported for skin irritation and paresthesia with Deltamethrin products among users in India.**

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Thank you very much for your kind attention

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Deltamethrin – Concern

by Toxicity to Aquatic Organisms

By : Dr. Raimund Grau
Eco – Toxicology Expert
Bayer CropScience, Germany

Standard Laboratory Toxicity Data

- Fish
  - Rainbow trout — a.i. — LC50 — 0.91 µg a.i./L
  - Rainbow trout — EC25 — LC50 — 0.26 µg a.i./L
  - Bluegill sunfish — a.i. — LC50 — 1.4 µg a.i./L
- Aquatic invertebrates
  - Daphnia magna — a.i. — EC50 — 0.56 µg a.i./L
- Algae
  - Green algae — EC25 — E_bC50 — 1700 µg a.i./L

➢ Deltamethrin is intrinsically toxic to aquatic organisms

Mitigating Factors in the Field

- hydrophobicity
  - surface spreading
  - hampering dissolution in water
- reduced bioavailability to lentic and lotic organisms due to very strong adsorption to suspended solids, plants and sediment
- fast disappearance from the water body through dissipation and degradation
- very short half-life in water (< 1 day)

➢ Risk to aquatic organisms overestimated from lab studies

Field Studies with Fish

- Summary of field studies in rice
  (Indonesia, Philippines, Taiwan)

  - 12.5 g a.i./ha (recommended dose)
    - No effects

  - 50 g a.i./ha (4x recommended dose)
    - No effects

Conclusions, Fish Toxicity

- Deltamethrin is toxic to aquatic organisms in standard laboratory studies
- Intrinsic toxicity is greatly mitigated under field conditions
- Deltamethrin is safe for fish in shallow water
  - at rates recommended and
  - even up to at least 4x the recommended dose

Deltamethrin Uses in India

Crop	Common name of pest	Dosage (g a.i./ha)
Cotton	Bollworms	12.5
	Sucking insects	10
Tea	Thrips	3 - 4
	Leaf roller	10
	Looper	2.5 - 3.75
Bhendi (okra)	Shoot & fruit borer	10 - 15
	Jassid	10
Groundnut	Leaf miner	12.5
Mango	Hoppers	0.033 - 0.05%
Chilli	Fruit borers, Heliothis, spodoptera	10 - 12.5
Chick Pea	Pod Borer (Heliothis)	10 - 12.5
Brinjal	Shoot & fruit borer (Leucinodes)	10 - 12.5
Rice	Stem borer, Leaf folder	10 - 12.5

Deltamethrin Use Categories, Application Rates

- Low growing crops (< ca. 50 cm)
  - 10 – 12.5 g a.i./ha
    - brinjal, chick pea, ground nut
- Medium high crops (up to ca. 2 m)
  - 3 – 12.5 g a.i./ha
    - cotton, tea, chilli, bhendi
- Rice
  - 10 – 12.5 g a.i./ha

Deltamethrin Use Categories, Aquatic Exposure

- Low growing crops (< ca. 50 cm)
  - Drift rate @ 1 m distance 2.77%
    - Loading ≤ 0.35 g a.i./ha
- Medium high crops (up to ca. 2 m)
  - Drift rate @ 3 m distance 8.02%
    - Loading ≤ 1.0 g a.i./ha
- Rice
  - Overspray with crop interception (50%)
    - Loading ca. 6.25 g a.i./ha

Conclusions, Use Pattern in India

- Rice
  - No treatment of fish rearing paddy fields under Indian agricultural contitions
    - Treatment of rice with contact insecticide only possible when water depth very low (2-3 in.)
    - Low water depth does not allow rearing of fish
    - Even if applied to fish containing shallow rice fields no effects expected
- Terrestrial crops
  - Aquatic exposure considerably lower than the level proven safe for fish under field conditions

➢ **Used according to the label, Deltamethrin is safe for the aquatic environment**

Bayer CropScience

Thank you very much for your kind attention

Dhanyavad !

Thank you very much for your kind attention

Annex-III-D

DIAZINON

REVIEW BY DR. C.D. MAYEE COMMITTEE ON 31.07.2006

DIAZINON

- Introduction.
- Concerns expressed by Review Committee.

3. Answers to the concern.

Diazinon – Concerns expressed by Review Committee

- High toxicity to bees
- Persistence in soil
- Poisonous to aquatic organisms
- Toxic to wild birds and mammals
- Causes ground water pollution
- Neurotoxicity due to its metabolite Diazoxan
- Teratogenicity

DIAZINON

- Diazinon is a Contact Organophosphorus Insecticide with a wide range of insecticidal activity.
- Diazinon is effective against adult and juvenile forms of flying insects, crawling insects, mites and soil dwelling insects.
- Diazinon use is on agricultural crops and household pests.
- Diazinon is extensively used as a veterinary medicinal product for livestock outside the world.
- Diazinon is registered in India as Emulsifiable Concentrate (20 % EC) Encapsulated materials (25% MEC) and ready to use solutions (2% RTU).

Diazinon – High toxicity to bees

- Hazard quotient are calculated based on application rates.
- Diazinon is applied @ > 1200 g / Ha in cereals and fruits in abroad whereas in India, it is applied ranging from 90 – 750 g / Ha.
- Diazinon is only recommended for the control of Diamondback moth and the crop is harvested before pre-flowering.

It is presumed that there won't be any bee mortality or its activity is hampered by Diazinon application.

(Ref. : 1. Diazinon Environmental Health Criteria, 198- P 100
2. CIB Regn. Certificate for Diazinon 20 EC)

Diazinon – Persistence in Soil

- Diazinon seldom migrates below the top 1.3 cm (1/2 inch) in soil.
- Stay biologically available for six month under conditions of low temperature and low moisture.
- Average time for 50% degradation in soil is 2 – 4 weeks.
- Bacterial enzyme can speed the breakdown of Diazinon.
- Breakdown rate is highly dependent on acidity of water.
- The main metabolite in soil is 2–Isopropyl-4 methyl 6 hydroxy pyrimidine which is unstable in soil.
- Soil degradation of Diazinon is also by photo degradation, volalitisation and mineralization.

(Ref : 3. Extoxnet : Pp 1-5
4. Pesticide residues in food (JMPR), 1993 – Pp 270-272)

Diazinon – Poisonous to Aquatic Organisms

- Toxicity to fresh water Snail – LC50 93 mg / lt
- Effect on Lymnaea – Haemolymph viscosity and density decreased.
- Growth and survival of fathead minnows are not affected at concentrations below 0.2 mg / lt
- Rainbow trout have a LC50 of 90-140 ppb.
- Lake trout and cut throat trout are more resistant
- Fathead minnows and gold fish are even more resistant.

Diazinon – Poisonous to Aquatic Organisms (contd.)

- Diazinon will not be expected to significantly bioconcentrate in aquatic systems.
- For Earthworms LC50 – 130 mg / kg soil. No-observed effect concentration of 12.3 mg / kg was reported.
- Mortality of earthworms did not differ between treated and control plots where 4.48 kg / ai / Ha of Diazinon applied in tobacco fields.
- Diazinon is not recommended on rice and the possibility for contaminating the water bodies doesn't arise and hence there is no concern on fish toxicity.

(Ref : 5. Diazinon Environmental Health Criteria, 198 – Pp 79-86, 101
6. Extoxnet – Pp 1-5)

Diazinon – Toxic to Wild birds

- Use of Diazinon for controlling flies in sheds used to house ducks led to the death.
- Application of 14 G granules could be lethal to sparrow sized birds.
- Exposing the turkeys to soil treated with 18 kg / Ha led to no poisoned birds.
- Exposure study with Diazinon @ 40 mg / kg did not result in effects on reproductive performance and no mortalities or avert signs of toxicity to bobwhite quail.
- Application of Diazinon on golf had caused death of waterfowl since it often congregates near ponds on golf courses.

Diazinon – Toxic to Wild birds

(contd.)

- Diazinon applied twice at 2.2 kg ai / Ha on turf do not produce any mortality to Canada geese despite extensive feeding on treated turf.
- LD50s for birds range from 2.75 mg / kg to 40.8 mg / kg / day

Application of Diazinon in poultry or soil treatment or in turf is not recommended and hence we do not anticipate any danger to the grazing birds either in the field or in turf.

(Ref : 7. Diazinon – Environmental Health Criteria 198 – Pp 87 – 91
8. Extoxnet – Diazinon – Pp 1 – 5
9. Diazinon – Pesticide News – Pp 1 – 5
10. Diazinon – Virginia Department of Health – Pp 1 – 3)

Diazinon – Causes ground water pollution

- Diazinon parent is moderately mobile and persistent.
- Based on monitoring data, there is no risk concern for either groundwater or surface derived drinking water exposure for chronic or acute.
- Modelling data indicate a possible concern for infants and children age 1 – 6 (acute) and children 1 – 6 (chronic) from surface derived drinking water only.
- Mobility studies with different soils, under non-saturated flow conditions, which are more similar to natural conditions, Diazinon should not be easily leached from the studied soils to ground water.

Diazinon – Toxic to mammals

- Samples tested before 1979 show a much higher acute toxicity particularly due to the content of high toxic by-product viz. TEPP. Improvements in the manufacturing of Diazinon did reduce the content of TEPP.
- Diazinon has moderate acute oral toxicity to mice and rats
- LD50 Rat – 300 – 850 mg / kg
  Varies with stability of product
- Dermal LD50 Rat – 2150 mg / kg
- WHO has classified Diazinon as moderately hazardous.

(Ref : 11. IPCS Inchem – Diazinon Pp – 1-28
12. Diazinon – Summary Report Pp – 1-3
13. Diazinon – EHC 198. Pp – 43-48)

Diazinon – Causes ground water pollution

(contd.)

- From 1985-87, a monitoring survey was conducted to determine the ponds selected pesticides in farm ditches located in the lower mass land of BC, Canada, Diazinon was not detected in ditch water.

(Ref : 14. USEPA – Diazinon Summary – Pp 1-2
15. Diazinon – Environment Health Criteria – Pp 14-22)

Diazinon – Neurotoxicity due to its metabolite Diazoxan

- A neurotoxicity study performed with hens @ 28 mg / kg bw / day for three weeks and then 13 mg / kg bw for further three weeks. This study did not reveal evidence of delayed neurotoxicity.
- Diazinon was evaluated in four human volunteers who received 0.025 mg / kg bw / day of Diazinon capsules for 34-36 days. There were no consistent treatment – related effects on plasma or erythrocyte cholinesterase activity, blood chemistry or urinalysis. No clinical effects were reported.
- Metabolism studies using radio labeled compound have been conducted in rats, dogs, sheep and goat in compliance with GLP. Diazinon is readily metabolized, principally by cleavage of the pyrimidinyl phosphorous ester band and eliminated predominantly via the urine. In rats 73-81 of the dose was recovered in the urine within 72 hours.

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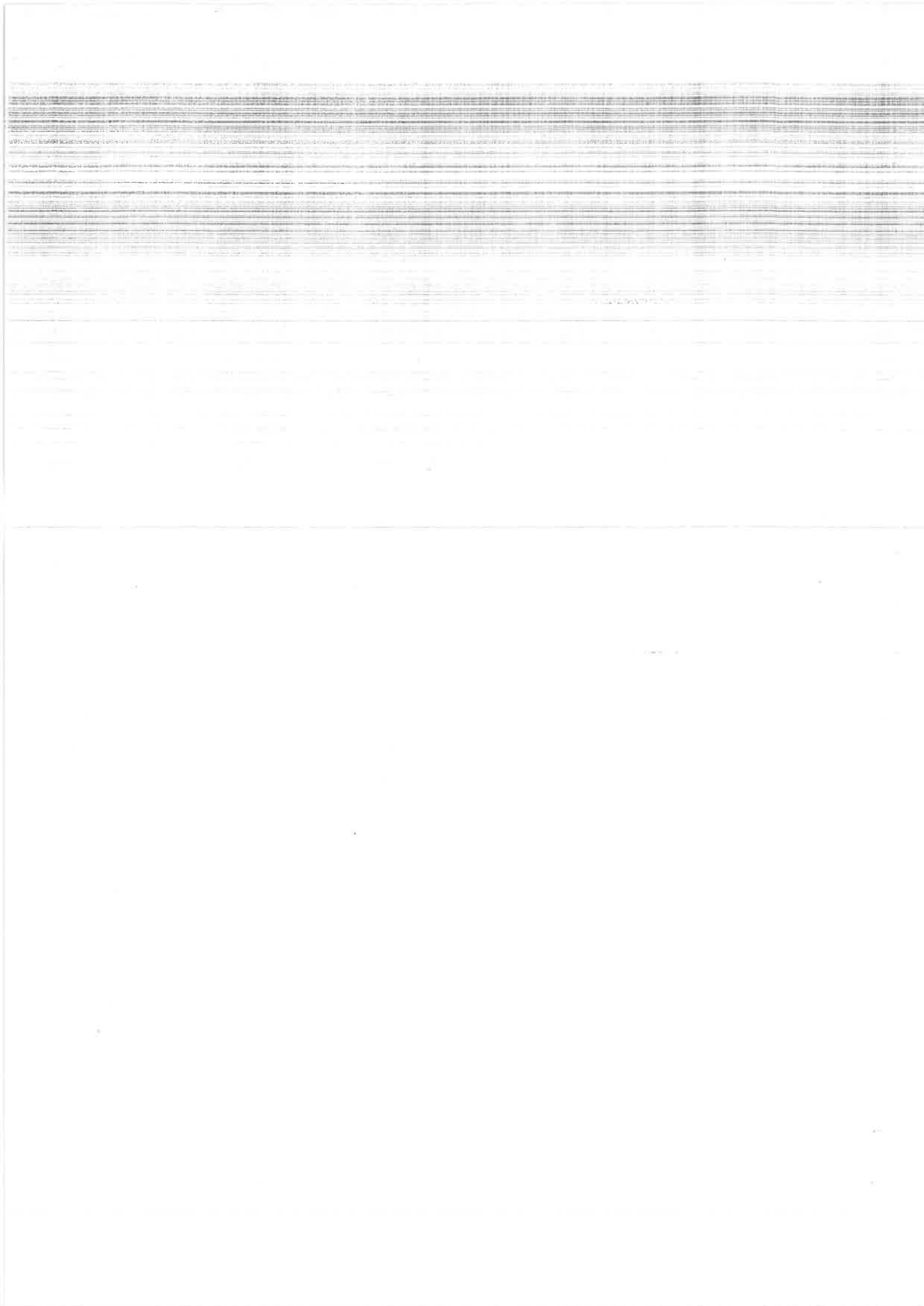

Diazinon – Neurotoxicity due to its metabolite Diazoxan

(contd.)

- Diazinon was found to be readily degraded and the metabolites formed were mainly eliminated via the kidneys. The main degradative pathway of Diazinon in mammals includes the oxidase / hydrolase – mediated cleavage of the ester bond leading directly via diazoxan to the pyrimidinol derivative 2-Isopropyl-6 methyl-4 (1H)-pyrimidinone, which is further oxidized at the isopropyl substitutent resulting in the hydroxyl pyrimidinols either excreted as such or further degraded to polar metabolites.
- Diazinon is rapidly metabolized in mammals and is excreted principally through the urine. It is metabolized in vivo by four enzyme systems, which include mixed function oxidases, hydrolases or phosphatases, glutathione – dependant transferases and non-specific esterases.

Diazinon – Neurotoxicity due to its metabolite Diazoxan

(contd.)

- In sheep and goat treated with exaggerated high dermal dose, parent compound was the only significant residue found in fat (85% and 68% respectively) and a minor residue in kidney and liver.
- Two pyrimidnyl metabolites were the major metabolites and these compounds show no acetyl cholinesterase inhibition power and more than 10 times lower acute LD50 toxicity values in rats compared to parent compound.
- These compounds were also found in rats and dogs, where inhibition of cholinesterase was identified as the principal effect of Diazinon. Parent compound was therefore the marker residue.

Diazinon – Neurotoxicity due to its metabolite Diazoxan

(contd.)

- Most in-vivo animal studies have demonstrated the production of diazoxan hydroxyl diazinon, isohydroxy diazinon and a propylene diazinon metabolite. Diazinon does not bioaccumulate in tissues or organs.

(Ref : 16. Diazinon – Virginia Department of Health – Pp – 1-3
17. Diazinon – European Agency for the evaluation of Medicinal Products – Pp 1-3
18. Diazinon – IPCs Inchem – Pp 1-28)

Diazinon – Teratogenicity

- Group of mice were given oral daily doses of 0, 0.18 or 9 mg / kg bw Diazinon throughout gestation. Examination of brain tissue of only 8 of a total number of 132 offspring at the high-dose level revealed morphological abnormalities in the fore-brain. The relationship of these findings to the observed behavioural changes in unknown. The evidence of morphological effects of Diazinon on the developing brain was considered insufficient by an expert.
- Groups of rats were treated with doses of Diazinon at 0, 10, 20 or 100 mg / kg bw / day by gave during gestation days 6 through 15. The treatment had no effects on the dams. No compound – related clinical signs and no abnormal gross pathological findings were observed in the dams.

Diazinon – Teratogenicity

- Diazinon was administered to groups of pregnant rabbits. Study gave no evidence for embryotoxic or teratogenic activity of Diazinon.
- Experimental evidence of teratogenic potential of Diazinon was found in studies on chicken embryos. However, as chicken embryo afford no parallel with the anatomical and physiological relationship existing between the pregnant mammal and her conceptus, Diazinon is not considered a teratogen to relevance to mammals.

(Ref : 19. Diazinon – IPCS Inchem – Pp 1-28
20. Diazinon – European Agency for the evaluation of Medicinal products – Pp 1-3)

Diazinon – Summary

- Diazinon is registered in India as Emulsifiable Concentrate (20 % EC) Encapsulated materials (25% MEC) and ready to use solutions (2% RTU).
- Diazinon is only recommended for the control of Diamondback moth and the crop is harvested before pre-flowering. We do not anticipate any bee mortality or its activity is hampered by Diazinon application.
- Soil degradation of Diazinon is also by photo degradation, volalitisation and mineralization and average time for 50% degradation in soil is 2 – 4 weeks.
- Diazinon is not recommended on rice and the possibility for contaminating the water bodies doesn't arise and hence there is no concern on fish toxicity.
- Application on Diazinon on poultry or soil treatment or in turf is not recommended and hence we do not anticipate any danger to the grazing birds either in the field or in turf.

Diazinon – Summary

- WHO has classified Diazinon as moderately hazardous.
- Based on monitoring data, there is no risk concern for either groundwater or surface derived drinking water exposure for chronic or acute.
- Metabolism studies using radio labeled compound have been conducted in rats, dogs, sheep and goat in compliance with GLP. Diazinon is readily metabolized, principally by cleavage of the pyrimidinyl phosphorous ester band and eliminated predominantly via the urine. In rats 73-81 of the dose was recovered in the urine within 72 hours.
- Diazinon was administered to groups of pregnant rabbits. Study gave no evidence for embryotoxic or teratogenic activity of Diazinon.

Annex - III - E

Dow AgroSciences

Review of Pesticides in India

Dinocap

Richard Billington, M.Sc., C.Biol., DABT, DRCPath.
Senior Toxicologist
Human Health Assessment Leader
Dow AgroSciences Europe

Dow AgroSciences

Items to be presented

- Teratogenicity
- Phytotoxicity in high temperature areas
- Efficacy in cucurbits
- Alternative products
- Aquatic toxicity
- Questions and answers

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Teratogenicity

Table 1: Dinocap - Summary of developmental effects in selected oral teratology studies

Species	Dosages mg/kg bw/day	Developt. NOEL mg/kg bw/day	Developt LOEL mg/kg bw/day	Developmental Effects at LOEL*	Vehicle, dinocap purity	Ref.
Rat	0, 10, 50, 150	50	150	Extra ribs ↓ dam wt gain @ 150	"Mulvocel", 98% pure	Solomon, 1989
Rabbit	0, 3, 12, 48, 84	12	48	↓ foetal weight, ↓ ossification	1% gum trag. 95.4% pure	Hoberman 1987
Mouse	0, 4, 10, 25	4	10	Cleft palate – 3.1% Open eyes – 0.8% (10 almost a NOEL)	1% gum trag. 94.4% pure	Lochry 1989
	0, 10, 15, 20, 60	0	10	Otolith agenesis - 14% (10 almost a NOEL)	Corn oil 84% pure	Rogers *et al.*, 1989

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Teratogenicity

Table 2: Dinocap - Summary of developmental effects in selected dermal teratology studies

Species	Dosages mg/kg bw/day	NOEL mg/kg bw/day	LOEL mg/kg bw/day	Effects at LOEL	Vehicle, dinocap purity	Ref.
Rabbit	0, 25, 50, 100	50	100	↓ ossification	None 87.8% pure	Costlow 1985b
Mouse	0, 1, 4, 10, 25 dinocap	10	25	Cleft palate - 4% Open eyes - 3% Otolith agenesis – 75%	Karathane LC, 36.2% dinocap	Foss 1995

Conclusion – mouse study was only a probe but tested the product and showed a higher NOEL by the dermal route; the main route of human exposure of workers.

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Teratogenicity - Summary

OECD test guideline and GLP-compliant studies in rats, rabbits and mice

Teratogenicity only in mice.

Foetal NOEL's are:

Mouse	4 mkd
Rabbit	12 mkd
Rat	50 mkd

Many published studies in mice, also hamsters, that investigated teratogenicity but do not change dinocap's hazard or risk - the lowest NOEL is 4 mkd.

Dermal NOEL in mice is 10 mkd of dinocap.

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Phytotoxicity in high temperature areas

Dinocap when used as recommended is very safe to crops and does not cause phytotoxicity even at high temperatures.

Dinocap was tested on Mango, Melons, Cucurbits, Summer squash during high temperature season – good efficacy, no phytotoxicity or crop damage.

(Bhatia and Thakur (1989); Sokhi *et al.* (1990); Gandhi and Maheshwari (2000) and Thind *et al.* (2004)

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Field workers - risk summary

Product	Crop	Dose Rate kg active/ha	Safe Dose for Workers* mg/kg bw/day	Dermal absorption %		Method of Application	% of Safe Dose for Workers	
				Product	Spray		No PPE	Gloves for mixing
Dinocap 48% EC	Grapes	0.108	0.003*	1	10	Knapsack	32	22
						Mist Blower	54	40

* Based on worst-case effects in dogs, not teratogenicity in mice.
Safe dose for teratogenicity = 0.006 mg/kg bw/day, so risk is lower by half of the above numbers.

Conclusion: a worst-case application shows that dinocap products can be used safely.
Gloves improve safety, including to acute hazards of the product - skin sensitisation.

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Efficacy against powdery mildew control in cucurbits

- Dinocap is recommended for use in following crops
  - Grapes
  - Mango
  - Chillies
  - Pumkin Melon Kakri
  - Cumin
  - Rose
  - Cowpea, Cluster bean, French bean
  - Apple, Pears
  - Ber
  - Okra
  - Poppy
  - Wheat, Fenugreek

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Efficacy against powdery mildew control in cucurbits

- Dinocap is a product of trust when disease intensity is severe. Farmers use it to reduce disease infestation fast.
- Dinocap is very popular as an alternate spray partner in a multiple powdery mildew spray schedule.
- Dinocap is also popular among cucurbit growers for effective control of powdery mildew and safety to the crop.

(Bhatia and Thakur (1989); Sharma and Kumar (1999); Gandhi and Maheshwari (2000), Thind *et al.* (2004)

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Better alternative available?

- Many fungicides are registered for control of powdery mildew in different crops but only a few are contact fungicides, including Dinocap
- Dinocap has been tested by many scientists for its efficacy and compared with other available powdery mildewicides
- Dinocap was as effective or better compared to available alternatives, including systemics

(Khosla *et al.* (1988); Sinha (1989, 1999); Das *et al.* (2000); Sharma *et al.* (2001); Gandhi and Maheshwari (2002); Som Prakash *et al.* (2002); Banyal and Rana (2003); Ray (2003); Narayana *et al.* (2005))

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Better alternative available?

- Most fungicides are systemic with "sterol biosynthesis inhibition" mode of action
- Dinocap is the best contact fungicide available with unique mode of action (uncoupling of oxidative phosphorylation)
- Plays a major roll in resistance management strategy

Dow AgroSciences

Aquatic toxicity

Complete data package of studies:

- Acute and chronic toxicity data - no gaps
  - GLP studies
  - USEPA, OECD and UBA guidelines
- Fish, Daphnia, Algae toxicity
- Fish Bioconcentration

Aquatic Toxicity - Summary

Species	Endpoint	Measurement	Reference
Acute exposure			
Rainbow trout	96 hr LC50	0.013 mg ai/L	Bowman and Schrier 1991
Bluegill sunfish	96 hr LC50	0.0053 mg ai/L	Sword and Leak 1994
Daphnia magna	48 hr EC50	0.0042 mg ai/L	Sword and Leak 1994
Daphnia magna	24 hr EC50	not determined	Ellgehausen 1983
Scenedesmus subspicatus	96 hr EC50	18.98 mg ai/L	Ellgehausen 1983
Selenastrum capricornutum	72 hr EC50	> 0.150 mg ai/L	Hicks and Leak 1997
Chronic exposure			
Fathead minnow	NOEC	0.00176 mg ai/	Rhodes and Leak 1994
Daphnia magna	NOEC	0.00094 mg ai/L	Forbis 1994
Bioconcentration			
Bluegill sunfish	BCF	992 to 837	Corden 1998

Aquatic Risk Summary

- Dinocap is toxic to fish, Daphnia
  - Avoid spray drift to surface waters
- Dinocap chronic toxicity nearly the same as acute toxicity
  - Little concern for long term effects
  - Dinocap not persistent in water or soil (hydrolyzes rapidly)

Dinocap – Global Registrations

Dinocap is registered around the world:

- **EU:** UK, France, Spain, Italy, Greece, Austria, Portugal...
- **Americas:** Brazil, Canada, Mexico, Peru
- **Eufrasia:** Algeria, Belarus, Bulgaria, Croatia, Egypt, Iran, Israel, Jordan, Morocco, Moldova, Montenegro, Serbia, South Africa Tunisia, Turkey, Ukraine
- **Asia/Pacific:** Indonesia, New Zealand, South Korea, Thailand

Dinocap – Overall summary and conclusions

Teratogenicity - Is a teratogen in mice but not other species. Hazard is classified in EU. Risk officially acceptable in EU and other regions.

Phytotoxicity - No issue, even in high temperature areas.

Efficacy in cucurbits - Good, fast and safe.

Alternative products - Dinocap has high efficacy, unique mode of action and no resistance issues.

Aquatic toxicity - Dinocap is toxic - avoid spray drift to surface waters using buffer zones - risk then officially acceptable in EU and other regions.

Dinocap has been used safely for 40 years and is still registered across the world.

Annex-II F

Review by Expert Group (RC)

ETOFENPROX

Defence Document

Presented by

Dr. P.K. Gupta
31-07-2006

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&

Dhanuka Group
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Carcinogenicity
(Thyroid adenomas plus carcinomas)

Mice (2 year study on toxicity / carcinogenicity) :-

NOAEL 30 ppm = 3.1 mg/kg b.w./day

There was no evidence of carcinogenicity.

Reference : JMPR - Part II, 1993

No carcinogenicity, no adverse effects.

Reference : Summary of Toxicology data, 'Etofenprox' California EPA, 11-04-2003.

Dogs (1 year study) :-

NOAEL 1000 ppm = 32 mg/kg b.w./day

Reference : JMPR-Part II,1993

Rats (2 year toxicity / carcinogenicity) :-
NOAEL 100 ppm = 3.7 mg/kg b.w./day
At only 4900 ppm only females showed increased incidence of thyroid adenoma.

Reference : JMPR - Part II, 1993

No dose response. Not a serious evidence of carcinogenicity.

Reference : 'Etofenprox' (Dossier according to directive 98/8/EC), Doc.IIC, Risk characterization for the use of the A.I. in the Biocidal Product. Competent Authority Austria.

Compared to NOAEL value, 4900 ppm is much higher value. This symptom / trend is not dose dependent and cannot be considered as a concrete evidence of carcinogenic trait of the molecule.

In normal use, a person is not at all expected to get exposed to such an extremely high concentration of Etofenprox by any mean. This stands for only academic interest.

It's potential to excrete through mother's milk

Pregnant / nursing rats were exposed, for a period, with Etofenprox at the level of 30 mg/kg b.w./day. Study revealed fatty tissue concentration in mammary glands which declined with a half life of 3.5 days. After cessation of exposure, the secretion in milk dropped considerably.

Ref. JMPR Part -II, 1993

This is only a lab study with a radio-labelled compound at very high concentration.

Metabolism studies with rat, revealed that 85 - 90% and 7 - 9% of administered Etofenprox was excreted through faeces and urine, respectively.

After 48 hours of exposure, 80% was excreted.
Retention in the body after 5 days was 3 - 4 % .

Ref. JMPR-Part II, 1993

If fat had high concentration, still it was very less and further the residue undergoes degradation. The scope for secretion through milk is very negligible.

Teratogenicity

Etofenprox is non-teratogenic.

NOAEL for fetotoxicity was 5000 mg/kg b.w./day and for maternal toxicity was 250 mg/kg b.w./day. Dose related maternal toxicity was observed in highest dose group only. No effects on mating performance, litter parameters, incidence of soft tissues or skeletal abnormalities were found in any groups of the tested rats.

Ref :- JMPR, Part- II,1993

Fish & Aquatic Toxicity

Fish

10% EC

***Poecilia reticulata* :**

LC_{50} (48 h) > 4.18 mg/l of water

LC_{50} (96 h) 2.12 mg/l of water

Technical

Cyprinus carpio LC_{50} (96 h) : 9.33 mg/l of water.

Daphnia magna

Technical

EC_{50} (48 h): 0.19 µg/l

10% EC

EC_{50} : 44.32 µg/l

Study with city water in greenhouse (23±5°C) showed 70 % and 93% decomposition after 1 and 3 weeks, respectively.

Photo-decomposition half-life of Etofenprox is 4 days.

Ref. JMPR Part - I, 1993

Under practical situation (field conditions) considering normal agricultural use, (as per recommendations , in paddy field), fish and aquatic organisms are not at risk.

States Where It Is Used, Quantities Sold

States	2004 Sales	2005 Sales	2006 Sales (Forecast)
Andhra Pradesh	30	45	55
Karnataka	8	12	15
Tamil Nadu	2	3	10
	40 KL	60 KL	80 KL

Conclusion

Etofenprox a.i : WHO class III (Table 5) ie. Product unlikely to present acute hazard in normal use.

Etofenprox formulation : U.S EPA Class IV

ADI= 0.03 mg/kg.b.w

MRL = Japan 0.5 mg/kg rice grain (unpolished)

Spain ----> 1.0 mg /kg rice

Ref. JMPR , Part- I , 1993,

Pesticide Manual, 1997

Health assesment of operators engaged in production of technical etofenprox for 1.5 - 5.5 years revealed no compound related effects.

Ref. JMPR , Part- I I, 1993,

Therefore,

1. Workplace exposure for men did not show adverse effect
2. Women are not expected to work in factory floor
3. Women are not seen to spray in the field to the best of our knowledge

Considering all these, only possible exposure to women is through diet.

The recommended practice (along with protective clothing) and waiting period will never allow the produce to contain more than MRL level of the molecule.

Thus rice which has MRL level of etofenprox, when consumed after storing, processing , washing, cooking will never give a men/women more than ADI level of the molecule.

The ADI is 1/100 th of the NOAEL carcinogenicity

Thus scope of carcinogenicity is Zero.

Considering MRL & ADI and metabolism in human body, the scope to excretion through mother's milk is nil.

The product is non teratogenic

Etofenprox is sold for application in paddy fields only.

It is not for use in aquatic body & paddy- fish culture .

Considering these and the photo-degradation in water, aquatic life is not at risk at all in practical situation & in normal agricultural use of this product.

Therefore it is very logical that this product must be allowed to be used in the domestic market

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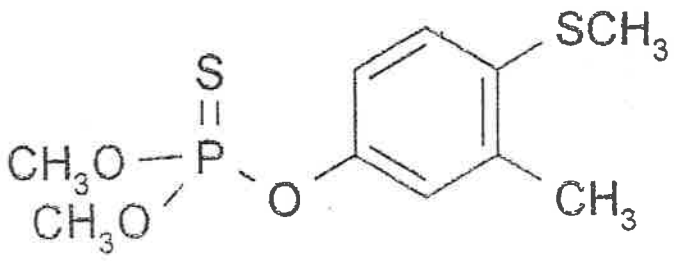
Fertilion - General Overview

By : Dr. Anil Kumar Makkapati
Head - Development
Bayer Environmental Science, India



Fenthion

An organophosphorus ester

In Crop Potection, Fenthion is mainly used as wide spectrum insecticide in rice, olives and fruits (Registered in more than 40 countries, including major markets such as Japan, Brazil and Australia)

In vector control it is used as mosquito larvicide and is evaluated and approved by WHO

Brand names:

Lebaycid (Crop)

Baycid (Crop)

Baytex (Vector Control)

Fenthion in India - General Overview

Fenthion is registered in 1974.

Fenthion Formulations are registered in 1975;

Fenthion 80 % EC (Lebaycid) for crop use

Discontinued since last five years for commercial reasons.

Fenthion 82.5 % EC and Fenthion 2% GR are sold in Public Health under brand name 'Baytex' for Mosquito Larval control.

Baytex 82.5 EC and 2% GR used in Public Health

More than 3 decades of extensive use in the country for mosquito larval control.

Esteemed customers – National Vector borne Diseases Control Programme (erstwhile NMEP), Army, Navy, State Health Directorates, Municipal Corporations of Mumbai, Chennai, Bangalore, Surat, etc.

Around 150 KL of Fenthion 82.5% EC and 100 MT of Fenthion 2% Granules are being sold per year.

Fenthion Salient Features :

- Only mosquito larvicide which is effective even at 0.1 ppm dose rate in polluted waters.
- Though approved, aerial and fogging applications are not being promoted by Bayer. Used only as surface spray as a mosquito larvicide.
- Sold only to professional users like NMEP, Army, Municipalities, Navy, Railways, etc.
- Effective post sales service by way of conducting training programmes on proper usage and safety.
- Product Stewardship – backed by Bayer.

Fenthion : Ban/ Restriction in Angola in 1990 (UN List 2002)

Reason : Ban for Health and Environmental reasons - The control action applies to Baytex 50 EC & Baytex 40 WP

Worldwide Fenthion products are registered and commercialized in more than 30 countries in Agriculture Sector and more than 20 countries in Public Health sector.

Baytex 50 EC & Baytex 40 WP were used as Indoor Residual Sprays for the adult Mosquito Control in Angola.

While Fenthion 82.5% EC & Fenthion 2% GR are mainly used in Public Health as outdoor application for mosquito larval control.

The restricted use of Fenthion in Angola for public health purpose (Indoors use) is based on WHO's blanket recommendation not to use Fenthion indoors.

Fenthion based products are currently allowed for use in Crop Protection (Out door application) in Angola.

Thus the restriction of use in Angola cannot be considered as a general ban of the product.

Fenthion : Concerns

The following concerns raised by the Pesticide Review Committee would be addressed by our experts :

- Reports on effect on neuromuscular function during exposure.
- Carcinogenicity - reported to be carcinogenic in male mice.
- Reported numbness and tingling in Nigerian workers, who did not use skin protection.
- Highly Toxic to Fish

Fenthion Formulations : Registrations and Use in India

PRODUCT	USE	REMARKS
Public Health		
Fenthion 82.5% EC (Baytex 1000 EC)	For the control of mosquito larvae	Approved by NVBDCP and WHO PES
Fenthion 2% GR (Baytex 2% GR)	For the control of mosquito larvae	Approved by NVBDCP and WHO PES
Crop Protection		
Fenthion 80% EC (Lebaycid)	For the control of pest in various crops	Discontinued since last five years due to commercial reasons.

Fenthion Dose Rates for Mosquito Larval Control

Depth of water	Quantity In ml	Water for dilution in litres	Surface to be treated in sq meters

Depth of water	Quantity In Kg	Surface to be treated in sq meters

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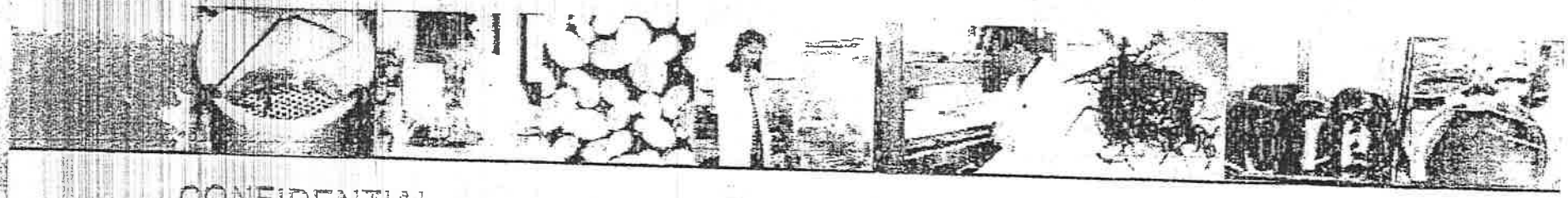
Fenthion - Concern

4) Fish Toxicity and Exposure

By : Dr. Raimund Grau
Eco – Toxicology Expert
Bayer CropScience, Germany



Fish Toxicity and Environmental Fate Data

- acute
  - Rainbow trout — a.i. — LC50 — 0.83 mg a.i./L
  - a.i. — NOLEC — 0.5 mg a.i./L
  - Golden orfe — a.i. — LC50 — 2.7 mg a.i./L
  - Bluegill sunfish — a.i. — LC50 — 1.7 mg a.i./L
- chronic
  - Rainbow trout — a.i. — TEC — 0.019 mg a.i./L

➢ Fenthion is intrinsically toxic to fish

- Half-life in water
  - water/sediment systems simulating pond and salt-marsh ecosystems **ca. 24 h**

➢ Fenthion is degraded rapidly in the aquatic environment

Fenthion Use Pattern and Products in India

○ Mosquito larvicide, vector control

Fenthion 82.5% EC (Baytex)

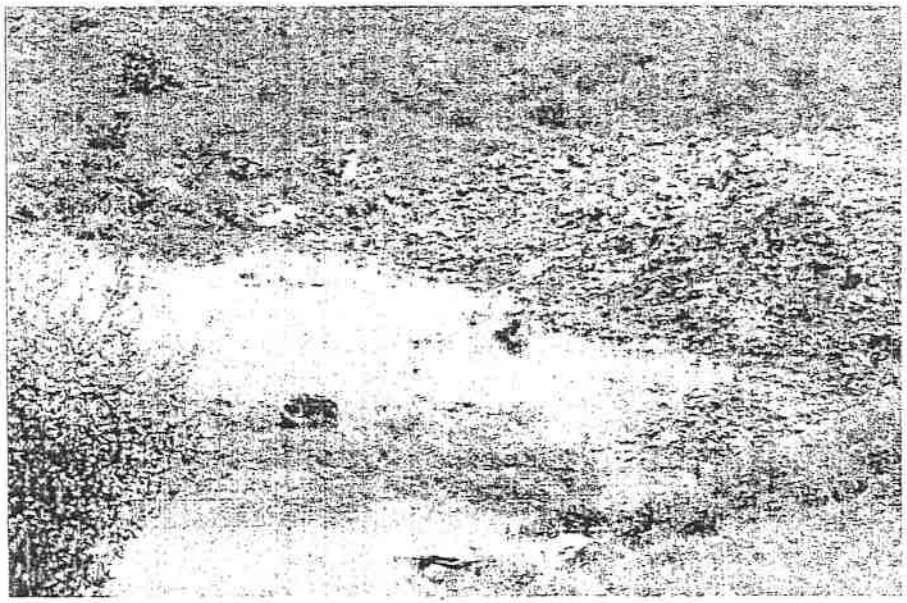
Depth of water	Quantity in mL/ha	Quantity in g a.i/ha	Conc. in water mg a.i/L
Up to 10 cm	115	94.9	0.095
Up to 50 cm	500	412.5	0.083

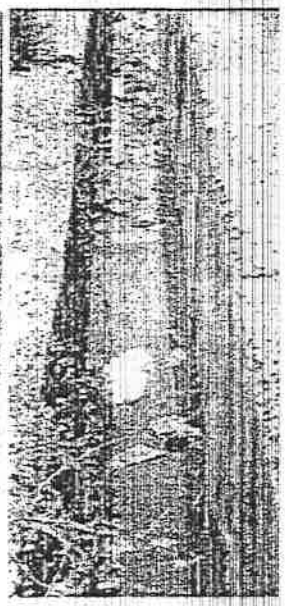
Fenthion 2% GR (Baytex)

Depth of water	Quantity in kg/ha	Quantity in g a.i/ha	Conc. in water mg a.i/L
Up to 10 cm	5	100	0.10
Up to 50 cm	25	500	0.10

Typical sites for Fenthion 82,5 EC use

The places where Fenthion 82.5% EC is used include gutters, drains, ...





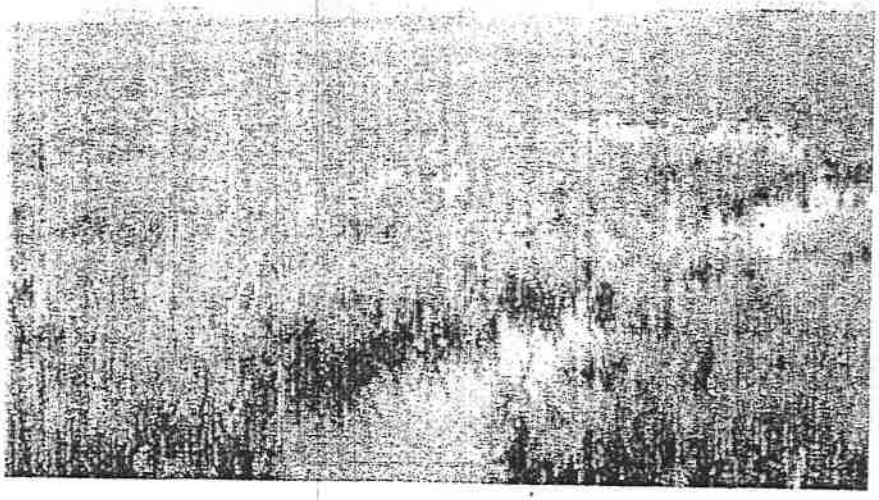
Typical sites for Fenthion 82.5 EC use

... cess pools, cess pits, septic tanks, etc.

- Typically highly polluted, non potable water bodies that do not support rearing of fish

Typical sites for Fenthion 2 GR use

The places where Fenthion 2% GR is used include marshy and grassy lands, where access for spraying EC is difficult or not feasible



- Temporary water bodies, no fish present

Conclusions

- **Fenthion 82.5% EC (Baytex)**
  - Treatment of highly polluted water bodies
- **Fenthion 2% GR (Baytex)**
  - Treatment of temporary water bodies

- Fish are not present in water bodies receiving treatment
- Fenthion is safe for fish when used as a mosquito larvicide according to the label

Thank you very much for your kind attention

Dhanyavad !

Bayer CropScience

Fenthion - Concerns

1) Reports on effect on neuromuscular function during exposure
2) Carcinogenicity – reported to be carcinogenic in male mice
3) Reported numbness and tingling in Nigerian workers, who did not use skin protection

By : Dr. (Ms.) Kerstin Henninger
Regulatory Toxicologist
Bayer CropScience, Germany

Fenthion : Recommendations

- National Vector borne Disease Control Program (NVBDCP)
- Evaluated by World Health Organisation's Pesticide Evaluation Scheme (WHOPES) for mosquito larva control

Table 4. WHO-recommended compounds and formulations for control of mosquito larvae

Insecticide	Chemical type	Dosage of ai (g/ha)	Formulation	WHO hazard classification of ai[a]
Fuel oil	–	*	Solution	–
B. thuringiensis israelensis	Biopesticide	*	Water-dispersible granule	–
Diflubenzuron	Insect growth regulator	25–100	Wettable powder	U
Methoprene	Insect growth regulator	20–40	Emulsifiable concentrate	U
Novaluron	Insect growth regulator	10–100	Emulsifiable concentrate	NA
Pyriproxyfen	Insect growth regulator	5–10	Granules	U
Chlorpyrifos	Organophosphate	11–25	Emulsifiable concentrate	II
Fenthion	Organophosphate	22–112	Emulsifiable concentrate, granules	II
Pirimiphos-methyl	Organophosphate	50–300	Emulsifiable concentrate	III
Temephos	Organophosphate	56–112	Emulsifiable concentrate, granules	U

- Fenthion was reviewed by Joint Meeting of Pesticides Scheme (JMPS) in 2004. Fenthion TC, EC & WP products were included in the programme for Development of FAO and WHO Specifications for Pesticides , taken for review in the year 2004.

Report on neuromuscular function during exposure

Arch Toxicol (1988) 62: 398–401

Archives of Toxicology
© Springer-Verlag 1988

A study of nerve conduction velocity, late responses and neuromuscular synapse functions in organophosphate workers in India

U. K. Misra[1], D. Nag[2], W. A. Khan[1], and P. K. Ray[3]

[1] Department of Neurology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, P.O. Box No. 25, Lucknow-226001, India
[2] Department of Neurology, K. G.'s Medical College, Lucknow-226003, India
[3] Industrial Toxicology Research Centre, P.O. Box No. 80, M. G. Marg, Lucknow-226001, U. P., India

- Misra et al. (1988) described changes in certain neuromuscular parameters in workers chronically exposed to Fenthion, which they interpreted as "neuromuscular dysfunction associated with organophosphate exposure".
- The affected workers did not show clinical signs of peripheral neuropathy or muscle weakness.
- Exposure: 5-6 h daily, 6 days per week, hand operated sprayer, no protective clothing, facemasks or gloves;

⇒ Besides Fenthion, they sprayed also copper acetoarsenite.

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Report on neuromuscular function during exposure

> Exposure per worker and month:

Fenthion : 1500 – 2000 L of a Fenthion suspension - prepared by diluting 100 mL of 82.6% Fenthion (w/w) with 100 L water ⟹ 2000 L contain 1.65 kg Fenthion

Copper acetoarsenite: 8- 9 kg a.i.

⟹ workers were exposed to a markedly higher amount of copper acetoarsenite than Fenthion.

> To ecological profile of copper acetoarsenite:

- Very toxic after ingestion and inhalation, LD_{50} in mammals: 2.5 – 33 mg/kg bw (Fenthion: 300-600 mg/kg in rat, 150 mg/kg in mouse and rabbit)
- Chronic effects after doses of 1-10 mg/kg, LDLO (Lethal Dose Low) man: 5 mg/kg p.o.
- Repeated or high exposure may lead to nerve damage (peripheral neuropathia) beginning with sensory symptoms in the lower extremities ("pins and needles") progressing to muscle weakness and subsequent loss of coordination in arms & legs.

Report on neuromuscular function during exposure

- Fenthion:

⟹ There was no evidence for a neuropathic effect in a comprehensive set of toxicity studies in mice, rats, rabbits, and dogs.

⟹ Special studies were conducted in hens as the most suitable animal model for organo-phosphate induced delayed polyneuropathy (OPIDP) in man. Neither high doses close to the LD_{50} nor repeated dosing for up to 3 months resulted in clinical or histopathological evidence for delayed neurotoxicity. Likewise, no inhibition of NTE (neuropathy target esterase) as a prerequisite for such a delayed effect was observed.

⟹ Although Fenthion is used now for more than 40 years as a pesticide or insecticide for veterinary use with partially very high exposure, there was never a recorded case of OPIDP.

We conclude that the observed effects on neuromuscular function were exclusively attributable to the exposure to copper acetoarsenite.

Carcinogenicity - reported to be carcinogenic in male mice

- Discussions on a possible sarcoma-inducing potential of Fenthion in male B6C3F1 mice came up in 1979 after publication of an oncogenicity study, which was conducted at the US National Cancer Institute (NCI).

- Study design: 50 male + 50 female mice/group received 0-10-20 ppm Fenthion in the diet for up to 103 weeks; controls: 25 males & 25 fsmales;

- Results:

  - No effects on body weight development & mortality

  - Clinical symptoms in treated animals: hair loss piloerection, accelerated breathing, distended abdomen, pale mucous membranes (starting 5 months months after study initiation, increasing intensity after 12 months)

  - No neoplastic lesions in females;
    In males: elevated incidence of sarcomas in dermal and subdermal locations;

Carcinogenicity - reported to be carcinogenic in male mice

Skin and subcutaneous tissues No. of male animals	Control (25)	10 ppm (49)	20 ppm (48)
Sarcoma, not otherwise specified	0	0	2
Fibrosarcoma	0	4	4
Rhabdomyosarcoma	0	3	2
Total	0	7	8

- Conclusion of the authors: „A connection between the treatment and the occurance of sarcomas in male mice is possible."

- FAO (1981): assessed Fenthion as non-carcinogenic, but did not exclude a possible sarcoma inducing potential in male B6C3F1 mice (based exclusively on the NCI study in question).

Carcinogenicity - reported to be carcinogenic in male mice

- Discussions on the study: "... fighting was observed among the male mice, particularly among dosed animals, and it resulted in severe bite wounds and death."

  ⟹ Male mice were housed in groups of 2-3 animals!

  ⟹ The integumentary system of rodents is sensitive to tumor induction, to some degree also to unspecific tumor induction.

  ⟹ Traumatic injuries may be considered as the probable cause for these integumental neoplasias.

- Subsequent study on B6C3F1 mice: 0-0.1-1-5-25 ppm Fenthion in the diet for 24 mo., 60/60 animals per dose level + 20/20 per dose level for sacrifice after 51 weeks (Leser & Suberg, 1990, 1992):

  ⟹ No indication for neoplastic lesion – animals were housed in single cages!

Carcinogenicity - reported to be carcinogenic in male mice

- There was no indication for an enhanced incidence for neoplastic lesions in three 2-year rat studies (NCI, 1979; Bomhard & Löser, 1977; Christenson, 1990), three 1-year dog studies (Doull et al., 1963, Hoffmann and Welscher, 1975; Christenson, 1990) and one 23-month study in Rhesus monkeys (Rosenblum, 1980).

- Enhanced tumor incidences in man have never been observed over more than 40 years of use, even in applicators who were exposed to Fenthion for many years.

- EU Monograph: "No evidence of Fenthion carcinogenic potential was found in long-term studies on mice and rats. A possible sarcoma inducing effect in male B6C3F1 mice was discussed. Traumatic injuries resulting from conflicts among males may be considered a probable cause of this finding. These findings were not verified in a more recent study with the same strain of mice."

There is no evidence that Fenthion is carcinogenic.

Reported numbness and tingling in Nigerian workers

Reported numbness and tingling in Nigerian workers who did not use skin protection:

"Numbness" and "tingling" may be signs of paresthesia, which has to our knowledge never been observed in connection with the use of Fenthion.

Furthermore, these signs could hint towards a nerve damage in terms of OPIDP, which is also not known for Fenthion

- A comprehensive literature search on a wide set of databases retrieved only two publications, which, however, do not cover the request cited above exactly.

Bull. Org. mond. Santé / *Bull. Wld Hlth Org.* 1963, 29, 213-218

Observations on Human Exposure to the Organophosphorus Insecticide Fenthion in Nigeria*

A. TAYLOR[1]

The search for substitutes for chlorinated hydrocarbon insecticides has led to the trial of organophosphorus compounds. Fenthion is promising as a residual spray in malaria eradication, but information on its human toxicology is scanty. In the work reported in this paper the inhabitants of a Nigerian village have been studied during a trial of fenthion. Moderate depressions of plasma cholinesterase were observed for five weeks after spraying, though there was no effect on red blood cell cholinesterase. A search was also made for other possible effects, including measurements of peak expiratory flow rate. No serious toxic effects were found.

Reported numbness and tingling in Nigerian workers

- Taylor (1963): studied the inhabitants of a Nigerian village during a trial of Fenthion used as residual spray in malaria eradication.

- One village: sprayed with 40% suspension of Fenthion at a rate of 1.5 g/m^2, another village: control;

- Fenthion sprayed village:

  ⇒ As expected there was a significant reduction in plasma ChE activity in almost all inhabitants (39.9, 16.5, 16.3 and 23.8% in age groups < 7, 7-14, 15-30 and > 30 years)

  ⇒ No change of RBC ChE activity

  ⇒ No signs of organophosphate poisoning

Reported numbness and tingling in Nigerian workers

Neurologic Findings among Workers Exposed to Fenthion in a Veterinary Hospital — Georgia

In July 1983, a neurologist in Georgia saw a patient who complained of shooting pains, muscle weakness, and numbness. The patient worked at a veterinary hospital (hospital A). The National Institute for Occupational Safety and Health (NIOSH) was asked to determine whether these symptoms were caused by occupational exposures (1). Investigators inter-

- Metcalf (1985): A worker at a veterinary hospital reported numbness and tingling of the hands and feet at night. Three other workers complained about shooting pains, muscle weakness, back pain and numbness, a fourth suffered occasionally a shooting pain in the back.
- The National Institute for Occupational Safety and Health (NIOSH) investigated the case.
  - ⟹ 22 different preparations of insecticides containing 12 types of pesticides were used or dispensed in the hospital.
  - ⟹ Most of the workers applied these preparations without using protective gloves.
  - ⟹ The authors suspected a 20% solution of Fenthion used for routine flea control in dogs to be responsible for the symptoms

Reported numbness and tingling in Nigerian workers

- The symptoms reported are on their own not symptomatic of Fenthion poisoning.
- The affected workers showed no decreased plasma ChE levels ⟹ no indication for an exposure to Fenthion;
- In other studies, there was never a hint for a neuropathic effect elicited by Fenthion,
  - ⟹ neither in toxicity studies in mice, rats, rabbits or dogs,
  - ⟹ nor in special studies on Organophosphate Induced Delayed Polyneuropathy (OPIDP) in hens, the most suitable animal model for this disease in man.
- Although Fenthion has now been used for more than 4 decades as a pesticide or as an insecticide for veterinary use there was no evidence for Fenthion induced nerve damage nor a health hazard from exposure to Fenthion.

Therefore, we conclude that the numbness and tingling reported in the study is not attributable to Fenthion.

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Thank you very much for your kind attention

Dhanyavad !!

Fenthion - Concerns

BACK-UP SLIDES

Special studies on OPIDP potential of Fenthion in hens

- Organophosphate induced delayed polyneuropathy (OPIDP): beginning 2-3 weeks after organophosphate poisoning:
  - Symptoms in man: initially sensory experiences in the lower extremities, numbness and tingling in the feet and perhaps in the hands, sharp, cramp-like pain in the calves, increasing weakness of the lower limbs;
  - Symptoms in hens (animal model most similar to man): gait abnormalities, ataxia;
  - Etiology: axonal degeneration and demyelinisation.

- Acute studies on OPIDP after oral and dermal administration (Flucke 1986):
  - White Leghorn hens received 1 x 40 mg/kg Fenthion p.o. or 1 x 200 mg/kg dermally under antidote protection, the dose was repeated after 3 weeks
  - Positive control: TOCP (Triorthocresylphosphate)
  - 200 mg/kg dermally: close to LD_{50} (222 mg/kg bw), 8/15 animals died, larger volumes not possible due to spilling;
  - Fenthion: No clinical signs of OPIDP, no histopathological changes like nerve lesions, axonal degeneration, demyelination or gliosis (these were seen after TOCP).

⇒ No evidence for OPIDP in acute studies with Fenthion in hens.

Special studies on OPIDP potential of Fenthion in hens

- Studies on NTE inhibition (Flucke & Eben, 1988):

The neurotoxic target esterase (NTE) is an enzyme involved in the etiology of OPIDP. It is found in the nervous tissue; an inhibition of 70-80% observed 1-2 days after poisoning seems to be a prerequisite for OPIDP.

- dose regimen: 40 mg/kg bw Fenthion p.o., 3 hens/time point were sacrificed 24 h, 48 h and 7 days after treatment ⟹ no inhibition of NTE (TOCP: clear inhibition)

- Dermal application (Flucke & Eben, 1988): 1 x 200 mg/kg and 2 x 200 mg/kg on two consecutive days (high mortality despite antidots protection) ⟹ no inhibition of NTE (TOCP: Inhibition > 90%)

- Subacute study (Kimmerle, 1988):

- 0, 10, 25, 50, 100 ppm Fenthion in the diet for 4 weeks + 4 weeks recovery period
- Cholinergic signs and ChE inhibition at doses >= 50 ppm (reversible)

⟹ No gait alterations, no histopathological changes.

Special studies on OPIDP potential of Fenthion in hens

➢ Subchronic study (Hayes & Ramm, 1988):

- 0, 1, 2, 4 mg/kg bw Fenthion in corn oil (gavage administration) for 3 months
- Clinical signs were observed after 2 and 4 mg/kg, 4 mg/kg: increased mortality, decreased food consumption and body weights, together with poor general condition leading to secondary walking problems; feather loss;
- Turf-test (forced running test): no difference between Fenthion treated animals and controls
- Histopathological investigations: no evidence for delayed neurotoxicity
- Positive control (TOCP, 10-60 mg/kg): ataxia, axonal degeneration and demyelination

⟹ No evidence for OPIDP after administration of Fenthion for 3 months

➢ The studies described above are only a selection of several similar designed studies on OPIDP in hens. However, none of them revealed a neuropathic effect of Fenthion.

Specially designed hen studies with Fenthion gave no evidence for OPIDP.

Annex-III-H

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Directorate of Plant Protection ,
Quarantine & Storage, NH IV,
Faridabad, Haryana

Our ref: CS4/skk

August 31, 2006

Metoxuron - Registration with our erstwhile company Sandoz India Limited - Withdrawl of Registration because of commercial reasons.

Dear Madam,

We would like to withdraw our registration of Metoxuron as we have no commercial interest in this product now as there are better herbicides for wheat available in the country. We accordingly request you to treat our registration certificate for Metaxouron as withdrawn because of no commercial interests in India in the product please.

Thanking you ,

Yours faithfully,
Syngenta India Limited

S.K. Khosla

Review of Pesticides in India

Trifluralin

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Human Health Assessment Leader
Dow AgroSciences Europe

Items to be presented

- Mutagenicity
- Carcinogenicity
- Persistence in soil
- Questions and answers

Mutagenicity – *in vitro* data

Table 1 - Summary of selected in vitro genotoxicity studies

Test	Test Object	Concentration	Result	Report Ref.
Point mutation assays				
Bacterial reverse mutation	*Salmonella typhimurium* (TA98, 100, 1535, 1537, 1538)	25-800 µg/plate, - S9 50-800 µg/plate, + S9	Negative	Probst, G.S. (1983) E01
Bacterial reverse mutation	*Salmonella typhimurium* (TA98, 100, 1535, 1537, 1538)	10-10,000 µg/plate, ± S9	Negative	Loveday, K.S. (1987) E10
Mammalian cell forward mutation	Mouse lymphoma L5178Y cells, thymidine kinase (TK) locus	0.5-20 µg/mL ± S9	Negative	Oberly, T.J. (1983) E02
Mammalian cell forward mutation	Chinese hamster ovary cells, HGPRT locus	50-700 µg/ml - S9 50-800 µg/ml + S9	Negative	Young, R.R. (1988) E11
Unscheduled DNA synthesis (UDS)				
In vitro mammalian UDS	Adult rat hepatocytes	0.214.48 µg/ml	Negative	Cifone, M.A. (1988) E12
Mammalian cytogenetic assay				
In vitro chromosome aberration	Chinese hamster ovary cells	5, 15 and 30 µg/ml - S9 25, 50 and 100 µg/ml + S9	Negative	Adams, E.E., *et al.* (1989) E05

Mutagenicity – *in vivo* data

Table 2 - Summary of in vivo genotoxicity studies in somatic and germ cells

Test	Test Object	Dose	Result	Report Ref.
Somatic cells				
Sister chromatid exchange	Chinese hamster bone marrow cells	200, 300, 400 and 500 mkd, single gavage	Negative	Neal, S.B. (1988) E03
Chromosome aberration	Mouse bone marrow cells	10, 62.5, 208 and 625 mkd, 5 days, gavage	Negative	Ivett, J.L. (1988) E13
Micronucleus	Mouse bone marrow cells	500, 1000 and 2000 mkd, single gavage	Negative, including kinetochore staining	Spencer, P.J. *et al.*, 2000, E18
Germ cells				
Dominant lethal	Rat *in utero* embryo-fetal survival	100 and 1000 mkd, 5 days, gavage	Negative	Hoyt, J.A. (1988) E04
Chromosome aberration	Mouse spermatogonial cells	62.5, 208 and 625 mkd, 5 days, gavage	Negative	Ivett, J.L. (1988) E13

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Mutagenicity - Summary

In vitro tests:

- no genotoxic potential
  - Ames, mouse lymphoma, HGPRT, chromosome aberration (CHO), UDS (rat liver)

In vivo tests:

- no genotoxic potential in somatic or germ cells

The number of test is much larger than requirements of Europe, USA and India.

All were OECD test guideline and GLP-compliant.

- Another complete package of GLP studies also negative (Hoechst; Ebert *et al.*, 1992)

Both EU (2005) and USA reviews (1997) concluded that trifluralin is not genotoxic.

Some positive findings published in open literature - new *in vivo* study (mouse MNT, including kinetochore staining to prove lack of aneuploidy) completed as part of the European review.

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Carcinogenicity – main studies

Table 3 - Trifluralin - Summary of long-term toxicity and carcinogenicity studies

Study	Species/ strain	Dosages mg/kg/day	NOAEL mg/kg/day	LOAEL mg/kg/day	Target organs/ principal effects	Report Ref.
2-year combined toxicity and carcinogenicity dietary	Rat Fischer 344	30, 128 and 272 (males)	2.6 mg/kg bw/day#	30 mg/kg bw/day	Kidney, urinary bladder and thyroid tumours	Emmerson, J.L. (1990) 187
		37, 154 and 336 (females)	2.6 mg/kg bw/day#	37 mg/kg bw/day	Urinary bladder tumours	
2-year combined toxicity and carcinogenicity dietary	Mouse B6C3F1	40, 180 and 420	40 mg/kg bw/day	180 mg/kg bw/day	No tumours ↓ bwt. anaemia, ↑ liver wt. CPCN	Emmerson, J.L. (1990) 191

NOEL of 2.6 mg/kg bw/day based on 90-day mechanistic study in male Fischer 344 rats (Usher *et al.*, 1985; D01)

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Carcinogenicity – male rat tumours

Table 4a: Incidence of selected neoplastic changes in male rats following 2 years' exposure to trifluralin

Trifluralin in diet ppm (mg/kg bw/day)	0	843 (30)	3250 (128)	6250 (272)
Number examined (group size of 60)	60	58	60	60
Urinary bladder				
transitional cell papilloma		1	1	1
Kidney				
transitional cell carcinoma		2	2	5
renal cell carcinoma			1	1
Thyroid				
follicular adenoma	1		3	10
follicular papillary adenoma	2		2	
follicular carcinoma	2	1	3	1
follicular cystadenoma				2
papillary cystadenoma		1		
Testes				
interstitial cell tumor	49	52	55	57

The mid- and high dose levels greatly exceeded a MTD

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Carcinogenicity – female rat tumours

Table 4b: Incidence of selected neoplastic changes in female rats following 2 years' exposure to trifluralin

Trifluralin in diet, ppm (mg/kg bw/day)	0	843 (37)	3250 (154)	6250 (336)
Number examined (group size of 60)	60	60	60	60
Urinary bladder				
transitional cell papilloma			1	3
transitional cell carcinoma				2
Kidney				
transitional cell carcinoma				
renal cell carcinoma				
Thyroid				
follicular adenoma		1		1
follicular papillary adenoma				1
follicular carcinoma			1	1
follicular cystadenoma				
papillary cystadenoma		1		

The mid- and high dose levels greatly exceeded a MTD

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Carcinogenicity – MTD

Table 5: Reductions in body weight gain (%) in comparison with concurrent controls at 24-months

Trifluralin in diet, ppm (mg/kg bw/day)	Reduction in group mean body weight gain (%) in comparison with concurrent controls after 2-years' treatment	
	Males	Females
810 (30)	5.6	8.5
3250 (128)	19	32
6250 (272)	38	66

Maximum tolerated dose (MTD)

The OECD carcinogenicity test guideline requires that '*the highest dose level should elicit signs of minimal toxicity, such as a slight depression of bodyweight gain (less than 10%) without substantially altering the normal lifespan due to effects other than tumours.*'

In the trifluralin study, large reductions in body weight gain occurred over the 2-year treatment period at the mid- and high dose levels, especially in females (Table 5). Based on this criterion alone, even the mid-dose level exceeded an MTD.

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Carcinogenicity – supplementary rat data

There are 3 additional studies of varying quality

1) Cox Sprague-Dawley study by Worth *et al.* 1966
   Tested 0, 200, 1000 and 2000 ppm (ca., 0, 10, 50, 100 mkd) for 2-years in groups of 25 males and 25 females. Neither test guideline nor GLP-compliant.

2) Osborne-Mendel study by Thomas *et al.*, 1978
   Tested 0, 4125 and 8000 ppm (TWA) for 78-weeks before termination after 2-years in groups of 50 males and 50 females. Neither test guideline nor GLP-compliant.

3) Wistar study by Hoechst 1986 (published by Ebert *et al.*, 1992).
   Tested 0, 200, 800 and 3200 ppm (ca. 0, 10, 40 and 160 mkd) for 122-weeks in groups of 60 males and 60 females. Both test guideline and GLP-compliant.
   - Kidneys – tumours in single animals only, including controls
   - U. bladder - tumours in single animals only
   - Thyroid – tumours in all groups, including controls, show no treatment effect
   - Testes – Leydig cell tumours, *highest* incidence in *control* males

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Carcinogenicity - Summary

Rats	Effects limited to F344 strain
Kidney	- No effect in females - tumours in males from 30 mkd (3.3%)
Urinary bladder	- tumours in males from 30 mkd (1.7%) & females from 154 mkd (1.7%)
Thyroid	- No effect in females - follicular cell tumours in males from 128 mkd (13%)
Testes	- slightly higher incidence in treated males but not significant

Mice

No effect in either sex at any dose - up to 420 mkd.

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Carcinogenicity – Relevance?

Kidney and Urinary bladder

- Associated with toxicity and calculi – NOEL is 2.6 mkd

Thyroid

- Known to be irrelevant to humans – NOEL is 30 mkd:
  Produced by enhanced liver metabolism, clearance of serum T4 and chronic TSH-related thyroid follicular cell stimulation. Rats lack high-affinity plasma protein for binding T4, humans have TBG. T4 readily removed from rat blood – T1/2 ~24h, 5-9 days in humans. Therefore, rats but not humans or other species have thyroid 'work hypertrophy' which can lead to tumours.

Testes

- Slightly higher incidence in treated males but not significant and very high natural incidence in F344 rats – of little or no relevance to humans

Trifluralin is a carcinogen in F344 rats and classified as such in EU and USA.

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Carcinogenicity – Human data

Manufacturing

- Trifluralin has been made on a commercial scale for over 40 years

- Medical surveillance data for workers manufacturing trifluralin and its formulations has not indicated any health issues to date.

Epidemiology

- Published data are available and show no correlation between trifluralin use and a range of cancers in adults and children.

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Field workers - risk summary

Product	Crop	Dose Rate kg a.s.a.w.ha	Safe Dose for Workers mg/kg bw/day	Dermal absorption %		Method of Application	% of Safe Dose for Workers	
				Product	Spray		No PPE	Gloves for mixing
Trifluralin ~45% EC	Cotton	1.2	0.028*	1	10	Tractor-mounted boom (open cab)	94	10

* This is >1000 times lower than the lowest tumourigenic dose in male rats

Conclusion: a worst-case application scenario shows that trifluralin products can be used safely.

Gloves improve safety, including to acute hazards of the product - skin sensitisation.

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Trifluralin – Persistence in soil

Laboratory Soil Degradation
- Degrades slowly in aerobic conditions in lab:
  - $DT_{50(lab)}$ range is 81 - 356 days at 22°C (mean 181 days)

Field Dissipation
- Studies in Europe and USA show slow field dissipation:
  - $DT_{50(field)}$ values ranged from 35 - 375 days (mean 164 days)
  - $DT_{90(field)}$ values ranged from 116 - 1246 days (mean 544 days)
- Lowest values in warmer climates, in USA

Field Accumulation
- 'Worst-case' studied in UK (colder conditions)
- Single treatment a year for 5 years
- Levels determined pre- and post-application in 0–10 and 0–30 cm soil layers

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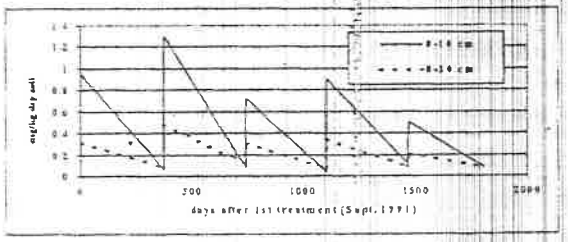
Trifluralin – Persistence in soil



Conclusion: Trifluralin did not accumulate.

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Trifluralin – Global Registrations

- Trifluralin is registered around the world:

- EU: UK, Germany, France, Italy, Spain, Austria ...
- Americas: USA, Canada, Argentina, Venezuela ...
- Asia/Pacific: Japan, Australia ...
- Eufrasia/Africa

- Key markets: Soybeans, Cotton, and Oilseeds
  - Over 40 minor crops: vegetables, fruits, beans, nuts, cotton ...

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Trifluralin – Overall summary and conclusions

- Mutagenicity
  Not an *in vivo* mutagen – opinion shared by regulators, including EU and USA.
- Carcinogenicity
  Is a carcinogen in F344 rats but not other strains or in mice.
  Effects probably not relevant to humans but hazard *is* classified in lowest category in EU and USA. Risk officially acceptable in these and other regions.
- Persistence in soil
  Half-lives shortest in warmer climates. Does not accumulate, even in colder locations (UK).
- Trifluralin has been used safely for 40 years and is still registered across the world.

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Trifluralin – Questions and Answers

Thank you for the opportunity to present our data and opinion and to answer your questions.

Annex - III - J

BIOSTADT

REVIEW OF VARIOUS PESTICIDES WHICH ARE BANNED IN OTHER COUNTRIES BUT ARE BEING USED IN INDIA – Regarding

Thiophanate methyl

BIOSTADT INDIA LIMITED
602 A, Poonam Chambers
Dr. Annie Besant Road
Worli 400 018
MUMBAI (INDIA)

Thiophanate methyl

BIOSTADT

INTRODUCTION

Registration of Technical for Import Only (Min. 94% purity)

Registration of Formulation Thiophanate methyl 70% WP

BIS Specifications Technical : IS 14551:1998

BIS Specifications WP Formulation: IS 14552:1998

Triangle : CAUTION (**GREEN**)

Approved Label :

Papaya	Powdery Mildew
Apple	Scab
Wheat	Brown Rust
	Leaf Blight
Tomato	Ring Rot
Bottle Gourd	Anthracnose
Cucurbits	Powdery Mildew
Pigeon Pea	Fusarium Wilt

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Thiophanate methyl

Country where pesticide: is banned	Denmark
Reasons for banned:	Unacceptable persistent in Soil and Toxic to Earthworm
Remark:	No uses allowed

Country where pesticide: is restricted	Sweden
Reasons for restriction:	Due to chemical relationship with benomyl and carbendazim

Remark:
Severly restricted for use as a pesticide. It was prohibited for the use in home gardens due to the chemical relationship with benomyl and carbendazim. Formulations containing thiophanate-methyl were reassigned to Class 1-May only be used professionally by someone holding a special permit. Uses allowed only against fangi of winter cereals and ornamentals (one treatment only per crop with thiophanate-methyl or carbendazim)

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Thiophanate methyl

Country where pesticide is banned: Denmark

Reasons for banned: Unacceptable persistent in Soil and Toxic to Earthworm

Remark: No uses allowed

- Registration Status: Not yet registered in Denmark
- Persistence in Soil and: Fully evaluated during reevaluation
  Impact on earthworm process in EU
- Remark:

Thiophanate methyl is allowed to reach soil surface upto 0.16 kg ai/ha based on a field study to evaluate earthworm population. This means application of 0.53 kg ai/ha to cereals (assuming interception 70 % at growth stage 71), 0.88 kg ai/ha to pome fruits (assuming interception 82% at growth stage 60-87) and 1.0 kg ai/ha to peas (assuming interception 85% at growth stages 71-79), considering interception rates of applied crops. **Thus it was concluded that there would be no adverse impact on earthworm provided that thiophanate-methyl is applied to each with the application rate.**

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....cont.

Denmark

"Acute Toxicity of Thiophanate methyl to the Earthworm *Eisenia foetida*" from NIPPON SODA, Japan

Result:

Thiophanate methyl is of low toxicity to earthworms at concentrations of 0.4 to 13.2 ppm ai in soil, equivalent to application rates of 0.25 to 8.00 kg ai/ha in this study. Since the normal range of application rates is 0.25 to 1.00 kg ai/ha, **the maximum dose level in this study is equivalent to between eight and thirty-two times normal rate.** The Test compound therefore appears to be safe when used as per the recommendation.

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Thiophanate methyl

Country where pesticide: is restricted	Sweden
Reasons for restriction:	Due to chemical relationship with benomyl and carbendazim
Remark:	Use restriction

Thiophanate-methyl is still classified in qualification class 1 because the Annex I inclusion does not automatically change this classification. However practically this is not an issue in Sweden since most of the growers have the special permits. Therefore no action is planned by the manufacturer.

Presently, Thiophanate methyl is registered for the winter cereals, apples, ornamentals and lawns in Sweden.

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....cont.

Sweden

Thiophanate-methyl was first time successfully included in the Annex I of Derivative 91/414/EEC which is a list of active substance of plant protection products qualified to be put on the EU market (Commission Directive 2005/52/EC of 16 September, 2005; **entered into force on 1 March, 2006).**

The end point list of thiophanate-methyl containing EU critical GAP is shown in European Commission, Health and Consumer Protection Directorate-General, 5030/IV/98 final.

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....cont.

Sweden

Carbendazim

It is still under discussion in the EU commission to decide whether carbendazim can be included into Annex I or not. According to an article of AGROW No.493 April 7th 2006, page 7, "EU commission has not suggested a restricted Annex I listing. This would be limited to only those uses that were evaluated at EU level. However, even if carbendazim is decided not to be included in Annex I, thiophanate-methyl would still remain on the EU market because thiophanate-methyl was authorised in EU voting in September, 2005, though carbendazim and thiophanate-methyl had been reevaluated simultaneously.

Thank You