ANNEX B

ENDOSULFAN

ADDENDUM B-6: TOXICOLOGY AND METABOLISM

For these reasons, and as mentioned in the table legends, we consider more appropriate to calculate the total absorbed dose as the addition of the amount present in epidermis + receptor fluid + tape strips (if available), as presented in the last row of tables B.6.12a.6-1, B.6.12a.6-2 and B.6.12a.6-3.

An additional interesting point for discussion is the fact that following application of the high and mid doses, a large proportion of the dose (mean of 26.8%) was associated with the donor chambers of the human and pig experiments, in contrast with that found with the rat experiments. It is indicated in the report that the reason might be that the residual dose on the surface of human and pig epidermis was still in liquid form, an effect which might have led to flow of a part of the dose to the edges of the chamber across the surface of the less densely haired human and pig epidermis. This had no effect on the actual dose levels to which epidermis was exposed, because the test substance was in liquid form, and therefore available for absorption. It is suggested that, under normal exposure conditions, this proportion of the dose would be removed as part of the skin wash. This effect was not apparent in the low dose formulation, because it had a higher proportion of water. The report mentions that rat epidermis was unaffected as the hairs remaining on the epidermis helped to contain the liquid dose. However, this might be arguable, since skin was shaved previously to sample collection.

Summarizing, the results obtained in this study demonstrate that the rate of penetration of endosulfan, as the commercially available 350g/l EC formulation or its aqueous dilutions (1/2.06 and 1/333 v/v), through human epidermis *in vitro* is much lower than through pig and rat epidermis. The following amounts of Endosulfan are considere available for absorption after 8 and 24 hours exposure:

	8 hours			**24 hours**		
Species	**Human**	**Pig**	**Rat**	**Human**	**Pig**	**Rat**
350 g/l conc. form. (3.58 mg/cm^2)	0.82	1.30	28.37	0.96	2.06	24.60
1/2.06 v/v aq. dil. (1.71 mg/cm^2)	0.37	7.20	21.48	0.69	5.48	33.11
1/333 v/v aq. dil. (0.01 mg/cm^2)	3.69	28.73	73.70	2.69	44.81	81.70

Data requirement 4.6: Main data submitter to recalculate exposure scenarios

Background

In a previous document (C010955) the notifier had proposed the values described below for the calculations of the operator exposure level:

- A NOAEL to define the systemic AOEL based on subchronic oral rat study
- Skin penetration factor for concentrate of 0.5% and for diluted of 1.5%, based on *in vivo* rat and in *vitro* human/rat/pig (C021864) studies.
- Additional data to demonstrate that there was not need to correct for bioavailability when calculating the systemic AOEL.

The RMS, since the submission:

- Considered that the AOEL should be based on the NOAEL of 0.6 mg/kg bw from the 1-year dog study.
- Correction factor of 70% should be applied for systemic absorption, based on toxicokinetics studies done in rat
- Taking into account all data, an AOEL of 0.0042 mg/kg/day could be established
- Skin penetration factors, based also on *in vivo* rat and on *in vitro* study that compared dermal absorption between human/rat/pig (C021864), were determined to be:
    - For concentrate 0.6%
    - For diluted 2.3%

Discussion of the different opinion between the notifier and the RMS about C021864 study is included in the open point 4.5.

The re-evaluation of the operator exposure submitted by the notifier had been done in this addendum including three points:

- summary of relevant use scenarios for exposure calculations
- summary of the re-evaluation submitted by the notifier
- new re-calculation of the acceptable exposure scenarios for operator, taking into account dermal penetration factors proposed by the RMS.

Summary

Safety uses for operator using PPE are expected in three scenarios:

- Tractor mounted boom sprayer in field crops
- Tractor mounted airblast sprayer in high crops
- Hand held sprayer Greenhouse (high crops)

Hand-held spray lance in citrus is not considered acceptable when BBA-model was applied. The notifier included an exposure study with acceptable levels of exposure for operator, taking into account the next PPE: gloves, coverall and mask during mixing and loading; gloves, coverall and hood+visor during application. In the RMS opinion, this last scenario is considered acceptable, as exposure study was well characterized

Individual study evaluation

B.6.14 Exposure data

Re-evaluation of the operator exposure and risk assessment for Thiodan 35 EC with a new data on skin penetration. [redacted] (2002) C022980

Performing laboratory: Aventis CropScience.

Date of the report: 22 May 2002

1-. Summary of relevant use scenarios for exposure calculations

Table 6.14-1: Use scenarios

Use scenarios		Application technique	Crop	Max. rate (kga.s./ha)	Expected work rate (ha/day)
1	Field crops	Tractor mounted boom sprayer	Cotton Sugar beet Potato	0.84 0.63 0.53	20
2	High crops	Tractor mounted airblast sprayer	Pome fruit Stone fruit	1.05 0.80	8
3	High crops	Hand held sprayer	Citrus Vines Tomato Cucurbits	1.05 1.05 0.53 0.53	1
4	Greenhouse (high crops)	Hand held sprayer	Tomato	0.80	1

Representative crops with the highest dose rates were taking for ensuring exposure evaluation that will cover the other crop uses in each use scenario:

- cotton for tractor mounted boom applications in field crops
- pome fruit for tractor mounted airblast applications in high crops
- citrus for hand held applications in high crops
- tomato for hand held applications in greenhouses

As Endosulfan is classified T+, the following specific instructions for operator protection have therefore been established:

- Wear protective gloves when handling the undiluted product
- Wear protective garment and sturdy footwear (e.g. rubber boots) when handling the undiluted product
- Wear rubber apron when handling the undiluted product
- Wear tight fitting goggles when handling the undiluted product
- Wear particle filtering half-mask FF2-SL or half-mask with particle filter P2 when handling the undiluted product.

2-. Summary of the re-evaluation submitted by the notifier

Evaluation of the operator exposure was carried out with the generic data base of the BBA-model (that better reflects the agricultural use conditions in shouthern Europe) and in addition with recently performed modern operator exposure studies in the relevant use scenarios. Results are described in tables 6.14-2 and 6.14-3.

Table 6.14-2: Systemic exposures obtained with BBA-model (with and without PPE)

Exposure scenarios					
Appl. technique	**Crop**	**Dose rate (kg a.s./ha)**	**Work rate (ha/day)**	**BBA model**	
				Without PPE	With PPE
Tractor boom	Cotton	0.84	20	0.0106	0.000793
Tractor airblast	Pome fruit	1.05	8	0.02437	0.00111
Hand held orchand	Citrus	1.05	1	0.013779	0.004861
Hand held greenhouse	Tomato	0.80	1	0.0105	0.00370

Table 6.14-3: Systemic exposures obtained with modern operator exposure studies (with PPE)

Modern operator exposure studies								
Appl. technique	**PPE used**	**Crop**	**Dose rate (kg a.s./ha)**	**Work Rate (ha/day)**	**Generic study, potato**	**Thiodan study, orchard airblast**	**Thiodan study, orchard hand held**	**Generic study, green house**
Tractor boom	Gloves, coverall, mask, hood+visor during mixing/loading; coverall during application	Potato	0.25	19-41	0.0000962			
Tractor airblast	Gloves, mask during mixing/loading;gloves, coverall, mask, hood+visor during application	Orchard	1.05	8		0.00224		
Hand held orchard	Gloves, coverall, mask during mixing/loading; gloves, hood+visor, coverall, mask during application	Orchard	1.05	1			0.00101	
Hand held greenhouse	Gloves, coverall, mask during mixing/loading; gloves, coverall during application	Tomato	0.80	1				0.00175

The degree of exposure is described in the table 6.14-4

Table 6.14-4: Risk assessment for Thiodan 35 EC

Crop	**Application technique**	**Source of data**	**Systemic exposure (mg/kg bw/day)**	**%AOEL (0.0042 mg/kgbw/day)**	**% AOEL (0.0147 mg/kg bw/day)**
Cotton	Tractor boom	BBA-model	0.000793	18.8%	5.4%
Potato	Tractor boom	Exposure study	0.0000962	2.3%	5.4%
Pome fruit	Tractor airblast	BBA-model	0.00111	26.4%	7.6%
		Exposure Study	0.00224	53%	16.3%
Citrus	Hand-held spray lance	BBA-model	0.004861	116%	33.1%
		Exposure Study	0.00101	24%	6.9%
Tomato	Hand-held glasshouse	BBA-model	0.0037	88%	25%
		Exposure Study	0.001752	42%	11.9%

3-. Summary of the re-evaluation submitted by the RMS

Table 6.14-5: Systemic exposures obtained with BBA-model (with and without PPE)

Exposure scenarios				BBA-model	
Appl. technique	**Crop**	**Dose rate (kg a.s./ha)**	**Work Rate (ha/day)**		
				Without PPE	With PPE
Tractor boom	Cotton	0.84	20	0.015	0.001075
Tractor airblast	Pome fruit	1.05	8	0.0357	0.001638
Hand held orchard	Citrus	1.05	1	0.01866	0.005052
Hand held greenhouse	Tomato	0.80	1	0.01421	0.00385

Table 6.14-6: Systemic exposures obtained with modern operator exposure studies (with PPE)

Modern operator exposure studies								
Appl. technique	**PPE used**	**Crop**	**Dose rate (kg a.s./ha)**	**Work Rate (ha/day)**	**Generic study, potato**	**Thiodan study, orchard airblast**	**Thiodan study, orchard hand held**	**Generic study, green house**
Tractor boom	Gloves, coverall, mask, hood+visor during mixing/loading; coverall during application	Potato	0.25	19-41	0.0001315			
Tractor airblast	Gloves, mask during mixing/loading; gloves, coverall, mask, hood+visor during application	Orchard	1.05	8		0.0023		
Hand held orchard	Gloves, coverall, mask during mixing/loading; gloves, hood+visor, coverall, mask during application	Orchard	1.05	1			0.0013	
Hand held greenhouse	Gloves, coverall, mask during mixing/loading; gloves, coverall during application	Tomato	0.80	1				0.001978

The degree of exposure is described in the table 6.14-7.

Table 6.14-7: Risk assessment for Thiodan 35 EC using PPE

Crop	Application technique	Source of data	PPE (with or without)	Systemic exposure (mg/kg bw/day)	%AOEL (0.0042 mg/kgbw/day)
Cotton	Tractor boom	BBA-model	Without PPE	0.015	357.14
			With PPE	0.001075	25.59
Potato	Tractor boom	Exposure study	With PPE	0.0001315	3.13
Pome fruit	Tractor airblast	BBA-model	Without PPE	0.0357	850
			With PPE	0.001638	39
		Exposure Study	With PPE	0.0023	54.76
Citrus	Hand-held spray lance	BBA-model	Without PPE	0.01866	444.28
			With PPE	0.005052	120.28
		Exposure Study	With PPE	0.0013	30.95
Tomato	Hand-held glasshouse	BBA-model	Without PPE	0.01421	338.33
			With PPE	0.00385	91.66
		Exposure Study	With PPE	0.001978	47.09

Conclusion:

According the table below, safety uses for operator using PPE are expected in three scenarios:

- Tractor mounted boom sprayer in field crops
- Tractor mounted airblast sprayer in high crops
- Hand held sprayer Greenhouse (high crops)

Hand-held spray lance in citrus is not considered acceptable when BBA-model was applied. The notifier included an exposure study with acceptable levels of exposure for operator, taking into account the next PPE: gloves, coverall and mask during mixing and loading; gloves, coverall and hood+visor during application. In the RMS opinion, this last scenario is considered acceptable, as exposure study was well characterized

B 6.9 Referents on.

Annex II or annex III point	Author (s) Year Title Reference	GLP GEP Y/N	Published	Owner	Data protection
IIA/5.4	[redacted] 2003 In vivo chromosome aberration assay in mouse spermatogonial cells C032454	Y	N	Aventis	NO
IIIA	[redacted] 1986 Dermal absorption in vivo rats A35730	Y	N	AgrAv	NO
IIIA	[redacted] 1988 Dermal absorption in vivo rats A39677	Y	N	AgrAv	NO
IIIA	[redacted] 1987 Dermal absorption in vivo monkeys A36685	Y	N	AgrAv	NO
IIIA	[redacted] 1995 Dermal absorption in vitro human and rats skin A54103	Y	N	AgrAv	NO
IIIA	[redacted] 1997 Biomonitoring study AA950305	Y	N	AgrAv	NO
IIIA	[redacted] 2002 Dermal absorption in vitro human, rat and pig skin C021864	Y	N	Aventis	YES
IIIA	[redacted] 2002 Re.evaluation of the operator exposure and risk assessment for Thiodan 35 EC with a new data on skin penetration C022980	Y	N	Aventis	NO
IIA/5.8	[redacted] 2002 Endosulfan lactone. Acute oral toxicity in rats. Acute classic method C024720	Y	N	Bayer	NO
IIA/5.8	[redacted] 2003 Endosulfan lactone: preliminary 28-day toxicity study in the rat by dietary administration C032189	Y	N	Bayer	NO
IIA/5.8	[redacted] 2003 Endosulfan lactone. 90-day toxicity study in the rat by dietary administration C032788	Y	N	Bayer	NO
IIA/5.8	[redacted] 2002 Endosulfan hydroxy carboxylic acid. Acute oral toxicity in rats. Acute toxic class method	Y	N	Bayer	NO