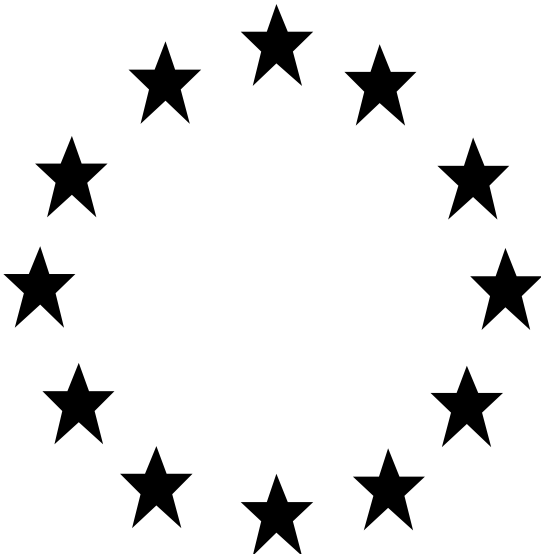


Final addendum to the

Draft Assessment Report (DAR)

- public version -

Initial risk assessment provided by the rapporteur Member State Finland for the existing active substance

TOLYLFLUANID

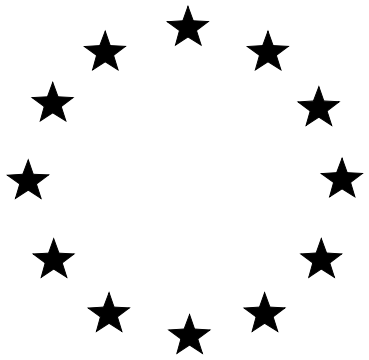
of the second stage of the review programme referred to in Article 8(2) of Council Directive 91/414/EEC

February 2005

CONTENT OF THE COMPILED ADDENDUM

European Commission

Peer Review Programme



EPCO-Meetings

TOLYLFLUANID

Volume 3

ANNEX B

Summary, Scientific Evaluation and Assessment

ADDENDUM 1

Rapporteur Member State: Finland

19 February 2004

This document has not been peer reviewed and does not represent the opinion of the other Member States nor the European Commission

PLANT PRODUCTION INSPECTION CENTRE
Pesticide Division
Vilhonvuorenkatu 11
P.O.Box 42 F
FIN-00501 HELSINKI, FINLAND

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B.9.1 Effects on birds

B.9.1.4 Summary and risk assessment for birds

The use pattern of tolylfluanid on which the revised risk assessments are based is shown in Table B.9.1.4-1.

Table B.9.1.4-1. Crops, application rates and intervals for tolylfluanid WG 50 formulation.

Crop	Northern Europe (NE)/ Southern Europe (SE)	Max. application rate kg ai/ha	Max. no. of applications	Application interval [d]
Apples / Pears	NE	1.125	7	7 - 14
Apples / Pears	SE	1.5	3	7 - 14
Grapes	NE	up to 1.8	8	10 -14
Grapes	SE	up to 2.0	3	8 - 19
Strawberries	NE	2.5	3	8 - 12
Strawberries	SE	1.25	3	7 - 10

For convenience, the toxicity endpoints for birds used in the original dossier are re-presented in Table B.9.1.4-2.

Table B.9.1.4-2. Toxicological endpoints for birds (tolylfluanid).

Organisms	Duration	Test-substance	Origin	Ecotoxicological endpoint
Bobwhite quail	Acute, oral	ai	Annex II, 8.1.1 /01	LD_{50} > **2,000** mg ai/kg bw
Bobwhite quail	Subchronic 5 d, dietary	ai	Annex II, 8.1.2 /01	LC_{50} > **5,000** mg ai/kg diet
Bobwhite quail	Reproduction 21 w, dietary	ai	Annex II, 8.1.3 /01	NOEC **791** mg ai/kg diet
Bobwhite quail	Acute, oral	DMST	Annex II, 8.1.1 /03	LD_{50} **> 2,000** mg ai/kg bw

value with **bold**: value used in risk assessment

B.9.1.4.1 Exposure of birds to tolylfluanid WG 50

The main potential route of exposure for birds to foliar applied agrochemicals is considered to be through the ingestion of residues on contaminated foliage and other prey items (e.g. insects and earthworms). Therefore in order to ensure a rigorous risk evaluation, a reasonable worst-case assessment has been conducted considering the maximum application rates, with the assumption that the principal route of exposure is through ingestion.

In accordance with Directive 91/414/EEC, the Tier 1 assessment considers standardised reasonable worst case scenarios that involve indicator species chosen to represent the upper limit of exposure. The assessments presented in this appendix are based on, and are consistent with, the recommendations laid out in the "Guidance Document on Risk Assessment for Birds and Mammals Under Council Directive 91/414/EEC" (SANCO/4145/2000 final September 2002).

For treatments such as Euparen M WG 50 that are foliar applied to grapes and apples, it is recommended that the standard indicator species used for acute, short-term and long-term exposure assessments are small insectivorous birds (e.g. the wren), which have a high food intake relative to body weight. In line with the guidance, the insectivorous bird used in this risk evaluation is assumed to weigh 10 g, with a daily food intake of 10.4 g fresh material/day, resulting in a food intake rate related to body weight of 1.04.

For leafy crops such as strawberries, the recommended indicator species is a medium sized herbivorous bird (e.g. partridge or pigeon), assumed to weigh 300 g, with a daily food intake of 228 g fresh material/day, resulting in a

food intake rate related to body weight of 0.76. In reality it is more likely that omnivorous birds such as the blackbird (*Turdus merula*) will be attracted to the ripening fruit, rather than herbivorous species feeding on the fibrous mature foliage of the strawberry plants. Weed and grass cover in the crop is also expected to be negligible as these plants are generally eliminated by mulching with plastic or straw, therefore there will be few non-crop food sources available to herbivorous birds within the treated area. Nevertheless, in order to ensure a rigorous worst-case evaluation, risk assessments are presented for both herbivorous and frugivorous species feeding in strawberries, although in reality it is expected that exposure for herbivorous species is likely to be negligible.

Table B.9.1.4-3. Assumptions regarding the assessment of risks to birds (based on recommendations detailed in the Birds and Mammals Guidance Document (SANCO/4145/2000 final Sept 2002)).

Generic species	Body weight (bw)	Feed	Food intake (FIR) [g fresh weight per day]	FIR/bw
[1]Medium herbivorous bird (e.g.: partridge or pigeon)	300 g	Leafy crops	228	0.76
[2]Small insectivorous bird (e.g.: wren)	10 g	Small insects	10.4	1.04
[3]Bird with mixed diet feeding exclusively on fruits (e.g. blackbird)	100 g	fruits	118.12	1.18

[1] and [2] according to the Birds and Mammals Guidance Document (SANCO/4145/2000 final Sept 2002)
[3] according to Nagy (1987)

With regard to predicted residues on food items following foliar spray applications, initial Tier 1 estimates are based on the worst-case values presented in tables 4, 6 and 7 of the SANCO guidance document. As recommended in the guidance, depending on the time scale of the exposure, either 90th percentile or arithmetic mean residue concentrations are used for acute or chronic exposures as appropriate.

In the refined Tier 2 risk assessments and in accordance with Appendix II of the SANCO/4145/2000 FINAL guidance, it is considered appropriate to use the residue values from the database presented by Fischer (1997). According to Luttik (2000) preference should be given to these values as the database is larger and more a reflection of the state of the art than the one used by Hoerger and Kenaga. In the short-term and long-term risk evaluations, averaging of residues is expected to occur over a period of days and so it is appropriate to use the 50th percentile for residues in food items. This results in a refined RUD of 2.7 mg/kg for foliar insects and 25.0 mg/kg for leaves and leafy crops (Luttik 2000).

B.9.1.4.2 Acute Risk Assessment - Tier 1

The Tier 1 risk assessment for acute exposure to birds shows that all TER-values (TER_a) for insectivorous birds are above the Annex VI -trigger of 10, even using worst-case assumptions (see Table B.9.1.4-4); although a refined risk assessment is required for herbivorous birds potentially exposed to residues in strawberries at a use rate of 2.5 kg ai/ha. However it should be noted that these acute TER values have all been calculated based on a LD_{50} value of >2000 mg ai/kg bw, a dose at which no mortality or treatment-related effects were recorded (Barfknecht, 2000); clearly this results in an over estimation of the potential risk and exaggerated TER values.

For acute exposure, as a reasonable worst-case, the 90th percentiles of the initial residue concentrations on potential food items are used. Calculations of the **E**stimated **T**heoretical **E**xposure (ETE) in terms of daily dose (mg/kg b.w.) are based on multiplication of the relative daily food intake (FIR/bw), by the **R**esidue per **U**nit

Dose (RUD), the **M**ultiple **A**pplication **F**actor (MAF) and the application rate (kg a.s./ha). The TER_a is then calculated by comparing the ETE with the most relevant LD_{50} value (>2000 mg a.s./kg bw). The initial worst-case calculations for tolylfluanid are presented in Table B.9.1.4-4 and are based on the default values presented in tables 3 and 4 of the Birds and Mammals Guidance Document.

Table B.9.1.4-4. TER calculations based on <u>acute</u> toxicity (calculations based on recommendations detailed in the Birds and Mammals Guidance Document (SANCO/4145/2000 final Sept 2002)).

Toxicological endpoint: Bobwhite quail, acute		**LD_{50} > 2,000 mg ai/kg bw**
Generic bird species[1]	medium herbivore	insectivore
Apples / Pears (Northern Europe): 1.125 kg ai/ha; 7 applications / 7 d interval		
RUD (90%)	87	52
Calculated maximum initial residues in feed [mg/kg feed]	-	58.5
FIR/bw	-	1.04
MAF (multiple application factor)	-	na
ETE [mg/kg bw/day]	-	60.84
TER_a [2]	**-**	**>32.9**
Refined Risk Assessment required	**na**	**No**
Apples / Pears (Southern Europe): 1.5 kg ai/ha; 3 applications / 7 d interval		
RUD (90%)	87	52
Calculated maximum initial residues in feed [mg/kg feed]	-	78
FIR/bw	-	1.04
MAF (multiple application factor)	-	na
ETE [mg/kg bw/day]	-	81.1
TER_a [2]	**-**	**>24.7**
Refined Risk Assessment required	**na**	**No**
Toxicological endpoint: Bobwhite quail, acute		**LD_{50} > 2,000 mg ai/kg bw**
Generic bird species[1]	medium herbivore	insectivore
Grapes (Northern Europe): 1.8 kg ai/ha; 8 applications / 10 d interval		
RUD (90%)	87	52
Calculated maximum initial residues in feed [mg/kg feed]	-	93.6
FIR/bw	-	1.04
MAF (multiple application factor)	-	na
ETE [mg/kg bw/day]	-	97.3
TER_a [2]	**-**	**>20.5**
Refined Risk Assessment required	**na**	**No**

[1] see Table B.9.1.4-3

[2] the risk is considered acceptable, if the TER-value is >10

Table to be continued

Table B.9.1.4-4 continued

Grapes (Southern Europe): 2.0 kg ai/ha; 3 applications / 8 d interval		
RUD (90%)	87	52
Calculated maximum initial residues in feed [mg/kg feed]	-	104
FIR/bw	-	1.04
MAF (multiple application factor)	-	na
ETE [mg/kg bw/day]	-	108.2
TER_a [2]	**-**	**>18.5**
Refined Risk Assessment required	**na**	**No**
Strawberries (Northern Europe): 2.5 kg ai/ha; 3 applications / 8 d interval		
RUD (90%)	87	52
Calculated maximum initial residues in feed [mg/kg feed]	217.5	130
FIR/bw	0.76	1.04
MAF (multiple application factor)	1.7	na
ETE [mg/kg bw/day]	281.0	135.2
TER_a [2]	**>7.1**	**>14.8**
Refined Risk Assessment required	**Yes**	**No**
Toxicological endpoint: Bobwhite quail, acute	**LD_{50} > 2,000 mg ai/kg bw**	
Generic bird species[1]	medium herbivore	insectivore
Strawberries (Southern Europe): 1.25 kg ai/ha; 3 applications / 7 d interval		
RUD (90%)	87	52
Calculated maximum initial residues in feed [mg/kg feed]	108.8	65
FIR/bw	0.76	1.04
MAF (multiple application factor)	1.7	na
ETE [mg/kg bw/day]	140.5	67.6
TER_a [2]	**>14.2**	**>29.6**
Refined Risk Assessment required	**No**	**No**

[1] see Table B.9.1.4-3
[2] the risk is considered acceptable, if the TER-value is >10

B.9.1.4.3 Acute Risk Assessment – Tier 2

According to the TER-values calculated in Table B.9.1.4-4 above, a refined risk assessment for acute-exposure to birds is necessary for herbivorous birds in strawberries at a use rate of 2.5 kg ai/ha. For insectivorous birds the risk is acceptable even using the worst-case assumptions of the tier 1 risk assessment.

A refined assessment for herbivorous avian species is not considered particularly relevant for strawberries as the crop will not provide an attractive food source for herbivorous birds; in addition weed and grass cover in the treated area will be minimised as a result of mulching. It is much more probable that opportunistic omnivorous species such as the blackbird (*Turdus merula*) will be attracted to the ripening fruit. However, in order to ensure that the potential risk has been effectively addressed two exposure scenarios are presented (both assessments are presented in Table B.9.1.4-5):

a) The first and most likely exposure assumes that an omnivorous bird would, for a limited period, obtain 100% of its diet from treated fruit. The residue intake calculations for this assessment are based on the highest measured initial residue in fruits on day 0 after the last application in field residue trials (7.9 mg/kg fresh weight fruit (three applications of 2.5 kg ai/ha), see B.7.6 Residues arising from supervised trials, Table B.7.6 – 12.

b) The second exposure assessment covers the unlikely possibility that a herbivorous bird might spend up to 60% of its time feeding on freshly treated strawberry leaves. Again it is important to note that these TER values are calculated based on a LD_{50} value of >2000 mg ai/kg bw which was also determined as the NOAEL for acute toxicity to the bobwhite quail (Barfknecht, 2000).

The refined exposure assessment, taking into account the proportion of time spent in the treated area is calculated using the following equation (SANCO/4145/2000-final):

One day dietary dose (mg tolylfluanid/kg body weight) =

$$ETE = (FIR/bw) * C * AV * PT * PD \qquad (mg/kg/bw/day)$$

Where:

FIR = Food intake rate (g fresh weight/day)
bw = Body weight (g)
PT = Proportion of food obtained from the treated area (unitless; number between 0 and 1)
PD = Proportion of food type in the diet (number between 0 and 1;one type or more types)
C = Concentration of tolylfluanid on fresh diet (mg a.s./kg)
AV = Avoidance factor (1 = no avoidance; 0 = complete avoidance)

Table B.9.1.4-5 TER calculations based on acute toxicity and more realistic exposure of tolylfluanid after the last application.

Toxicological endpoint: Bobwhite quail, acute		**LD_{50} > 2,000 mg ai/kg bw**
Generic bird species[1]	frugivore	herbivore
Food type	**strawberry fruits**	**leaves**
Strawberries (Northern Europe): 2.5 kg ai/ha; 3 applications / 8 d interval		
Calculated maximum initial residues in feed [mg/kg feed]	7.90 (residue trials data)	217.5 (based on a theoretical RUD of 87 mg/kg)
FIR/bw	1.18	0.76
MAF (multiple application factor)	na	1.7
AV (avoidance factor)	na	1
PT (proportion of food obtained in treated area i.e. 60%)	na	0.6
PD (proportion of food type in diet i.e. 100 %)	na	1
ETE [mg/kg bw/day]	9.32	168.6
TER_a[2]	**>214.5**	**>11.9**
Refined Risk Assessment required	**No**	**No**

[1] see Table B.9.1.4-3

[2] the risk is considered acceptable, if the TER-value is >10

Based on this refined evaluation and considering the more realistic exposure scenarios presented in Table B.9.1.4-5, all tier 2 TER_a values are above the Annex VI - trigger of 10, indicating no unacceptable acute risk to birds.

B.9.1.4.4 Short-term Risk Assessment - Tier 1

The short-term risk assessment shows that the TER-values (TER_{st}) for insectivorous birds foraging in orchards and vineyards treated with tolylfluanid are above the Annex VI -trigger of 10 (Table B.9.1.4-6). Similarly Tier 1 TER values are above 10 for both herbivorous and insectivorous birds feeding in strawberry crops sprayed at 1.25 kg ai/ha. A Tier 2 refinement with more realistic exposure scenarios is therefore only required for birds feeding in strawberry fields sprayed at the maximum rate of 2.5 kg ai/ha.
The short-term exposure assessment aims at a time frame of a few days. Therefore initial residues are more appropriate than time–weighted averages (twa). As usual in a first tier assessment, birds are assumed to feed on treated food items only, however over a few days they will gather food in a larger area with greater variation in the residue levels. Averaging of residues is therefore expected to occur, so it is appropriate to use the arithmetic means for residues in food items. In addition it is important to note that for insects it is considered inappropriate to apply a MAF, as accumulation of residues is not expected due to rapid residue declines as a result of a number of factors including population development. The relevant calculations for short-term avian exposure to formulations containing tolylfluanid are summarised in Table B.9.1.4-6. These initial Tier 1 calculations are based on the default values presented in Tables 5 and 6 of the Birds and Mammals Guidance Document.

Table B.9.1..4-6. TER calculations based on <u>short-term</u> (5 day) toxicity (calculations based on recommendations detailed in the Birds and Mammals Guidance Document (SANCO/4145/2000 final Sept 2002)).

Toxicological endpoint: Bobwhite quail, subchronic	**LC_{50} > 5,000 mg ai/kg wet diet corresponding to LC_{50} > 726.3 mg ai/kg bw$^+$**	
Generic bird species[1]	medium herbivore	insectivore
Apples / Pears (Northern Europe): 1.125 kg ai/ha; 7 applications / 7 d interval		
RUD (50%)	40	29
Calculated maximum initial residues in feed [mg/kg wet weight feed]	-	32.6
FIR/bw	-	1.04
MAF (multiple application factor)	-	na
ETE [mg/kg bw/day]	-	33.9
TER_{st} [2]	**-**	**>21.4**
Refined Risk Assessment required	**na**	**No**

[1] see Table B.9.1.4-3

[2] the risk is considered acceptable, if the TER-value is >10

Table to be continued

Table 9.1.4-6 continued

Apples / Pears (Southern Europe): 1.5 kg ai/ha; 3 applications / 7 d interval		
RUD (50%)	40	29
Calculated maximum initial residues in feed [mg/kg wet weight feed]	-	43.5
FIR/bw	-	1.04
MAF (multiple application factor)	-	na
ETE [mg/kg bw/day]	-	45.2
TER_{st} [2]	**-**	**>16.1**
Refined Risk Assessment required	**na**	**No**
Generic bird species[1]	medium herbivore	insectivore
Grapes (Northern Europe): 1.8 kg ai/ha; 8 applications / 10 d interval		
RUD (50%)	40	29
Calculated maximum initial residues in feed [mg/kg wet weight feed]	-	52.2
FIR/bw	-	1.04
MAF (multiple application factor)	-	na
ETE [mg/kg bw/day]	-	54.3
TER_{st} [2]	**-**	**>13.4**
Refined Risk Assessment required	**na**	**No**
Grapes (Southern Europe): 2.0 kg ai/ha; 3 applications / 8 d interval		
RUD (50%)	40	29
Calculated maximum initial residues in feed [mg/kg wet weight feed]	-	58
FIR/bw	-	1.04
MAF (multiple application factor)	-	na
ETE [mg/kg bw/day]	-	60.3
TER_{st} [2]	**-**	**>12.0**
Refined Risk Assessment required	**na**	**No**
Strawberries (Northern Europe): 2.5 kg ai/ha; 3 applications / 8 d interval		
RUD (50%)	40	29
Calculated maximum initial residues in feed [mg/kg wet weight feed]	100	72.5
FIR/bw	0.76	1.04
MAF (multiple application factor)	2.0	na
ETE [mg/kg bw/day]	152	75.4
TER_{st} [2]	**>4.8**	**>9.6**
Refined Risk Assessment required	**Yes**	**Yes**

[1] see Table B.9.1.4-3

[2] the risk is considered acceptable, if the TER-value is >10

Table to be continued

Strawberries (Southern Europe): 1.25 kg ai/ha; 3 applications / 7 d interval		
RUD (50%)	40	29
Calculated maximum initial residues in feed [mg/kg wet weight feed]	50	36.3
FIR/bw	0.76	1.04
MAF (multiple application factor)	2.0	na
ETE [mg/kg bw/day]	76	37.7
TER_{st} [2]	**>9.6**	**>19.3**
Refined Risk Assessment required	**No**	**No**

[1] see Table B.9.1.4-3
[2] the risk is considered acceptable, if the TER-value is >10

B.9.1.4.5 Short-term Risk Assessment - Tier 2

According to the TER-values calculated in Table B.9.1.4-6 above, a refined risk assessment for short-term exposure to birds is necessary for herbivorous and insectivorous birds in strawberry crops at the maximum use rate of 2.5 kg ai/ha.

In the refined risk assessment for insectivorous birds and in accordance with Appendix II of the SANCO/4145/2000 guidance it is appropriate to use the residue values from the database presented by Fischer (1997). According to Luttik (2000) preference should be given to these values as the database is larger and more a reflection of the state of the art than the one used by Hoerger and Kenaga. In the short-term risk evaluation, averaging of residues is expected to occur over a period of days and so it is appropriate to use the 50^{th} percentile for residues in food items. This results in a refined RUD of 2.7 mg/kg for foliar insects and 25.0 mg/kg for leaves/leafy crops.

As already stated, birds feeding in strawberry crops are unlikely to consume treated leaves, but exposure is possible through birds feeding on strawberry fruits. For these calculations, a bird with a mixed diet, but feeding exclusively on strawberry fruits (e.g. a blackbird) is taken into consideration (for dietary intake assumptions see Table B.9.1.4-3). Since the food intake rate of birds feeding on a mixed diet (e.g. a blackbird), is substantially higher than that of herbivorous birds, the risk even in this case is considered to be overestimated. The fruit residue calculations are based on the highest measured initial residue in fruits on day 0 after the last application in field trials (7.9 mg/kg fresh weight fruit (three applications of 2.5 kg ai/ha).

Although it is highly unlikely that birds will feed on the strawberry foliage, an additional risk assessment is presented to cover this exposure scenario. Although this route of exposure is unlikely, these calculations add confidence to the overall conclusion of low risk. For this assessment a refined RUD of 25.0 mg/kg is used for residues on leaves and the MAF is refined using the equation given in Section 5.3 of the guidance document and based on the mean measured DT_{50} value on grass of 2.47 days (Barfknecht, 2003).

It should be noted that the TER values for the short-term risk assessment are calculated based on a LC_{50} value of >726.3 mg ai/kg bw, this concentration was also confirmed as the NOEC for dietary toxicity to bobwhite quail (Grau, 1990). Nevertheless, based on this refined evaluation and considering the more realistic exposure scenarios presented in Table B.9.1.4-7, all tier 2 TER_{st} values are above the Annex VI - trigger of 10, indicating no unacceptable short-term risk to birds.

Table B.9.1.4-7. TER calculations based on short-term (5 days) toxicity and more realistic exposure of tolylfluanid after the last application.

Toxicological endpoint: Bobwhite quail, subchronic **LC_{50} > 5,000 mg ai/kg diet corresponding to a daily dietary dose of > 726.3 mg/kg bw/day**		
Generic bird species[1]	insectivore	
Typical initial residues in feed[2] (based on application of 1 kg/ha) [mg/kg feed]	**foliar insects** 2.7	
Strawberries (Northern Europe): 2.5 kg ai/ha; 3 applications / 8 d interval		
Calculated maximum initial residues in feed[3] [mg/kg feed]	6.75	
FIR/bw	1.04	
ETE [mg/kg bw/day]	7.02	
TER_{st}[4]	**103.5**	
Refined Risk Assessment required	**No**	
Toxicological endpoint: Bobwhite quail, subchronic **LC_{50} > 5,000 mg ai/kg diet corresponding to a daily dietary dose of > 726.3 mg/kg bw/day**		
Generic bird species[1]	frugivore	herbivore
Food type	**strawberry fruits**	**leaves**
1.1.1.1Strawberries (Northern Europe): 2.5 kg ai/ha; 3 applications / 8 d interval		
Calculated maximum initial residues in feed [mg/kg feed][2]	7.90 (residue trials data)	62.5 (based on a theoretical RUD of 25 mg/kg)
MAF (multiple application factor)	na	1.12
FIR/bw	1.18	0.76
ETE [mg/kg bw/day]	9.3	53.2
TER_{st}[3]	**77.9**	**13.7**
Refined Risk Assessment required	**No**	**No**

[1] see Table B.9.1.4-3
[2] for leaves/leafy crops: typical initial residue according to Luttik (2000)
[3] the risk is considered acceptable, if the TER-value is >10

B.9.1.4.6 Long-term Risk Assessment - Tier 1

This exposure estimate is very similar to the short-term assessment, with the use of residue estimates based on arithmetic means and multiple application factors. In contrast to the short-term assessment time-weighted average (twa) residues are used as these better reflect long-term exposure. However in the case of insects, no time-weighted average is used as the time course of the residue decline is unknown. The relevant calculations for long-term avian exposure are summarised in Table B.9.1.4-8; these initial Tier 1 calculations are based on the default values presented in Tables 5 and 7 of the Birds and Mammals Guidance Document.

The long-term TER-values (TER_{lt}) are all below the Annex VI -trigger of 5, showing that a tier 2 refined risk assessment is required for both insectivorous and herbivorous birds in all crop scenarios.

Table B.9.1.4-8. TER calculations based on long-term toxicity (147 days) (calculations based on recommendations detailed in the Birds and Mammals Guidance Document (SANCO/4145/2000 final Sept 2002)).

Toxicological endpoint: Bobwhite quail, reproduction **NOEC 791 mg ai/kg wet diet corresponding to a daily dietary dose of 78.1 mg ai/kg bw/day**		
Generic bird species[1]	medium herbivore	insectivore
Apples / Pears (Northern Europe): 1.125 kg ai/ha; 7 applications / 7 d interval		
RUD (50%)	40	29
Calculated maximum initial residues in feed [mg/kg wet weight feed]	-	32.6
FIR/bw	-	1.04
MAF (multiple application factor)	-	na
ETE [mg/kg bw/day]	-	33.9
TER_{lt} [2]	**-**	**2.3**
Refined Risk Assessment required	**na**	**Yes**
Apples / Pears (Southern Europe): 1.5 kg ai/ha; 3 applications / 7 d interval		
RUD (50%)	40	29
Calculated maximum initial residues in feed [mg/kg wet weight feed]	-	43.5
FIR/bw	-	1.04
MAF (multiple application factor)	-	na
ETE [mg/kg bw/day]	-	45.2
TER_{lt} [2]	**-**	**1.7**
Refined Risk Assessment required	**na**	**Yes**
Grapes (Northern Europe): 1.8 kg ai/ha; 8 applications / 10 d interval		
RUD (50%)	40	29
Calculated maximum initial residues in feed [mg/kg wet weight feed]	-	52.2
FIR/bw	-	1.04
MAF (multiple application factor)	-	na
ETE [mg/kg bw/day]	-	54.3
TER_{lt} [2]	**-**	**1.4**
Refined Risk Assessment required	**na**	**Yes**

[1] see Table B.9.1.4-3
[2] the risk is considered acceptable, if the TER-value is > 5

Table to be continued

Table B.9.1.4-8 continued

Toxicological endpoint: Bobwhite quail, reproduction **NOEC 791 mg ai/kg wet diet corresponding to a daily dietary dose of 78.1 mg ai/kg bw/day**[+]		
Generic bird species[1]	medium herbivore	insectivore
Grapes (Southern Europe): 2.0 kg ai/ha; 3 applications / 8 d interval		
RUD (50%)	40	29
Calculated maximum initial residues in feed [mg/kg wet weight feed]	-	58
FIR/bw	-	1.04
MAF (multiple application factor)	-	na
ETE [mg/kg bw/day]	-	60.3
TER_{lt} [2]	**-**	**1.3**
Refined Risk Assessment required	**na**	**Yes**
Strawberries (Northern Europe): 2.5 kg ai/ha; 3 applications / 8 d interval		
RUD (50%)	40	29
Calculated maximum initial residues in feed [mg/kg wet weight feed]	100	72.5
FIR/bw	0.76	1.04
MAF (multiple application factor)	2.0	na
f_{twa}	0.53	na
ETE [mg/kg bw/day]	80.56	75.4
TER_{lt} [2]	**1.0**	**1.04**
Refined Risk Assessment required	**Yes**	**Yes**
Strawberries (Southern Europe): 1.25 kg ai/ha; 3 applications / 7 d interval		
RUD (50%)	40	29
Calculated maximum initial residues in feed [mg/kg wet weight feed]	50	36.3
FIR/bw	0.76	1.04
MAF (multiple application factor)	2.0	na
f_{twa}	0.53	na
ETE [mg/kg bw/day]	40.3	37.7
TER_{lt} [2]	**1.9**	**2.1**
Refined Risk Assessment required	**Yes**	**Yes**

[1] see Table B.9.1.4-3
[2] the risk is considered acceptable, if the TER-value is > 5

B.9.1.4.7 Long-term Risk Assessment - Tier 2

According to the Tier 1 TER-values calculated in Table B.9.1.4-8 above, a refined risk assessment for long-term exposure to birds is required for both insectivorous and herbivorous birds in all crop scenarios. Based on this refined evaluation and considering the more realistic exposure scenarios presented in Table B.9.1.4-9, all tier 2 TER_{lt} values are above the Annex VI - trigger of 5, indicating no unacceptable risk long-term risk to birds.

In the refined risk assessment for insectivorous birds and in accordance with Appendix II of the SANCO/4145/2000 guidance, it is appropriate to use the residue values from the database presented by Fischer (1997). According to Luttik (2000) preference should be given to these values as the database is larger and more a reflection of the state of the art than the one used by Hoerger and Kenaga. In the long-term risk evaluation, averaging of residues is expected to occur over a period of days and so it is appropriate to use the 50^{th} percentile for residues in food items. This results in a refined RUD of 2.7 mg/kg for foliar insects and 25.0 mg/kg for leaves/leafy crops (Luttik 2000).

As already stated, birds feeding in strawberry crops are unlikely to consume treated leaves, but avian exposure is possible through feeding on strawberry fruits. For these calculations, a bird with a mixed diet, but feeding exclusively on freshly sprayed strawberry fruits (e.g. a blackbird) is taken into consideration (for dietary intake assumptions see Table B.9.1.4-3). Since the food intake rate of birds feeding on a mixed diet is substantially higher than that of herbivorous birds, the risk even in this case is considered to be overestimated. The fruit residue calculations are based on the highest measured initial residue in fruits on day 0 after the last application in field trials (7.9 mg/kg fresh weight fruit (three applications of 2.5 kg ai/ha). The use of this residue level also overestimates avian exposure for applications in strawberries in Southern Europe by a factor of 2. This is because in Southern Europe only 3 applications at 1.25 kg ai/ha are applied.

Although it is highly unlikely that birds will feed exclusively on the strawberry foliage, an additional risk assessment is presented to cover this exposure scenario. These calculations confirm that in the unlikely event that a bird obtains 60% of its diet from freshly treated strawberry leaves over a prolonged period of time, the TER values are within acceptable limits and the potential risk is low. For this assessment a refined RUD of 25.0 mg/kg is used for residues on leaves and the MAF and Twa are refined using the equations given in Sections 5.3 of the guidance document and based on the mean measured DT_{50} value on grass of 2.47 days (Barfknecht, 2003).

Since the relevant toxicity value for a long-term exposure is based on a 147-days study and the measured half-life of tolylfluanid in plant material is very short (grass, mean 2.47 days; see Barfknecht, 2003), a more realistic exposure is calculated using the 7-day twa exposure (according to current guidelines, in the case of repeated applications the averaging time should not be longer than the spray interval; thus for tolylfluanid a 7-day twa is appropriate).

Table B.9.1.4-9. TER calculation based on long-term toxicity (147 days) and more realistic exposure of tolylfluanid after the last application.

Toxicological endpoint: Bobwhite quail, reproduction **NOEC 791 mg ai/kg wet diet corresponding to a daily dietary dose of 78.1 mg ai/kg bw/day**	
Generic bird species[1]	insectivore
RUD[2] (based on application of 1 kg/ha) [mg/kg feed]	**foliar insects** 2.7
1.1.1.2Apples / Pears (Northern Europe): 1.125 kg ai/ha; 7 applications / 7 d interval	
Calculated maximum initial residues in feed [mg/kg feed]	3.04
FIR/bw	1.04
ETE [mg/kg bw/day]	3.16
TER_{lt} [3]	**24.7**
Refined Risk Assessment required	**No**
1.1.1.3Apples / Pears (Southern Europe): 1.5 kg ai/ha; 3 applications / 7 d interval	
Calculated maximum initial residues in feed [mg/kg feed]	4.05
FIR/bw	1.04
ETE [mg/kg bw/day]	4.21
TER_{lt} [3]	**18.5**
Refined Risk Assessment required	**No**
1.1.1.4Grapes (Northern Europe): 1.8 kg ai/ha; 8 applications / 10 d interval	
Calculated maximum initial residues in feed[3] [mg/kg feed]	4.86
FIR/bw	1.04
ETE [mg/kg bw/day]	5.05
TER_{lt} [3]	**15.5**
Refined Risk Assessment required[7]	**No**
1.1.1.5Grapes (Southern Europe): 2.0 kg ai/ha; 3 applications / 8 d interval	
Calculated maximum initial residues in feed[2] [mg/kg feed]	5.4
FIR/bw	1.04
ETE [mg/kg bw/day]	5.61
TER_{lt} [3]	**13.9**
Refined Risk Assessment required	**No**

[1] see Table B.9.1.4-3
[2] for foliar insects: median 50-percentile residue value according to Luttik (2000)
[3] the risk is considered acceptable, if the TER-value is > 5

Table to be continued

Table B.9.1.4-9 continued

Toxicological endpoint: Bobwhite quail, reproduction **NOEC 791 mg ai/kg wet diet corresponding to a daily dietary dose of 78.1 mg ai/kg bw/day**			
Generic bird species[1]	frugivore	herbivore	insectivore
Food type	**strawberry fruits**	**leaves**	**foliar insects**
Strawberries (Northern Europe): 2.5 kg ai/ha; 3 applications / 8 d interval			
Calculated maximum initial residues in feed [mg/kg feed]	7.90 (based on residue trials data)	62.5 (based on mean RUD of 25.0)	6.75 (based on mean RUD of 2.7)
FIR/bw	1.18	0.76	1.04
MAF (multiple application factor)	na	1.12	na
f_{twa}[2]	0.44	0.44	na
AV (avoidance factor)	na	1	na
PT (proportion of food obtained in treated area i.e. 60%)	na	0.6	na
PD (proportion of food type in diet i.e. 100 %)	na	1	na
ETE [mg/kg bw/day]	4.1	14.0	7.02
TER_{lt}[3]	**19.0**	**5.6**	**11.1**
Refined Risk Assessment required	**No**	**No**	**No**
Strawberries (Southern Europe): 1.25 kg ai/ha; 3 applications / 7 d interval			
Calculated maximum initial residues in feed [mg/kg feed]	7.90 (based on residue trials data)	31.3 (based on mean RUD of 25.0)	3.38 (based on mean RUD of 2.7)
FIR/bw	1.18	0.76	1.04
MAF (multiple application factor)	na	1.16	na
f_{twa}[2]	0.44	0.44	na
AV (avoidance factor)	na	1	na
PT (proportion of food obtained in treated area i.e. 60%)	na	0.6	na
PD (proportion of food type in diet i.e. 100 %)	na	1	na
ETE [mg/kg bw/day]	4.1	7.3	3.51
TER_{lt}[3]	**19.0**	**10.7**	**22.3**
Refined Risk Assessment required	**No**	**No**	**No**

[1] see Table B.9.1.4-3

[2] time weighed average residues (based on an averaging time of 7 days, the minimum spray interval and a mean DT50 value of 2.47 days, as determined on grass (Barfknecht 2003))

[3] the risk is considered acceptable, if the TER-value is > 5

B.9.1.7 Effects of secondary poisoning

In accordance with current guidance (Birds and Mammals Guidance Document (SANCO/4145/2000-Final September 2002) the bioaccumulation potential to birds from secondary poisoning was re-assessed. The assumptions made regarding the amount of fresh intake per day and hence the food intake factors for the generic indicator species have altered. However, there is no impact on the outcome of the original assessment i.e. no risk from secondary poisoning via earthworms or fish. Appropriate changes to food intake factors, endpoints and subsequent refined risk assessments are presented below for your convenience.

Pesticides with a high bioaccumulation potential could theoretically bear a risk of secondary poisoning for birds if contaminated prey like fish or earthworms are taken up. The log P_{ow} for tolylfluanid is 3.90, therefore a risk assessment for a generic earthworm eating bird and a generic fish eating bird is performed to evaluate the risk of secondary poisoning from the use of tolylfluanid.

Table B.9.1.7-1. Assumptions for the assessment of risks from secondary poisoning to birds.

Generic bird species	Body weight (bw)	Feed	Food intake [g wet weight per day]	Food intake factor
earthworm-eating bird	100 g	earth-worms	113	1.1
fish-eating bird	1000 g	fish	206	0.21

B.9.1.7.1 Risk for earthworm eating birds

For a worst case risk assessment from secondary poisoning of earthworm eating birds an estimated BCF for earthworms is calculated according to Jager (1998) with the following equation: $BCF = (0.84 + 0.01 \times K_{OW}) / (f_{OC} \times K_{OC})$. The BCF is based on earthworm fresh weight and soil dry weight. K_{OW} represents the octanol-water partition coefficient: for tolylfluanid this value is 8,000 (log P_{OW} = 3.90). "f_{OC}" represents the organic carbon content of the soil. A value of 0.02 is used in the calculations. K_{OC} is the organic carbon adsorption coefficient: for tolylfluanid this value is 2,220 mL/g (Sommer, 2000).

The estimated residues in earthworms are calculated as follows: $PEC_{worm} = PEC_{soil}(TWA) \times BCF$. The daily dietary dose is calculated by multiplying the PEC_{worm} with 1.1 (food intake factor for earthworm eating birds, see Table B.9.1.7-1). The daily dietary dose for birds is compared to the bird long term NOEC and the risk is considered to be acceptable, if the TER_{lt} value is > 5. In this case, for the PEC_{worm} calculations, not the $PEC_{soil}(TWA)$ but even the maximum initial residues of tolylfluanid after the last application are used. Even with these unrealistic worst case assumptions, the TER values are clearly above the Annex VI - trigger of 5, indicating no risk from secondary poisoning for earthworm eating birds.

Table B.9.1.7-2. Risk from secondary poisoning for earthworm eating birds calculated with the <u>maximum exposure</u> of earthworms under worst case assumptions.

Toxicological endpoint: Bobwhite quail, reproduction **NOEC (daily dietary dose): 78.1 mg ai/kg bw/day** *)	
Apples / Pears (Northern Europe): 1.125 kg ai/ha; 7 applications / 7 d interval	
PEC_{soil} [1] [mg ai/kg d.wt.s.]	0.426
Estimated BCF[2]	1.821
PEC_{worm} [3] [mg ai/kg]	0.776
Intake factor[4]	1.1
Maximum daily residue intake[5] [mg ai/kg bw]	0.862
TER_{lt} [7]	**90.6**
Refined Risk Assessment required [6]	**No**
Apples / Pears (Southern Europe): 1.5 kg ai/ha; 3 applications / 7 d interval	
PEC_{soil} [1] [mg ai/kg d.wt.s.]	0.644
Estimated BCF[2]	1.821
PEC_{worm} [3] [mg ai/kg]	1.172
Intake factor[4]	1.1
Maximum daily residue intake[5] [mg ai/kg bw]	1.301
TER_{lt} [7]	**60.0**
Refined Risk Assessment required [6]	**No**
Grapes (Northern Europe): 1.8 kg ai/ha; 8 applications / 10 d interval	
PEC_{soil} [1] [mg ai/kg d.wt.s.]	0.294
Estimated BCF[2]	1.821
PEC_{worm} [3] [mg ai/kg]	0.534
Intake factor[4]	1.1
Maximum daily residue intake[5] [mg ai/kg bw]	0.593
TER_{lt} [7]	**132**
Refined Risk Assessment required [6]	**No**
Grapes (Southern Europe): 2.0 kg ai/ha; 3 applications / 8 d interval	
PEC_{soil} [1] [mg ai/kg d.wt.s.]	0.531
Estimated BCF[2]	1.821
PEC_{worm} [3] [mg ai/kg]	0.967
Intake factor[4]	1.1
Maximum daily residue intake[5] [mg ai/kg bw]	1.07
TER_{lt} [7]	**72.7**
Refined Risk Assessment required [6]	**No**

*) see Long-term toxicity evaluation
[1] maximum PEC_{soil} after the last application.
[2] BCF calculated as described above
[3] 'PEC_{soil}' × 'BCF', see above
[4] Intake factor according to Table B.9.1.7-1
[5] TER for a long term time scale: NOEC (daily dietary dose) / maximum daily residue intake
[6] the risk is considered acceptable, if the TER-value is >5

Table to be continued

Table B.9.1.7-2 continued

Toxicological endpoint: Bobwhite quail, reproduction **NOEC (daily dietary dose): 78.1 mg ai/kg bw/day** *)	
Strawberries (Northern Europe): 2.5 kg ai/ha; 3 applications / 8 d interval	
PEC_{soil}[1] [mg ai/kg d.wt.s.]	1.601
Estimated BCF[2]	1.821
PEC_{worm}[3] [mg ai/kg]	2.92
Intake factor[4]	1.1
Maximum daily residue intake[5] [mg ai/kg bw]	3.24
TER_{lt}[7]	**24.1**
Refined Risk Assessment required [6]	**No**
Strawberries (Southern Europe): 1.25 kg ai/ha; 3 applications / 7 d interval	
PEC_{soil}[1] [mg ai/kg d.wt.s.]	1.066
Estimated BCF[2]	1.821
PEC_{worm}[3] [mg ai/kg]	1.94
Intake factor[4]	1.1
Maximum daily residue intake[5] [mg ai/kg bw]	2.15
TER_{lt}[7]	**36.2**
Refined Risk Assessment required [6]	**No**

*) and [1-6] Explanations see above.

Consideration of effects posed by metabolites

Tolylfluanid degrades in the soil very rapidly to DMST (the only major metabolite in soil), which is more hydrophilic (log P_{OW} = 1.99) than the parent compound (log P_{OW} = 3.90). Thus, the bioaccumulation potential of DMST in earthworms is lower than that of the ai. Additionally, the maximum residue values of DMST in soil are also lower than those of tolylfluanid. Therefore, a risk of secondary poisoning of birds by DMST via earthworms is not to be expected.

B.9.1.7.2 Risk for fish eating birds

Tolylfluanid is unstable in water (dissipation time in the water phase of a water-sediment study: DT_{50} 2.7 hours; Scholz (1997). Therefore, an exposure of fish to tolylfluanid is to be expected only for a very short time. Since the depuration measured in the fish-BCF study is very fast (whole fish clearance time: $t_{½}$ 0.38 days), bioaccumulation of tolylfluanid is not expected. Nevertheless, a risk assessment has been performed.

For a worst case risk assessment from secondary poisoning of fish eating birds, the steady state BCF of 74 for the whole fish, based on TRR of a flow-through study with bluegill sunfish is used. The estimated residues in fish (PEC_{fish}) are usually calculated as follows: $PEC_{water}(TWA) \times BCF$. Nevertheless, not the $PEC_{water}(TWA)$, but the maximum initial concentrations of tolylfluanid are used in this case for the PEC_{fish} calculations. The daily dietary dose for birds is calculated by multiplying the PEC_{fish} with 0.21 (food intake factor for fish eating birds. The daily dietary dose is compared to the bird long term NOEC (78.1 mg ai/kg bw/day) and the risk is considered to be acceptable if the TER_{lt} value is > 5. Even with these unrealistic worst case assumptions, the TER values are clear above the Annex VI - trigger of 5, indicating no risk from secondary poisoning for fish eating birds.

Table B.9.1.7-3. Risk from secondary poisoning for fish eating birds calculated with the maximum exposure of fish under worst case assumptions.

Toxicological endpoint: Bobwhite quail, reproduction **NOEC (daily dietary dose): 78.1 mg ai/kg bw/day** *)	
Apples / Pears (Northern Europe): 1.125 kg ai/ha; 7 applications / 7 d interval (reduced buffer zone scenario according to table 10.2/02a)	
PEC_{water} [1] [mg ai/L]	0.0442
BCF [2]	74
PEC_{fish} [3] [mg ai/kg]	3.27
Intake factor [4]	0.21
Maximum daily residue intake [5] [mg ai/kg bw]	0.69
TER_{lt} [6]	**114**
Refined Risk Assessment required [7]	**No**
Apples / Pears (Northern Europe): 1.125 kg ai/ha; 7 applications / 7 d interval	
PEC_{water} [1] [mg ai/L]	0.0747
BCF [2]	74
PEC_{fish} [3] [mg ai/kg]	5.53
Intake factor [4]	0.21
Maximum daily residue intake [5] [mg ai/kg bw]	1.16
TER_{lt} [6]	**67**
Refined Risk Assessment required [7]	**No**
Apples / Pears (Southern Europe): 1.5 kg ai/ha; 3 applications / 7 d interval	
PEC_{water} [1] [mg ai/L]	0.0421
BCF [2]	74
PEC_{fish} [3] [mg ai/kg]	3.12
Intake factor [4]	0.21
Maximum daily residue intake [5] [mg ai/kg bw]	0.65
TER_{lt} [6]	**119**
Refined Risk Assessment required [7]	**No**

*) see Long-term toxicity evaluation
[1] maximum PEC_{water}
[2] BCF (whole fish, see above)
[3] 'PEC_{water}' × 'BCF', see above
[4] Intake factor according to Table B.9.1.7-1
[5] 'PEC_{fish}' × 'intake factor'
[6] TER for a long term time scale: NOEC (daily dietary dose) / maximum daily residue intake
[7] the risk is considered acceptable, if the TER-value is >5

Table to be continued

Table B.9.1.7-3 continued

Toxicological endpoint: Bobwhite quail, reproduction **NOEC (daily dietary dose): 78.1 mg ai/kg bw/day** *)	
Grapes (Northern Europe): 1.8 kg ai/ha; 8 applications / 10 d interval	
PEC_{water} [1] [mg ai/L]	0.0216
BCF[2]	74
PEC_{fish} [3] [mg ai/kg]	1.60
Intake factor[4]	0.21
Maximum daily residue intake[5] [mg ai/kg bw]	0.34
TER_{lt} [6]	**233**
Refined Risk Assessment required [7]	**No**
Grapes (Southern Europe): 2.0 kg ai/ha; 3 applications / 8 d interval	
PEC_{water} [1] [mg ai/L]	0.0241
BCF[2]	74
PEC_{fish} [3] [mg ai/kg]	1.78
Intake factor[4]	0.21
Maximum daily residue intake[5] [mg ai/kg bw]	0.37
TER_{lt} [6]	**209**
Refined Risk Assessment required [7]	**No**
Strawberries (Northern Europe): 2.5 kg ai/ha; 3 applications / 8 d interval	
PEC_{water} [1] [mg ai/L]	0.00477
BCF[2]	74
PEC_{fish} [3] [mg ai/kg]	0.353
Intake factor[4]	0.21
Maximum daily residue intake[5] [mg ai/kg bw]	0.074
TER_{lt} [6]	**1,054**
Refined Risk Assessment required [7]	**No**
Strawberries (Southern Europe): 1.25 kg ai/ha; 3 applications / 7 d interval	
PEC_{water} [1] [mg ai/L]	0.00238
BCF[2]	74
PEC_{fish} [3] [mg ai/kg]	0.176
Intake factor[4]	0.21
Maximum daily residue intake[5] [mg ai/kg bw]	0.037
TER_{lt} [6]	**2,112**
Refined Risk Assessment required [7]	**No**

*) and [1-7] Explanations see above.

Consideration of effects posed by metabolites

Tolylfluanid degrades in water very rapidly to DMST (the only major metabolite in water), which is more hydrophilic (log P_{OW} = 1.99) than the parent compound (log P_{OW} = 3.90). Thus, the bioaccumulation potential of DMST in fish is lower than that of the ai. In addition, since the maximum PEC_{sw} values of DMST are in the same range as the maximum initial concentrations of tolylfluanid (see Table 10.6/02c), the TER values for DMST would be even lower and a risk of secondary poisoning of birds by DMST via fish is not to be expected.

B.9.3 Effects on terrestrial vertebrates other than birds

The toxicological endpoints for mammals used in the original dossier and in this revised risk assessment are presented in Table B.9.3-1.

Table B.9.3-1. Toxicological endpoints for mammals.

Organisms	Duration	Test-substance	Origin	Ecotoxicological endpoint	
Rat	Acute, oral	ai	Annex II, 5.2.1	LD_{50}	> 5,000 mg ai/kg bw
Rat	Subchronic 28 d, dietary	91% premix	Annex II, 5.8.2	NOEC	1,500 mg ai/kg diet
Rat	Chronic 434 d, dietary	ai	Annex II, 5.6.1	NOEC	100 mg ai/kg diet
Rat	Teratogenicity 20 d, oral	ai	Annex II, 5.6.2	NOEL	100 mg ai/kg bw/day
4-Hydromethyl-DMST (metabolite III)					
Rat	Acute, oral	metabolite	Annex II, 5.8.1	LD_{50}	> 5,000 mg ai/kg bw
2-Hydrophenyl-DMST (metabolite V)					
Rat	Acute, oral	metabolite	Annex II, 5.8.1	LD_{50}	> 5,000 mg ai/kg bw

B.9.3.1 Exposure of mammals to tolylfluanid WG 50

The main potential route of exposure for mammals to foliar applied agrochemicals is considered to be through the ingestion of residues on contaminated food items. Therefore in order to ensure a rigorous risk evaluation, a reasonable worst-case assessment has been conducted considering the maximum application rates, with the assumption that the principal route of exposure is through ingestion. The use pattern of tolylfluanid on which this revised risk assessment is based is shown in Table B.9.1.4-1.

In accordance with Directive 91/414/EEC, the Tier 1 assessment considers standardised reasonable worst case scenarios that involve indicator species chosen to represent the upper limit of exposure. The assessments presented in this appendix are based on, and are consistent with, the recommendations laid out in the "Guidance Document on Risk Assessment for Birds and Mammals Under Council Directive 91/414/EEC" (SANCO/4145/2000 final, September 2002).

For treatments such as Euparen M WG 50 that are foliar applied to grapes and apples, it is recommended that the standard indicator species used for acute and long-term exposure assessments is a small herbivorous mammal

(e.g. a vole), which has a high food intake relative to body weight. In-line with the guidance, the small herbivorous mammal used in this risk evaluation is assumed to weigh 25 g, with a daily food intake of 34.8 g fresh material/day, resulting in a food intake rate related to body weight of 1.39.

For leafy crops such as strawberries, the recommended indicator species is a medium sized herbivorous mammal (e.g. a hare), assumed to weigh 3000 g, with a daily food intake of 832 g fresh material/day, resulting in a food intake rate related to body weight of 0.28. In reality it is more likely that mammals will be attracted to the ripening fruit, rather than to the fibrous mature foliage of the strawberry plants. Weed and grass cover in the crop is also expected to be negligible as these plants are generally eliminated by mulching with plastic or straw, therefore there will be few non-crop food sources available to herbivorous mammals within the treated area. Nevertheless, in order to ensure a rigorous worst-case evaluation, risk assessments are presented for both herbivorous and frugivorous species feeding in strawberries, although in reality it is expected that exposure for herbivorous species is likely to be minimal.

Table B.9.3-2. Assumptions regarding the assessment of risks to mammals (based on recommendations detailed in the Birds and Mammals Guidance Document (SANCO/4145/2000 final, Sept 2002)).

Generic species[1]	Body weight (bw)	Feed	Food intake (FIR) [g fresh weight per day]	FIR/bw
small herbivorous mammal (e.g.: vole)	25 g	Grasses	34.8	1.39
medium herbivorous mammal (e.g.: hare)	3000 g	Leafy crops	832	0.28

[1] according to recommendations detailed in the Birds and Mammals Guidance Document (SANCO/4145/2000 final, Sept 2002)

With regard to predicted residues on food items following foliar spray applications, initial Tier 1 estimates are based on the worst-case values presented in Tables 4 and 7 of the SANCO guidance document. As recommended in the guidance, depending on the time scale of the exposure, either 90th percentile or arithmetic mean residue concentrations are used for acute or chronic exposures as appropriate.

In the Tier 2 risk assessment for long-term exposure, TER values have been refined using measured field residues on short grass (Barfknecht, 2003) and refined twa residue concentrations and MAF values. Consideration has also been given to the appropriate interception factors in orchards and vineyards based on the timing of applications. Additionally, in accordance with Appendix II of the SANCO/4145/2000 guidance, it is considered appropriate to use the residue values from the database presented by Fischer (1997). According to Luttik (2000) preference should be given to these values as the database is larger and more a reflection of the state of the art than the one used by Hoerger and Kenaga. In the long-term risk evaluation, averaging of residues is expected to occur over a period of days and so it is appropriate to use the 50th percentile for residues in food items. This results in a refined RUD of 25.0 mg/kg for leaves and leafy crops (Luttik 2000). Further details of these refinements are given in the relevant sections below.

B.9.3.2 Acute Risk Assessment - Tier 1

The Tier 1 risk assessment for acute exposure to mammals shows that all TER-values (TER_a) for herbivorous mammals are above the Annex VI -trigger of 10, even if the TER-values are calculated on the basis of maximum exposure after multiple applications. This confirms a high margin of safety for mammals from the use of tolylfluanid under practical conditions (see Table B.9.3-3). A refined risk assessment for the acute toxicity of tolylfluanid to mammals is therefore not required.

For acute exposure, as a reasonable worst-case, the 90th percentiles of the initial residue concentrations on potential food items are used. Calculations of the **E**stimated **T**heoretical **E**xposure (ETE) in terms of daily dose (mg/kg b.w.) are based on multiplication of the relative daily food intake (FIR/bw), by the **R**esidue per **U**nit **D**ose (RUD), the **M**ultiple **A**pplication **F**actor (MAF) and the application rate (kg a.i./ha). The TER_a is then calculated by comparing the ETE with the most relevant LD_{50} value (>5000 mg a.s./kg bw). The initial worst-case calculations tolylfluanid are presented in Table B.9.3-3 and are based on the default values presented in Tables 3 and 4 of the Birds and Mammals Guidance Document.

Table B.9.3-3. TER calculations based on <u>acute</u> toxicity (rat) (calculations based on recommendations detailed in the Birds and Mammals Guidance Document (SANCO/4145/2000 final, Sept 2002)).

Toxicological endpoint: Rat, acute		**LD_{50} > 5,000 mg ai/kg bw**
Generic mammal species[1]	small herbivore	medium herbivore
RUD (90%)	85[2]	87
Apples / Pears (Northern Europe): 1.125 kg ai/ha; 7 applications / 7 d interval		
Calculated maximum initial residues in feed [mg/kg feed]	95.6	-
FIR/bw	1.39	-
MAF (multiple application factor)	2.0	-
ETE [mg/kg bw/day]	265.8	-
TER_a [3]	**18.8**	**-**
1.1.1.6Refined Risk Assessment required	**No**	**na**
Apples / Pears (Southern Europe): 1.5 kg ai/ha; 3 applications / 7 d interval		
Calculated maximum initial residues in feed [mg/kg feed]	127.5	-
FIR/bw	1.39	-
MAF (multiple application factor)	1.7	-
ETE [mg/kg bw/day]	301.3	-
TER_a [3]	**16.6**	**-**
Refined Risk Assessment required	**No**	**na**

[1] see Table 9.3-2
[2] an interception factor of 0.4 is included in the RUD value
[3] the risk is considered acceptable, if the TER-value is >10

Table to be continued

Table B.9.3-3 continued

Toxicological endpoint: Rat, acute		**LD_{50} > 5,000 mg ai/kg bw**
Generic mammal species[1]	small herbivore	medium herbivore
RUD (90%)	[2]85	87
Grapes (Northern Europe): 1.8 kg ai/ha; 8 applications / 10 d interval		
Calculated maximum initial residues in feed [mg/kg feed]	153	-
FIR/bw	1.39	-
MAF (multiple application factor)	1.6	-
ETE [mg/kg bw/day]	340.3	-
TER_a [3]	**14.7**	**-**
Refined Risk Assessment required	**No**	**na**
Grapes (Southern Europe): 2.0 kg ai/ha; 3 applications / 8 d interval		
Calculated maximum initial residues in feed [mg/kg feed]	170	-
FIR/bw	1.39	-
MAF (multiple application factor)	1.7	-
ETE [mg/kg bw/day]	401.7	-
TER_a [3]	**12.4**	**-**
Refined Risk Assessment required	**No**	**na**
Strawberries (Northern Europe): 2.5 kg ai/ha; 3 applications / 8 d interval		
Calculated maximum initial residues in feed [mg/kg feed]	-	217.5
FIR/bw	-	0.28
MAF (multiple application factor)	-	1.7
ETE [mg/kg bw/day]	-	103.5
TER_a [3]	-	**48.3**
Refined Risk Assessment required	**na**	**No**

Strawberries (Southern Europe): 1.25 kg ai/ha; 3 applications / 7 d interval		
Calculated maximum initial residues in feed [mg/kg feed]	-	108.8
FIR/bw	-	0.28
MAF (multiple application factor)	-	1.7
ETE [mg/kg bw/day]	-	51.8
TER_a [3]	-	**96.5**
Refined Risk Assessment required	**na**	**No**

[1] see Table 9.3-2
[2] an interception factor of 0.4 is included in the RUD value
[3] the risk is considered acceptable, if the TER-value is >10

B.9.3.3 Short-term Risk Assessment

In line with current guidance a short-term assessment is not presented for mammals. This is because the distinction between short-term and long-term TERs for mammals is poorly defined according to the toxicity data input; therefore these assessments are combined into one long-term assessment; the resultant assessment addresses both short and long-term risk to mammals.

B.9.3.4 Long-term Risk Assessment - Tier 1

Due to the instability of tolylfluanid in the environment, a long-term exposure to wild mammals in the chronic rat study (434 days) is considered an excessive overestimate of the potential exposure under field conditions, given that a maximum to 8 treatments are applied, typically with a 7 to 10 day interval. Thus the 20-day NOEC from the teratogenicity study (test substance administration via gavage) is considered to be more relevant for use in the risk assessment than the rat two-generation study endpoint, obtained during a 434 day study. Hence an endpoint of 100 mg/kg bw/day has been used to calculate the long-term TER values.

The long-term exposure assessment aims at a time frame of a few weeks, therefore residue estimates are based on arithmetic means. In addition, multiple application factors are incorporated into the assessment and time-weighted average (twa) residues are used as these better reflect long-term exposure. As usual in a first tier assessment, mammals are assumed to feed on treated food items only. The relevant calculations for long-term mammalian exposure to formulations containing tolylfluanid are summarised in Table B.9.3-4. These initial Tier 1 calculations are based on the default values for all parameters presented in Tables 5 and 7 of the Birds and Mammals Guidance Document.

The worst-case Tier 1 TER_{lt} values for mammals presented in Table B.9.3-4 are all below the Annex VI -trigger of 5 with the exception of applications in strawberries at a rate of 1.25 kg ai/ha. A Tier 2 refinement with more realistic exposure scenarios is therefore required for all but one scenario.

Table B.9.3-4. TER calculations based on teratogenic toxicity (20 days-rat) (calculations based on recommendations detailed in the Birds and Mammals Guidance Document (SANCO/4145/2000 final Sept 2002)).

Toxicological endpoint: Rat, teratogenicity **NOEC (daily dietary dose) 100 mg ai/kg bw/day**		
Generic mammal species[1]	small herbivore	medium herbivore
RUD (50 %)	[2]46	40
Apples / Pears (Northern Europe): 1.125 kg ai/ha; 7 applications / 7 d interval		
Calculated maximum initial residues in feed [mg/kg feed]	51.8	-
FIR/bw	1.39	-
MAF (multiple application factor)	2.5	-
f_{twa}	0.53	-
ETE [mg/kg bw/day]	95.4	-
TER_{lt} [3]	**1.05**	**-**
Refined Risk Assessment required	**Yes**	**na**

[1] see Table 9.3-2
[2] an interception factor of 0.4 is included in the RUD value
[3] the risk is considered acceptable, if the TER-value is >5

Table to be continued

Toxicological endpoint: Rat, teratogenicity **NOEC (daily dietary dose) 100 mg ai/kg bw/day**		
Generic mammal species[1]	small herbivore	medium herbivore
RUD (50 %)	[2]46	40
Apples / Pears (Southern Europe): 1.5 kg ai/ha; 3 applications / 7 d interval		
Calculated maximum initial residues in feed [mg/kg feed]	69	-
FIR/bw	1.39	-
MAF (multiple application factor)	2.0	-
f_{twa}	0.53	-
ETE [mg/kg bw/day]	101.7	-
TER_{lt} [3]	**0.98**	**-**
Refined Risk Assessment required	**Yes**	**na**
Grapes (Northern Europe): 1.8 kg ai/ha; 8 applications / 10 d interval		
Calculated maximum initial residues in feed [mg/kg feed]	82.8	-
FIR/bw	1.39	-
MAF (multiple application factor)	2.0	-
f_{twa}	0.53	-
ETE [mg/kg bw/day]	122.0	-
TER_{lt} [3]	**0.82**	**-**
Refined Risk Assessment required	**Yes**	**na**
Grapes (Southern Europe): 2.0 kg ai/ha; 3 applications / 8 d interval		
Calculated maximum initial residues in feed [mg/kg feed]	92	-
FIR/bw	1.39	-
MAF (multiple application factor)	2.0	-
f_{twa}	0.53	-
ETE [mg/kg bw/day]	135.6	-
TER_{lt} [3]	**0.74**	**-**
Refined Risk Assessment required	**Yes**	**na**

[1] see Table B.9.3-2
[2] an interception factor of 0.4 is included in the RUD value
[3] the risk is considered acceptable, if the TER-value is >5

Table to be continued

Table B.9.3-4 continued

Toxicological endpoint: Rat, teratogenicity **NOEC (daily dietary dose) 100 mg ai/kg bw/day**		
Generic mammal species[1]	small herbivore	medium herbivore
RUD (50 %)	[2]46	40
Strawberries (Northern Europe): 2.5 kg ai/ha; 3 applications / 8 d interval		
Calculated maximum initial residues in feed [mg/kg feed]	-	100
FIR/bw	-	0.28
MAF (multiple application factor)	-	2.0
f_{twa}	-	0.53
ETE [mg/kg bw/day]	-	29.7
TER_{lt} [3]	-	**3.37**
Refined Risk Assessment required	**na**	**Yes**
Strawberries (Southern Europe): 1.25 kg ai/ha; 3 applications / 7 d interval		
Calculated maximum initial residues in feed [mg/kg feed]	-	50
FIR/bw	-	0.28
MAF (multiple application factor)	-	2.0
f_{twa}	-	0.53
ETE [mg/kg bw/day]	-	14.8
TER_{lt} [3]	-	**6.76**
Refined Risk Assessment required	**na**	**No**

[1] see Table B.9.3-2
[2] an interception factor of 0.4 is included in the RUD value
[3] the risk is considered acceptable, if the TER-value is >5

B.9.3.5 Long-term Risk Assessment - Tier 2

According to the Tier 1 TER-values calculated in Table 9.3-4 above, a refined risk assessment for long-term exposure to mammals is required for all scenarios with the exception of strawberries at the lower application rate of 1.25 kg ai/ha.

The long-term TER values have been refined in-line with current guidance using measured residues on short grass (Barfknecht, 2003), refinement of the twa and MAF values and reconsideration of the appropriate interception factors in orchards and vineyards based on the timing of applications. The details of these refinements are presented below:

Refinement of Mammalian Exposure in Orchards and Vineyards

In the refined risk assessment for orchards and vineyards, the dietary intake of small herbivores feeding predominately on grass is considered. In order to refine this exposure, residues data have been generated in field trials in which Tolylfluanid WG 50 was applied on three grass plots (10 x 1.5 m) at an application rate of 1.125 kg product/ha (corresponding to 562.5 g ai/ha). The three grass plots were treated at different times to catch different climatic conditions (Barfknecht, 2003). From each plot a 100 g sample of grass was harvested on days 0, 1, 2, 4, 7, 10 and 14 after treatment and analysed for residues of tolylfluanid and its metabolite DMST. From

these data, the mean measured DT_{50} value for tolylfluanid on grass was determined as 2.47 days and the initial residue concentration was calculated as 19.62 mg ai/kg wet grass, based on an application rate of 562.5 g ai/ha. For the purposes of the risk assessment, the residue concentration is normalised to 34.88 mg ai/kg wet grass for an application rate of 1 kg/ha (this is the value used to calculate the refined TER_{lt} values presented in Table 10.3/05).

Since the toxicity value used in this assessment is based on a 20-day rat teratogenicity study and the measured half-life of tolylfluanid in plant material is very short (grass, mean value of 2.47 days), a more realistic longer term exposure is calculated using the 7 day -twa residues rather than the initial residue concentrations (according to the guidance in the case of repeated applications, the averaging time should not be longer than the spray interval; the shortest interval for tolylfluanid being 7 days). For tolylfluanid the twa values have been refined based on the calculation presented below, using a 7-day averaging time and the mean measured DT_{50} in grass (2.47 days):

$F_{twa} = (1-e^{-kt})/kt$

k: ln2/DT50 (velocity constant)

t: averaging time

Similarly the MAF has been recalculated using the following equation and assuming first-order kinetics:

$MAF = (1-e^{-nki})/(1-e^{-ki})$

k: ln2/DT50 (velocity constant)

n: Number of applications

i: Interval between applications (days)

For fungicides such as tolylfluanid applied in tall-growing crops such as orchards and vineyards it is assumed that a fraction of 60% of the applied spray reaches the ground. This is a default value which is applied to crop stages without leaves (FOCUS 2000). Following application in later crop stages, the interception is higher and accordingly the deposition is lower; for refinement the values given in FOCUS (2000) have been used. For early applications in orchards at a rate of 1.125 kg/ha, 50 % crop interception is assumed. Whereas in orchards and vineyards for late applications (once the foliage has developed) at rates of 1.5 to 2.0 kg/ha, 70 % crop interception is assumed. In accordance with the guidelines these interception values are included in the calculation of the TER values presented in Table 10.3/05.

Refinement of Mammalian Exposure in Strawberry Crops

In the refined risk assessment for strawberry crops, the dietary intake of medium herbivores (e.g. hares) feeding on leafy vegetation is considered. In general hares have a large home range (dependent on season) and feeding habitats are influenced by food choice and safety from predators (Wolfe & Hayden 1996). Their diet consists mainly of grasses (in winter), herbs (in summer) and arable crops e.g. cereals at early growth stages (Gurney et al. 1998). It can therefore be concluded that leafy foliage (e.g. strawberry leaves) are unlikely to be a preferred food source. Additionally, in strawberries a short grass scenario is not relevant as weed and grass cover within the treated area will be minimised by mulching. Although, mammals feeding in strawberry crops are unlikely to consume treated leaves, a risk assessment is presented in Table 10.3/05 to cover this unlikely scenario, adding confidence to the overall conclusion of low risk. In the long-term risk evaluation, averaging of residues is expected to occur over a period of days and so it is appropriate to use the 50^{th} percentile for residues in food items. Therefore a refined RUD of 25.0 mg/kg (Luttik, 2000) is used for residues on leaves and the f_{twa} and MAF have been refined using the same DT_{50} value and spray interval as for the orchard and vineyard exposures (see above). The refined TER values are presented in Table 10.3/05.

Mammalian exposure to tolylfluanid residues in strawberries is possible through feeding on the ripening fruits, since the diet of e.g. the fat dormouse (*Glis glis*), includes strawberries (Storch 1978). Fruit residue calculations are based on the highest measured initial residues in strawberry fruit on day 0 after the last application in field trials (7.9 mg/kg fresh weight fruit (three applications of 2.5 kg ai/ha), see Annex II, chapter 6: report No. 8253-87). Due to the direct application in strawberries, a crop interception factor is not applicable in this case. A MAF is also not applicable on the fruit as the measured residue already accounts for multiple applications. The twa for fruit residue concentrations has been refined based on a 7-day averaging time and the measured DT_{50} value on grass.

Table B.9.3-5. TER calculations based on teratogenic toxicity (20 days-rat) and more realistic exposure of tolylfluanid after the last application.

Toxicological endpoint: Rat, teratogenicity **NOEC (daily dietary dose): 100 mg ai/kg bw/day**	
Generic mammal species[1]	small herbivore
Measured initial residues in feed (normalised for an application rate of 1 kg/ha) [mg/kg feed]	**grass** 34.88
Apples / Pears (Northern Europe): 1.125 kg ai/ha; 7 applications / 7 d interval	
Spray Interception Factor (FOCUS, 2000)	50% (early application)
Calculated maximum initial residues in feed [mg/kg feed]	19.62
MAF (multiple application factor)	1.16
f_{twa}	0.44
FIR/bw	1.39
ETE [mg/kg bw/day]	13.92
TER_{lt} [2]	**7.2**
Refined Risk Assessment required	**No**
1.1.2 Apples / Pears (Southern Europe): 1.5 kg ai/ha; 3 applications / 7 d interval	
Spray Interception Factor (FOCUS, 2000)	70% (late application)
Calculated maximum initial residues in feed [mg/kg feed]	15.69
MAF (multiple application factor)	1.16
f_{twa}	0.44
FIR/bw	1.39
ETE [mg/kg bw/day]	11.13
TER_{lt} [2]	**9.0**
Refined Risk Assessment required	**No**

[1] see Table B.9.3-2
[2] the risk is considered acceptable, if the TER-value is >5

Table to be continued

Table B.9.3-5 continued

Toxicological endpoint: Rat, teratogenicity **NOEC (daily dietary dose): 100 mg ai/kg bw/day**		
Generic mammal species[1]	small herbivore	
Measured initial residues in feed (normalised for an application rate of 1 kg/ha) [mg/kg feed]	**grass** 34.88	
Grapes (Northern Europe): 1.8 kg ai/ha; 8 applications / 10 d interval		
Spray Interception Factor (FOCUS, 2000)	70% (late application)	
Calculated maximum initial residues in feed [mg/kg feed]	18.83	
MAF (multiple application factor)	1.06	
f_{twa}	0.44	
FIR/bw	1.39	
ETE [mg/kg bw/day]	12.21	
TER_{lt} [2]	**8.2**	
Refined Risk Assessment required	**No**	
Grapes (Southern Europe): 2.0 kg ai/ha; 3 applications / 8 d interval		
Spray Interception Factor (FOCUS, 2000)	70% (late application)	
Calculated maximum initial residues in feed [mg/kg feed]	20.92	
MAF (multiple application factor)	1.12	
f_{twa}	0.44	
FIR/bw	1.39	
ETE [mg/kg bw/day]	14.33	
TER_{lt} [2]	**7.0**	
Refined Risk Assessment required	**No**	
Toxicological endpoint: Rat, teratogenicity **NOEC (daily dietary dose): 100 mg ai/kg bw/day**		
Generic mammal species[1]	medium herbivore	
Food type	**strawberry fruits**	**leaves**
Strawberries (Northern Europe): 2.5 kg ai/ha; 3 applications / 8 d interval		
Calculated maximum initial residues in feed [mg/kg feed]	7.90 (residue trials data)	62.5 (based on a theoretical RUD of 25 mg/kg)
MAF (multiple application factor)	na	1.12
f_{twa}	0.44	0.44
FIR/bw	0.28	0.28
ETE [mg/kg bw/day]	0.97	8.62
TER_{lt} [2]	**103.1**	**11.6**
Refined Risk Assessment required	**No**	**No**

[1] see Table B.9.3-5
[2] the risk is considered acceptable, if the TER-value is >5

Based on this Tier 2 evaluation and considering the more realistic exposure scenarios presented in Table B.9.3-5, all tier 2 TER_{lt} values are above the Annex VI - trigger of 5, indicating no unacceptable risk long-term risk to mammals.

Considerations of effects posed by metabolites

Mammals may be exposed to metabolites of tolylfluanid by the consumption of treated food or drinking water. All major metabolites in water and plants (with two exceptions, see below), are also found in the metabolism studies with rats. Thus, the potential effects of these metabolites are covered by the results of mammalian studies with the active ingredient and are considered to be addressed in the risk assessments above.

The metabolites 4-hydroxymethyl-DMST and 2-hydroxyphenyl-DMST and their glucosides are found in relevant concentrations only in grapes. Since the glucosides will be transformed to 4-hydroxymethyl-DMST and 2-hydroxyphenyl-DMST, respectively, in the stomach of mammals which may feed on grapes, studies on the acute toxicity for rats are performed with these metabolites. The results of these studies (LD_{50} > 5,000 mg/kg bw for each of the metabolites show, that the metabolites are not more toxic than the active ingredient.

Since the possible residues of these metabolites in food or drinking water are much lower than the residues for the ai in the risk assessment, TER values calculated for these metabolites would be even higher than those for the ai. Therefore, an unacceptable risk of poisoning of mammals with 2-hydroxyphenyl-DMST and 4-hydroxymethyl-DMST and their glucosides can be excluded.

B.9.3.6 Mammals – effects of secondary poisoning

In accordance with current guidance (Birds and Mammals Guidance Document (SANCO/4145/2000-Final, September 2002) the bioaccumulation potential to mammals from secondary poisoning has been re-assessed. The assumptions made regarding the amount of fresh intake per day and hence the food intake factors for the generic indicator species have altered. However, there is no impact on the outcome of the original assessment i.e. no risk from secondary poisoning via earthworms or fish. Appropriate changes to food intake factors, endpoints and subsequent refined risk assessments are presented below.

Pesticides with a high bioaccumulation potential could theoretically bear a risk of secondary poisoning for mammals, if contaminated prey like fish or earthworms are taken up. The log P_{ow} of tolylfluanid is 3.90, therefore a risk assessment for a generic earthworm eating mammal and a generic fish eating mammal is performed to evaluate the risk of secondary poisoning from the use of tolylfluanid.

Table B.9.3-6. Assumptions for the assessment of risks from secondary poisoning to mammals.

Generic mammal species	Body weight (bw)	Feed	Food intake [g wet weight per day]	Food intake factor
earthworm-eating mammal	10 g	earth-worms	14	1.4
fish-eating mammal	3000 g	fish	390	0.13

B.9.3.6.1 Risk assessment for earthworm eating mammals

For a worst case risk assessment from secondary poisoning of earthworm eating mammals an estimated BCF for earthworms is calculated according to Jager (1998) with the following equation: $BCF = (0.84 + 0.01 \times K_{OW}) / (f_{OC} \times K_{OC})$. The BCF is based on earthworm fresh weight and soil dry weight. K_{OW} represents the octanol-water partition coefficient: for tolylfluanid this value is 8,000 (log P_{OW} = 3.90). "f_{OC}" represents the organic carbon content of the soil. A value of 0.02 is used in the calculations. K_{OC} is the organic carbon adsorption coefficient: for tolylfluanid this value is 2,220 mL/g (Sommer, 2000).

The estimated residues in earthworms are calculated as follows: $PEC_{worm} = PEC_{soil}(TWA) \times BCF$. The daily dietary dose is calculated by multiplying the PEC_{worm} with 1.4 (food intake factor for earthworm eating mammals, see Table B.9.3-6). The daily dietary dose for mammals is compared to the relevant mammal long term NOEC (i.e. 100 mg/kg bw/day, see B.9.3.4) and the risk is considered to be acceptable, if the TER_{lt} value is > 5. In this case, for the PEC_{worm} calculations, not the $PEC_{soil}(TWA)$ but even the maximum initial residues of tolylfluanid after the last application are used. Even with these worst case assumptions, the TER values are clearly above the Annex VI - trigger of 5, indicating no unacceptable risk from secondary poisoning for earthworm eating mammals.

Table B.9.3-7. Risk from secondary poisoning for earthworm eating mammals calculated with the maximum exposure of residues in earthworms under worst case assumptions.

Toxicological endpoint: Rat, teratogenicity **NOEC (daily dietary dose): 100 mg ai/kg bw/day** *)	
Apples / Pears (Northern Europe): 1.125 kg ai/ha; 7 applications / 7 d interval	
PEC_{soil}[1] [mg ai/kg d.wt.s.]	0.426
Estimated BCF[2]	1.821
PEC_{worm}[3] [mg ai/kg]	0.776
Intake factor[4]	1.4
Maximum daily residue intake[5] [mg ai/kg bw]	1.086
TER_{lt}[7]	**92.1**
Refined Risk Assessment required [6]	**No**
Apples / Pears (Southern Europe): 1.5 kg ai/ha; 3 applications / 7 d interval	
PEC_{soil}[1] [mg ai/kg d.wt.s.]	0.644
Estimated BCF[2]	1.821
PEC_{worm}[3] [mg ai/kg]	1.172
Intake factor[4]	1.4
Maximum daily residue intake[5] [mg ai/kg bw]	1.640
TER_{lt}[7]	**61.0**
Refined Risk Assessment required [6]	**No**
Grapes (Northern Europe): 1.8 kg ai/ha; 8 applications / 10 d interval	
PEC_{soil}[1] [mg ai/kg d.wt.s.]	0.294
Estimated BCF[2]	1.821
PEC_{worm}[3] [mg ai/kg]	0.535
Intake factor[4]	1.4
Maximum daily residue intake[5] [mg ai/kg bw]	0.749
TER_{lt}[7]	**133.5**
Refined Risk Assessment required [6]	**No**
Grapes (Southern Europe): 2.0 kg ai/ha; 3 applications / 8 d interval	
PEC_{soil}[1] [mg ai/kg d.wt.s.]	0.531
Estimated BCF[2]	1.821
PEC_{worm}[3] [mg ai/kg]	0.967
Intake factor[4]	1.4
Maximum daily residue intake[5] [mg ai/kg bw]	1.354
TER_{lt}[7]	**73.9**
Refined Risk Assessment required [6]	**No**

*) see chapter B.9.3.4: Long-term toxicity
[1] maximum PEC_{soil} after the last application
[2] BCF calculated as described above
[3] 'PEC_{soil}' × 'BCF', see above
[4] Intake factor according to Table B.9.3-6
[5] TER for a long term time scale: NOEC (daily dietary dose) / maximum daily residue intake
[6] the risk is considered acceptable, if the TER-value is >5

Table to be continued

Table B.9.3-7 continued

Toxicological endpoint: Rat, teratogenicity **NOEC (daily dietary dose): 100 mg ai/kg bw/day** *)	
Strawberries (Northern Europe): 2.5 kg ai/ha; 3 applications / 8 d interval	
PEC_{soil}[1] [mg ai/kg d.wt.s.]	1.601
Estimated BCF[2]	1.821
PEC_{worm}[3] [mg ai/kg]	2.92
Intake factor[4]	1.4
Maximum daily residue intake[5] [mg ai/kg bw]	4.09
TER_{lt}[7]	**24.4**
Refined Risk Assessment required [6]	**No**
Strawberries (Southern Europe): 1.25 kg ai/ha; 3 applications / 7 d interval	
PEC_{soil}[1] [mg ai/kg d.wt.s.]	1.066
Estimated BCF[2]	1.821
PEC_{worm}[3] [mg ai/kg]	1.94
Intake factor[4]	1.4
Maximum daily residue intake[5] [mg ai/kg bw]	2.72
TER_{lt}[7]	**36.8**
Refined Risk Assessment required [6]	**No**

*) and [1-6] Explanations see above.

Consideration of effects posed by metabolites

Tolylfluanid degrades in the soil very rapidly to DMST (the only major metabolite in soil), which is more hydrophilic (log P_{OW} = 1.99) than the parent compound (log P_{OW} = 3.90). Thus, the bioaccumulation potential of DMST in earthworms is lower than that of the active ingredient. Additionally, the maximum residue values of DMST in soil are also lower than those of tolylfluanid. Therefore, a risk of secondary poisoning of mammals by DMST via earthworms is even lower than for the active ingredient.

B.9.3.6.2 Risk assessment for fish eating mammals

Tolylfluanid is unstable in water (dissipation time in the water phase of a water-sediment study: DT_{50} 2.7 hours; Scholz (1997). Therefore, an exposure of fish to tolylfluanid is given only for a very short time. Since the depuration measured in the fish-BCF study is very fast (whole fish clearance time: $t_{½}$ 0.38 days), a bioaccumulation of tolylfluanid cannot be expected. Despite these facts, a risk assessment for secondary poisoning via fish is performed in the following.

For a worst case risk assessment from secondary poisoning of fish eating mammals, the steady state BCF of 74 for the whole fish, based on TRR of a flow-through study with bluegill sunfish is used. The estimated residues in fish (PEC_{fish}) are usually calculated as follows: PEC_{water}(TWA) × BCF. Nevertheless, not the PEC_{water}(TWA), but the maximum initial concentrations of tolylfluanid are used in this case for the PEC_{fish} calculations. The daily dietary dose for mammals is calculated by multiplying the PEC_{fish} with 0.13 (food intake factor for fish eating mammals). The daily dietary dose for mammals is compared to the relevant mammal long term NOEC (i.e. 100 mg/kg bw/day) and the risk is considered to be acceptable, if the TER_{lt} value is > 5. Even with these

worst-case assumptions, the TER values are clearly above the Annex VI - trigger of 5, indicating no unacceptable risk from secondary poisoning for fish eating mammals.

Table B.9.3-8. Risk from secondary poisoning for fish eating mammals calculated with the maximum exposure of residues in fish under worst case assumptions.

Toxicological endpoint: Rat, teratogenicity **NOAEL (daily dietary dose): 100 mg ai/kg bw/day** *)	
Apples / Pears (Northern Europe): 1.125 kg ai/ha; 7 applications / 7 d interval (reduced buffer zone scenario according to table 10.2/02a)	
PEC_{water} [1] [mg ai/L]	0.0442
BCF [2]	74
PEC_{fish} [3] [mg ai/kg]	3.27
Intake factor [4]	0.13
Maximum daily residue intake [5] [mg ai/kg bw]	0.43
TER_{lt} [6]	**232.6**
Refined Risk Assessment required [7]	**No**
Apples / Pears (Northern Europe): 1.125 kg ai/ha; 7 applications / 7 d interval	
PEC_{water} [1] [mg ai/L]	0.0747
BCF [2]	74
PEC_{fish} [3] [mg ai/kg]	5.53
Intake factor [4]	0.13
Maximum daily residue intake [5] [mg ai/kg bw]	0.72
TER_{lt} [6]	**138.9**
Refined Risk Assessment required [7]	**No**
Apples / Pears (Southern Europe): 1.5 kg ai/ha; 3 applications / 7 d interval	
PEC_{water} [1] [mg ai/L]	0.0421
BCF [2]	74
PEC_{fish} [3] [mg ai/kg]	3.12
Intake factor [4]	0.13
Maximum daily residue intake [5] [mg ai/kg bw]	0.41
TER_{lt} [6]	**243.9**
Refined Risk Assessment required [7]	**No**
Grapes (Northern Europe): 1.8 kg ai/ha; 8 applications / 10 d interval	
PEC_{water} [1] [mg ai/L]	0.0216
BCF [2]	74
PEC_{fish} [3] [mg ai/kg]	1.60
Intake factor [4]	0.13
Maximum daily residue intake [5] [mg ai/kg bw]	0.21
TER_{lt} [6]	**476.2**
Refined Risk Assessment required [7]	**No**

*) see chapter B.9.3.4: Long-term toxicity
[1] maximum PEC_{water}
[2] BCF (whole fish, see above)
[3] 'PEC_{water}' × 'BCF', see above
[4] Intake factor according to Table B.9.3-6
[5] 'PEC_{fish}' × 'intake factor'
[6] TER for a long term time scale: NOEC (daily dietary dose) / maximum daily residue intake
[7] the risk is considered acceptable, if the TER-value is >5

Table to be continued

Table B.9.3-8 continued

Toxicological endpoint: Rat, teratogenicity **NOEC (daily dietary dose): 100 mg ai/kg bw/day** *)	
Grapes (Southern Europe): 2.0 kg ai/ha; 3 applications / 8 d interval	
PEC_{water} [1] [mg ai/L]	0.0241
BCF[2]	74
PEC_{fish} [3] [mg ai/kg]	1.78
Intake factor[4]	0.13
Maximum daily residue intake[5] [mg ai/kg bw]	0.23
TER_{lt} [6]	**434.8**
Refined Risk Assessment required [7]	**No**
Strawberries (Northern Europe): 2.5 kg ai/ha; 3 applications / 8 d interval	
PEC_{water} [1] [mg ai/L]	0.00477
BCF[2]	74
PEC_{fish} [3] [mg ai/kg]	0.353
Intake factor[4]	0.13
Maximum daily residue intake[5] [mg ai/kg bw]	0.046
TER_{lt} [6]	**2173.9**
Refined Risk Assessment required [7]	**No**
Strawberries (Southern Europe): 1.25 kg ai/ha; 3 applications / 7 d interval	
PEC_{water} [1] [mg ai/L]	0.00238
BCF[2]	74
PEC_{fish} [3] [mg ai/kg]	0.176
Intake factor[4]	0.13
Maximum daily residue intake[5] [mg ai/kg bw]	0.023
TER_{lt} [6]	**4347.8**
Refined Risk Assessment required [7]	**No**

*) and [1-7] Explanations see above.

Consideration of effects posed by metabolites

Tolylfluanid degrades in water very rapidly to DMST (the only major metabolite in water), which is more hydrophilic (log P_{OW} = 1.99) than the parent compound (log P_{OW} = 3.90). Thus, the bioaccumulation potential of DMST in fish is lower than that of the active ingredient. In addition, since the maximum PEC_{sw} values of DMST are in the same range as the maximum initial concentrations of tolylfluanid, the TER values for DMST would be lower and a risk of secondary poisoning of mammals by DMST via fish is lower than for the active ingredient.

B.9.11 References relied on

Author (s)	Section reference number	Year	Title **Source** (where different from company) **Company name, Report No., Date,** **GLP status** (where relevant), **published or not**	Data protect. claimed	Owner
Barfknecht, R.	B.9.1.4	2000	Tolylfluanid techn. ai.: Acute oral toxicity for bobwhite quail Bayer AG, ReportNo.: BAR/LD031 Date: 10.01.2000 GLP, Non Published	Yes	BAY
Barfknecht, R.	B.9.1.4.3	2003	Residues of Tolylfluanid on Grass After Spray Application of Euparen M WG 50. Bayer AG, ReportNo.: BAR/FS 012 Date: 02.06.2003 GLP, Non Published	Yes	BAY
Fischer, D.L. and Bowers, L.M.	B.9.3	1997	Summary of field measurements of pesticide concentrations in invertebrate prey of birds Publisher: SETAC, San Francisco, Year: 1997 Journal: SETAC 18th annual meeting Pages: 147-148 ff ReportNo.: MO-00-003803 Date: 20.11.1997 Non GLP, Published	No	
Grau, R.	B.9.1.4	1990	Subacute oral LC50 (5 day feeding study) of tolylfluanid techn. to bobwhite quail Bayer AG, ReportNo.: VB-014 Date: 17.01.1990 GLP, Non Published	Yes	BAY
Hoeeger, F.D. and Kenaga, E.E.	B.9.3	1972	Pesticide Residues on Plants: Correlation of Representative Data as a Basis for Estimation of Their Magnitude in the Environment Journal: Environmental Quality and Safety, p. 9-28, 1972. ReportNo.: MO-98-000358 Date: 01.01.1972 Non GLP, Published	No	
Jager, T.	B.9.1.7 B.9.3.6.1	1998	Mechanistic approach for estimating bioconcentration of organic chemicals in earthworms (Oligochaeta) SETAC Press Publisher: SETAC Press Journal: Environmental Toxicology and Chemistry, 17(1998) 2080. Report No.: Lit. 7868 Date: 16.03.1998 Non GLP, Published	No	
Luttik, R.	B.9.3 B.9.3.4	2000	Residues of plant protection products on food items for birds and mammals ReportNo.: FSM001/00 Date: 30.11.2000 Non GLP, Published	No	

Author (s)	**Section reference number**	**Year**	**Title** **Source** (where different from company) **Company name, Report No., Date, GLP status** (where relevant)**, published or not**	**Data protect. claimed**	**Owner**
Nagy, K.A.	B.9.3	1987	Field metabolic rate and food requirement scaling in mammals and birds Year: 1987 Journal: Ecological Monographs Pages: 111-128 ReportNo.: MO-99-018830 Date: 01.01.1987 Non GLP, Published	No	
Scholz, K.	B.9.1.7.1 B.9.3.6.2	1987b	Degradation of Tolylfluanid in the water-sediment-system Bayer AG, ReportNo.: PF2783 Date: 24.04.1987 Non GLP, Non Published	Yes	BAY
Anon.		2000	Working Document: Guidance document on risk assessment for birds and mammals under Council Directive 91/414 EEC.SANCO/4145/2000- final. Date: 25 September 2002.	No	
Anon.	B.9.3.4	2000	FOCUS 2000: FOCUS Groundwater Scenarios in the EU review of active substances. Report of the FOCUS Groundwater Scenarios Workgroup, EC Document reference SANCO/321/2000 rev. 2, 202 pp.	No	
Gurney J.E., Perrett, J., Crocker D.R., & Pascual J.A.	B.9.3.4	1998	1998 Update - Contract PN0919: Milestone Report Mammals and farming: Information for Risk Assessment. CSL Project No.: M37 Date of issue: November 1998 Non GLP, Non Published	No	
Storch, C.	B.9.3.4	1978	*Glis glis* (Linnaeus 1766) - Siebenschläfer. (in: Niethammer, J. B. & Krapp, F. Handbuch der Säugetiere Europas 1(1), 243-258. Akademische Verlagsgesellschaft, Wiesbaden).	No	
Wolfe, A., Whelan, J., & Hayden, T.J.	B.9.3.4	1996	Dietary overlap between the Irish mountain hare *Lepus timidus hibernicus* and the rabbit *Oryctolagus cuniculus* on coastal grassland. Journal: Biology and Environment 96B Pages: 89-95 Non GLP, Published	No	

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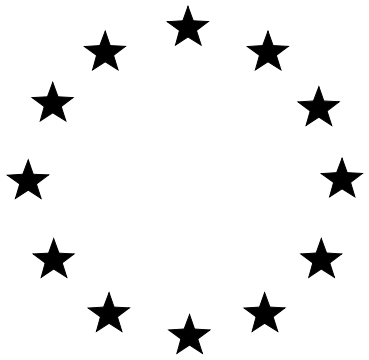

EPCO-Meetings

TOLYLFLUANID

Volume 3

ANNEX B

Summary, Scientific Evaluation and Assessment

ADDENDUM 2

Rapporteur Member State: Finland

19 May 2004

This document has not been peer reviewed and does not represent the opinion of the other Member States nor the European Commission

PLANT PRODUCTION INSPECTION CENTRE
Pesticide Division
Vilhonvuorenkatu 11
P.O.Box 42 F
FIN-00501 HELSINKI, FINLAND

CONTENTS **Page**

B.8 Environmental fate and behaviour

B.8.1 Route and rate of degradation in soil

B.8.1.3 Summary of degradation in soil

• Background

The comments of other Member States on this section of the draft evaluation report:

- NL: As just for one of the soils the data showed a good fit there is only 1 reliable DT_{50} value for the parent compound available instead of 4 required. For the parent 3 additional DT_{50} values in soil should be available unless the parent can be seen as a precursor. Data requirement to be added in volume 1, level 4.

Evaluation meeting 12.3.2004:

- Open point 4.4: The need of additional DT_{50} values for the degradation of tolylfluanid in soil to be discussed in an expert meeting.

• The response of the Rapporteur Member State

The study commented by NL is presented detailed in Chapters B.8.1.1.1 and B.8.1.2.1 of the DAR (study 1). In that laboratory study the rate and route of tolylfluanid and its main metabolite DMST in soil were investigated using four soil types. The DT_{50} values for tolylfluanid were low (0.5-2.6 days, geometric mean 1.5 days, 20 ^{o}C). The r^2 value from loamy silt (0.955) indicated a good fit to the data. However, the r^2 values from other soils were low (0.270 and 0.616) or it was not possible to calculate the r^2 value (clay silt, Laacherhof) because the model did not adequately represent the experimental data.

The RMS and the notifier agree that most r^2 values obtained did not indicate a good fit of the data and 1st order kinetics may not be appropriate for description of the degradation curve when a compound decreases fast at very beginning of the study. Nevertheless 1st order kinetic degradation rates were calculated since they were required for modeling. **However, regardless of the correlation coefficient of the kinetic curves, the visual inspection of experimental data suggests for all 4 soils that the half-life is clearly less than 1 day.** The percentages of the applied radioactivity in the course of the study are presented in Table B.8.1-1 (Table B.8.1-3 of the DAR). **Thus the RMS considers that the recalculation of the DT_{50} values for the parent substance would not give much new information nor have influence on risk assessment.**

Table B.8.1-1 Distribution of radioactivity present as parent compound and its degradation products after application of [phenyl-UL-^{14}C]tolylfluanid to soil and aerobic incubation at 22 °C (in % of the applied radioactivity).

Soil	Days after application	Tolylfluanid	DMST (Met. II)	Met. IX	Met. XI	Met. XII	CO_2	Others
Monheim I[a] -loamy sand	0	49.2	41.0	-	-	-	-	-
	1	23.7	57.1	-	1.1	-	0.4	-
	4	17.8	40.3	2.4	3.2	0.2	3.0	1.7
	8	14.5	23.1	1.5	1.8	1.4	8.3	1.9
	15	8.5	15.6	1.0	0.6	-	16.0	2.5
	32	9.2	6.1	0.3	0.2	0.2	23.4	2.3
	64	7.7	3.6	0.4	0.3	-	29.6	3.5
	99	6.8	2.8	0.2	0.2	-	34.0[b]	2.8
Höfchen[b] -clay silt	0	22.0	61.2	-	0.7	-	-	0.4
	1	4.0	45.8	0.7	2.2	0.7	1.2	2.2
	4	4.8	12.9	0.8	1.7	0.7	9.2	2.5
	8	0.8	3.3	-	0.4	-	20.0	3.4
	15	1.8	2.7	1.7	-	-	25.1	2.1
	32	1.2	1.8	0.1	0.1	<0.1	27.6	2.4
	64	0.2	0.4	0.1	0.2	-	32.2	2.2
	99	0.4	0.6	0.2	0.2	-	38.8	1.8
Laacherhof[b] -clay silt	0	28.2	58.9	-	1.4	-	-	0.9
	1	2.1	55.3	-	1.8	-	0.3	2.2
	4	1.2	14.8	1.3	4.1	-	2.9	2.5
	8	1.0	4.7	-	1.0	-	9.7	4.0
	15	0.9	1.9	0.4	-	-	14.0	3.4
	32	0.1	2.0	0.3	-	-	17.8	2.8
	64	0.1	1.0	0.2	0.4	0.1	21.1	2.1
	99	0.1	0.8	0.3	0.1	-	24.7	2.3
Speyer II[b] -loamy silt	0	26.0	60.2	-	-	-	-	3.0
	1	5.9	73.7	-	1.0	-	0.6	2.8
	4	2.8	52.5	1.3	2.6	1.4	3.7	4.6
	8	2.4	33.4	0.2	2.6	1.0	11.2	5.4
	15	2.1	14.8	0.7	0.5	-	21.4	6.2
	32	1.3	3.4	0.4	0.2	0.2	32.2	5.3
	64	1.0	1.7	0.5	0.2	-	29.9	4.2
	99	0.8	1.0	0.3	0.2	-	40.0	3.9

a = mean of two values
b = one value
DMST (Met. II) = dimethylaminosulfotoluidide
Met. IX = methylaminosulfotoluidide
Met. XI = 4-(dimethylaminosulfonylamino)benzoic acid
Met XII = 4-(methylaminosulfonylamino)benzoic acid

B.8.3 Predicted environmental concentrations in soil (PEC_s) (Annex IIIA 9.1.3)

• Background

The comments of other Member States on this section of the draft evaluation report:

- Sweden: PEC_{soil} should generally be calculated by use of realistic worst case DT_{50}. In this case, mean DT_{50} values for a.s. and DMST were used. The FOCUS-scenarios used take worst-case conditions for leaching on board, by use of worst-case weather and soil scenarios. Therefore, mean DT_{50} values are acceptable for $PEC_{groundwater}$, but not for PEC_{soil}. We realize though that in this case the risk assessment is not likely to change by this.
- UK: PEC_s not calculated in accordance with Commission doc 7617/VI/96 (FOCUS soil persistence guidance). Approach used may underestimate worst case PEC_s, particularly for mobile metabolite DMST. UK considers that PEC_s for endpoints should be recalculated in accordance with 7617/VI/96.

- NL: PEC_{soil} calculations should be performed with worst-case DT_{50} values. This should then also be corrected in Volume 1.

Evaluation meeting 12.3.2004:
- Open point 4.1: RMS to provide an addendum to the draft assessment report on the use of mean DT_{50} values for the PEC_{soil} calculations and the impact with respect the use of worst case.

• The response of the Rapporteur Member State
The notifier has conducted new PEC_{soil} calculations, which have been presented below.

Report: Schad, T. (2004): Addendum to Report MR-053/01: Recalculation of PEC_{soil} of Tolylfluanid and its Metabolite Tolylfluanid-Dimethylaminosulfotoluidide (DMST) – Use in Applies, Grapes, and Strawberries in Europe. Bayer CropScience AG, unpublished report No. MEF-04/211. Date: 2004-05-06

Test method
Predicted environmental concentrations of tolylfluanid and DMST in soil were recalculated with a standard Excelsheet approach as described in the FOCUS Soil Modelling Work group report on "Soil persistence models and EU registration" (7617/VI/96). In accordance with this document calculations were based on standard parameters like a soil depth of 5 cm, dry soil bulk density of 1.5 g/cm³, simple first order degradation half-lives and standard equations for $PEC_{initial}$ and time dependent $PEC_{s.}$

According to the intended safe uses of tolylfluanid the use in apples, grapes and strawberries was assessed, with different use patterns for Northern and Southern Europe. In PEC_s simulations minimum application intervals were taken into account. Crop interception values were taken from the last FOCUS groundwater report (2002) and are given in Table B.8.3-1 for each application.

DT_{50} values from laboratory study 1 presented in Chapters B.8.1.1.1 and B.8.1.2.1 of the DAR were used to describe degradation of tolylfluanid and DMST in soil. The half-life values were normalized from the actual experimental temperature of 22 °C to the standard experimental temperature of 20 °C. In order to describe realistic worst-case conditions but exclude extreme single events, 90^{th} percentile DT_{50} values were used. These were DT_{50} = 2.4 days for tolylfluanid and DT_{50} = 6.0 days for DMST.

Instead of the $PEC_{initial}$ at day 0 after the last application the maximum PEC_{soil} occurring at any time during or after the application period was defined and reported as max. PEC_s. Because of the fast degradation of both compounds and the increasing crop interception for application in apples and grapes due to increasing foliage this max. PEC_s was not necessarily reached after last application.

Table B.8.3-1 Use patterns of tolylfluanid and amounts actually reaching the soil used for calculation of PEC_s (Excelsheet approach with realistic worst case DT_{50} and minimum application interval).

Crop	Region	Intended application rate (kg as/ha)	Crop interception (%)	Amount of as reaching the soil (g as/ha)	Minimum appl. interval (days)
Apple	Northern Europe	7 x 1.125	50, 50, 65, 70, 80, 80, 80	563, 563, 394, 338, 225, 225, 225	7
Apple	Southern Europe	3 x 1.5	70, 80, 80	450, 300, 300	7
Grape	Northern Europe	0.6 / 0.8 / 1.2 / 1.4 / 1.6 / 3 x 1.8	50, 60, 70, 85, 85, 85, 85, 85	300, 320, 360, 210, 240, 270, 270, 270	10
Grape	Southern Europe	3 x 2.0	85, 85, 85	300, 300, 300	8
Strawberry	Northern Europe	3 x 2.5	60, 60, 60	1000, 1000, 1000	8
Strawberry	Southern Europe	3 x 1.25	60, 60, 60	500, 500, 500	7

Results
The predicted environmental concentrations of tolylfluanid are presented in Tables B.8.3-2 (actual values) and B.8.3-3 (time weighted values). The predicted environmental concentrations of DMST are presented in Tables B.8.3-4 (actual values) and B.8.3-5 (time weighted values).

The max. PEC_s for tolylfluanid after use in apples in Southern and Northern Europe were 600.0 and 850.1 µg/kg, respectively. In grapes the max. PEC_s in Southern and Northern Europe were 443.6 and 505.0 µg/kg, and in strawberries the max. PEC_s were 1478 µg/kg for Northern Europe and 766.6 µg/kg for Southern Europe.

For DMST max. PEC_s occurring at any time during or after the application period in apples were 340.3 (SE) and 507.4 µg/kg (NE). In grapes the max. PEC_s in Northern and Southern Europe were 298.8 and 295.0 µg/kg, respectively, and in strawberries the max. PEC_s were 983.2 µg/kg for Northern Europe and 526.3 for Southern Europe.

Table B.8.3-2 Actual PEC_s values of tolylfluanid calculated with worst-case DT_{50} and Excelsheet approach (upper 5 cm soil layer).

Crop	Region	**Actual tolylfluanid concentration in soil** on certain days after the maximum concentration (µg/kg)								
		0 d	1 d	2 d	4 d	7 d	21 d	28 d	50 d	100 d
Apple	NE	850.1	636.8	477.1	267.8	637.9	370.9	349.1	4.5	<0.05
Apple	SE	600.0	449.5	336.7	189.0	479.5	61.4	8.1	<0.05	<0.05
Grape	NE	505.0	378.3	283.4	159.1	66.9	252.6	33.5	381.2	<0.05
Grape	SE	443.6	332.3	249.0	139.7	58.8	1.0	0.1	<0.05	<0.05
Strawberry	NE	1478.7	1107.8	829.9	465.8	195.8	3.4	0.5	<0.05	<0.05
Strawberry	SE	766.6	574.3	430.3	241.5	101.5	1.8	0.2	<0.05	<0.05

Table B.8.3-3 TWA PEC_s values of tolylfluanid calculated with worst-case DT_{50} and Excelsheet approach (upper 5 cm soil layer).

Crop	Region	**TWA tolylfluanid concentration in soil** on certain days after the maximum concentration (µg/kg)								
		0 d	1 d	2 d	4 d	7 d	21 d	28 d	50 d	100 d
Apple	NE	850.1	743.5	654.7	517.8	447.2	376.3	343.6	262.0	133.3
Apple	SE	600.0	524.7	462.1	365.5	319.3	245.4	191.6	109.4	55.3
Grape	NE	505.0	441.7	388.9	307.6	226.7	187.7	174.5	155.0	117.9
Grape	SE	443.6	388.0	341.6	270.2	199.1	203.2	163.5	93.8	47.4
Strawberry	NE	1478.7	1293.3	1138.8	900.8	663.8	677.5	545.1	312.7	157.9
Strawberry	SE	766.6	670.5	590.4	467.0	422.2	348.6	273.5	156.3	78.9

Table B.8.3-4 Actual PEC_s values of DMST calculated with worst-case DT_{50} and Excelsheet approach (upper 5 cm soil layer).

Crop	Region	**Actual DMST concentration in soil** on certain days after the maximum concentration (µg/kg)								
		0 d	1 d	2 d	4 d	7 d	21 d	28 d	50 d	100 d
Apple	NE	507.4	502.5	479.4	410.9	461.0	316.7	289.3	31.3	0.1
Apple	SE	340.3	326.9	306.2	257.4	188.6	38.1	17.0	1.3	<0.05
Grape	NE	298.8	293.8	279.2	238.3	176.1	216.3	196.6	244.6	1.0
Grape	SE	295.0	286.2	269.7	228.2	167.8	34.0	15.1	1.2	<0.05
Strawberry	NE	983.2	954.0	899.1	760.7	559.4	113.3	50.5	4.0	<0.05
Strawberry	SE	526.3	508.5	478.0	403.3	296.1	59.9	26.7	2.1	<0.05

Table B.8.3-5 TWA PEC_s values of DMST calculated with worst-case DT_{50} and Excelsheet approach (upper 5 cm soil layer).

Crop	Region	**TWA DMST concentration in soil** on certain days after the maximum concentration (µg/kg)								
		0 d	1 d	2 d	4 d	7 d	21 d	28 d	50 d	100 d
Apple	NE	507.4	505.0	496.6	483.2	471.8	438.4	410.4	346.3	189.1
Apple	SE	340.3	339.9	335.6	325.4	304.4	274.1	242.7	153.9	78.4
Grape	NE	298.8	296.3	292.9	283.5	264.4	230.1	220.2	207.2	166.2
Grape	SE	295.0	292.2	290.2	279.8	260.5	219.9	200.5	131.5	67.2
Strawberry	NE	983.2	973.9	967.3	932.6	868.2	733.0	668.4	438.5	224.0
Strawberry	SE	526.3	523.2	518.3	500.9	464.4	385.1	342.3	219.7	112.0

Comparisons of the new PECs values with the PECs values presented in the DAR
Max. PEC_s calculated with the Excelsheet approach and worst-case DT_{50} values as well as max. PEC_s calculated with FOCUS-PELMO and geometric mean DT_{50} values (presented in tables B.8.3-7 and B.8.3-9 of the DAR) are compared in Table B.8.3-6. Calculations in both reports were based on the same use patterns with minimum application intervals.

Table B.8.3-6 Comparison of max. PEC_s calculated with worst-case DT_{50} and Excelsheet approach with $PEC_{s,initial}$ calculated with mean DT_{50} and FOCUS-PELMO.

Crop	Region	Tolylfluanid		DMST	
		max. PEC_s (Excelsheet, worst-case DT_{50})	$PEC_{s,\ initial}$ (FOCUS-PELMO, geo. mean DT_{50})*	max. PEC_s (Excelsheet, worst-case DT_{50})	max. $PEC_{s,}$ (FOCUS-PELMO, geo. mean DT_{50})*
Apple	NE	850.1	426.3	507.4	420.0
Apple	SE	600.0	643.5	340.3	362.9
Grape	NE	505.0	293.5	298.8	142.2
Grape	SE	443.6	531.2	295.0	278.8
Strawberry	NE	1478.7	1601.0	983.2	949.1
Strawberry	SE	766.6	1066.0	526.3	589.5

* = presented in Tables B.8.3-7 and B.8.3.9 of the DAR

Comparison of the recalculated max. PEC_s (Excelsheet, worst-case DT_{50}) with $PEC_{s,initial}$ (FOCUS-PELMO, mean DT_{50}) doesn't show a clear influence of the DT_{50} on the resulting PEC. For tolylfluanid max. PEC_s calculated with the Excel-approach and worst-case DT_{50} are higher than corresponding values calculated with FOCUS-PELMO and mean DT_{50} for use in apples and grapes in Northern Europe but lower for strawberries in Northern Europe and all crops in Southern Europe. For DMST maximum concentrations when calculated with worst-case DT_{50} were higher for grapes in both regions and apples and strawberries in Northern Europe, but lower for apples and strawberries in Southern Europe.

Obviously, **in case of** the fast degrading **tolylfluanid** other model parameters implemented in the FOCUS scenarios like **temperature, weather conditions or dry bulk soil density, and the definition of the initial PEC_s as maximum** during of after the application period **have much more influence on the maximum concentration than the mean or worst-case DT_{50} in soil.**

Even **for DMST**, which has a worst-case DT_{50} in a similar order of magnitude as the minimum application interval, for several uses **the max. PEC_s is obviously less influenced by the DT_{50} value and more by other model parameters.**

Possible influence on the final risk assessment
The ecotoxicological risk assessment for terrestrial organisms (see Chapters B.9.5.3 and B.9.6 of the DAR) was based on initial PEC_s (initial after last application) for tolylfluanid and max. PEC_s for DMST. Lowest TERs for earthworms (acute and reproductive) as well as folsomia were calculated for use of tolylfluanid in strawberries in Northern Europe. Since the recalculated max. PEC_s of tolylfluanid based on worst-case DT_{50} for this use is lower

than the value calculated with FOCUS-PELMO, the risk assessment of tolylfluanid is not affected by the new PEC_s calculation. For DMST re-calculation of the TERs for earthworm and folsomia with new PEC_s would decrease the TERs from 105 to 102 for earthworms and from 263 to 254 for folsomia.

Therefore, it is concluded that **the recalculation of PEC_s with worst-case DT_{50} values has negligible influence of the risk assessment for terrestrial organisms.**

B.8.6 Predicted environmental concentrations in surface water and ground water (PEC_{sw}, PEC_{gw}) (Annex IIIA 9.2.1, 9.2.3)

B.8.6.1 Predicted environmental concentrations in surface water (PEC_{sw})

• Background

The comments of other Member States on this section of the draft evaluation report:

- NL: Why is the high value for DT_{50} sediment DMST used for the calculations? Because of the short incubation time of the test, the extrapolated value for DT_{50} sediment cannot be guarded as reliable. The DT_{50} value for DMST in sediment is much longer than in the 1st experiment and seem unrealistic. In the 3rd experiment sampling was performed until 7 days after application. There was only one sample point after the maximum was reached in the water and it is not clear that the maximum in the sediment has been reached. The extrapolation of DT_{50} in the sediment has led to unrealistic high values
- Sweden: Generally, realistic worst-case DT_{50} values should be used for calculation of PEC_{sw}. In this case, it appears that both mean and worst-case values were used. The use of mean values should be justified.
- NL: Temperature correction of the DT_{50} to 15 °C is not common in Tier 1 evaluation. PEC_{sw} should, to our opinion, be recalculated using DT_{50} at 20 °C. Does the Model EXAMS provide the same data as standard input calculations? It looks like the same dimensions are used as in standard calculations, we would like a confirmation on this.

Evaluation meeting 12.3.2004:

- Open point 4.2: Appropriateness of DT_{50} sediment DMST used for calculations to be discussed in an expert meeting
- Open point 4.3: MS to discuss whether the DT_{50} value and the methods employed for the PEC_{sw} calculation is acceptable in an expert meeting

• The response of the Rapporteur Member State

Appropriateness of DT_{50} sediment

In the DAR (presented in Chapter B.8.6.1) the concentrations of tolylfluanid and its major metabolite DMST in surface water under environmental conditions were calculated by using the model EXAMS (version 2.94). These simulations were performed concerning the use of tolylfluanid in apples, grapes and strawberries in Northern and Southern Europe and considering different widths of a buffer strip between the field and the water body.

Loading to the surface water via spray drift was estimated based on the updated drift tables by BBA (2000). Depending the maximum number of applications in season, the corresponding percentiles of the individual measured drift values were used in order to establish overall 90th percentile worst case conditions. Mean half-lives at 15 °C (tolylfluanid: 7.0 h in water and 5.3 h in sediment, DMST: 752 h in water and $>10^4$ h in sediment) were used to calculate PEC_{sw} under representative conditions.

Due to the rapid degradation of tolylfluanid in sediment and water the concentration of tolylfluanid after an application hardly depends on previous applications but can be considered as a single event. Therefore, the maximum PEC_{sw} of tolylfluanid were also calculated applying the higher drift values of single applications (BBA, 2000) and mean half-lives presented above.

Additionally, in order to address worst-case conditions, additional simulation runs for PEC_{sw} were performed based on the longest half-lives and minimum intended application intervals. Half-lives, which were used to calculate worst-case PEC_{SW} were 9.0 h and 7.1 h for tolylfluanid in water and sediment, respectively, and 770.7 and $>10^4$ h for DMST.

All the half-lives mentioned in this chapter were obtained in study 3 reported in Chapter B.8.4.3.2 of the DAR. NL commented that the high value for DT_{50} sediment of DMST was not reliable because there was only one sample point after the maximum in the sediment had been reached. The RMS agrees with NL that the study was too short to describe the metabolism of DMST in sediment properly (study duration 7 days, samples 0, 0.5 h, 2 h,

4 h, 7 h, 24 h, 3 days and 7 days after application). However, according to information provided by the notifier in EXAMS simulations degradation of the parent substance and formation and degradation of metabolites depend from each other. Therefore the notifier was of the opinion that it was important to use DT_{50} values for tolylfluanid and DMST derived from the same study and that a mix of the results from different studies would have weakened the results of EXAMS calculations. Consequently, in view of the aquatic risk assessment, which is more critical for tolylfluanid than for DMST, DT_{50} values were taken from that study which delivers most reliable data for the parent compound. **Thus the RMS did not find it necessary to recalculate these values because the notifier was of the opinion that these possibly unrealistically high DT_{50} values of DMST were acceptable. Additionally the RMS considers that changing the high value for DT50 sediment of DMST to a lower value would not influence the risk assessment.**

Acceptability of the DT_{50} value and the methods employed for the PEC_{sw} calculation

The ecotoxicological risk assessment of **DMST** was made on the basis of the PEC_{sw} values obtained by using **worst-case DT_{50} values**. The RMS also presented in the DAR the PEC_{sw} values of tolylfluanid calculated by using worst-case DT_{50} values. However, **the PEC_{sw} values of tolylfluanid calculated applying the drift of single applications and mean DT_{50} values were higher than the PEC_{sw} values obtained by using worst-case DT_{50} values and drift values of multiple applications** (because of the very short half-life the PEC_{sw} value after one application is not affected by the previous application). Additionally due to the ecotoxicological properties of tolylfluanid the aquatic risk assessment of the compound is based on the initial PECsw values only. Thus **the risk assessment of tolylfluanid was made on the basis of initial PEC_{sw} values after one application applying single application drift values** – and was not affected by the applied DT_{50} value at all. In any case, the mean DT_{50} of tolylfluanid in water of 7 hours at 15 ^{o}C, which was used in the PECsw calculations, can be regarded as a worst-case compared to the proposal of Sweden to use the worst-case DT_{50} of 6 hours at 20 ^{o}C.

The RMS agrees with NL on the fact that PEC_{sw} should be calculated using the DT_{50} values at 20 ^{o}C. However, as presented above the risk assessment of tolylfluanid was not affected by the choice of the DT_{50} value (15 ^{o}C versus 20 ^{o}C or mean values versus worst-case DT_{50} values). **Therefore the RMS considers that the mean DT_{50} value of tolylfluanid at 15 ^{o}C is suitable for ecotoxicological risk assessment. In case of DMST the aquatic toxicity is low and even TER values calculated on the basis of DT_{50} values at 15 ^{o}C were over trigger values. Thus, no necessity for recalculation of the PEC_{sw} values of tolylfluanid and DMST is seen.**

Additional information on simulation model EXAMS (not presented in the DAR)

Concerning the comments of NL the notifier (Schöfer, 2004) has submitted some information on simulation model EXAMS.

At the time the submission of the tolylfluanid dossier was prepared (2000/2001) different simulation models describing the fate and behaviour of plant protection products in surface water were available for calculation of PEC_{sw}. The most reliable models, which were normally used, were TOXSWA and EXAMS. These so-called surface water fate models describe the partitioning and disappearance of a compound in the aquatic system.

Both EXAMS and TOXWA can be regarded as in principal equivalent, although some significant differences exist. TOXSWA includes slow water flow, while EXAMS simulates a standing water body. EXAMS distinguish plankton from other suspended solids when describing sorption processes. TOXSWA is the only model where macrophytes or rooted water plants are present. However, the most important difference between EXAMS and TOXSWA is that EXAMS considers metabolites. With EXAMS the processes of degradation and partitioning of the parent compound and the simultaneous formation and degradation of a metabolite can be described, whereas TOXSWA simulates only the degradation and partitioning of one compound. Accordingly, when calculating PEC_{sw} values for a parent compound and its metabolite with EXAMS, for reasons of consistency the input data set of degradation/dissipation data should also build up the dependency of degradation of parent and formation and degradation of the metabolite. So, for both compounds DT_{50} values generated in the same study should be used.

B.8.10 References relied on

Annex point/ reference number	Author(s)	Year	Title **Source** (where different from company) **Company name, Report No., Date**, **GLP status** (where relevant), published or not	Data protect. claimed	Owner
III A, 9.1.3	Schad, T.	2004	Addendum to report MR-053/01: Recalculation of PECsoil of tolylfluanid and its metabolite tolylfluanid-dimethylaminosulfotoluidide (DMST) – Use in apples, grapes, and strawberries in Europe Bayer CropScience AG, ReportNo.:MEF-04/211 Date:10.05.2004 Non GLP, Non Published	Yes	BAY
III A, 9.2.3	Schöfer, S.	2004	Tolyfluanid – Comments on Calculation of PEC_{sw} of tolylfluanid and DMST – Answer to open points 4.2 and 4.3 in the Evaluation Table Bayer CropScience AG, Report No. MO-04-004881 Date:28.04.2004 Non GLP, Non Published	Yes	BAY

B.9.2 Effects on aquatic organisms

• Background
Evaluation meeting 12.3.2004:
- Data requirement 5.1: Notifier to submit new acute toxicity test with zebrafish at different pH values.

B.9.2.1 Acute toxicity to fish

Report: Dorgerloh, M. (2004): Acute toxicity of Tolylfluanid WG 50 to fish (*Danio rerio*) at different pH values of test water under static conditions. Bayer CropScience AG, unpublished report DOM 23100.
Guidelines: EU Directive 92/69/EEC, C.1 (1992) and OECD 203 (rev. 1992).
GLP: yes (certified laboratory)

Material and methods
The acute toxicity of Euparen M WG 50 (tolylfluanid 50.0 %) to zebrafish (D*anio rerio*, mean body length 3.3 ± 0.09 cm, mean body weight 0.3 g) was studied for 96 h under static test conditions. Each test concentration and each control group contained 10 fish. At pH 6 fish were exposed to nominal concentrations of 30.1 (15.1), 40.6 (20.3), 54.9 (27.4), 74.1 (37.0) and 100 (50.0) µg test substance/L (µg a.i/L). At pH 7 fish were exposed to nominal concentrations of 40.6 (20.3), 54.9 (27.4), 74.1 (37.0), 100 (50.0) and 135 (67.4) µg test substance/L (µg a.i./L). At pH 8 fish were exposed to nominal concentrations of 54.9 (27.4), 74.1 (37.0), 100 (50.0), 135 (67.4) and 182 (91.0) µg test substance/L (µg a.i/L). The control groups were exposed to untreated test water. The temperature in the different test media with different pH was between 20.8 – 22.8 °C and dissolved oxygen 97 - 102 % of oxygen saturation. Recoveries of tolylfluanid and DMST were measured in the freshly prepared stock solutions and in all test levels at initiation (< 30 min), after 1 hour, 4 hours, 8 hours, 48 hours and 96 hours of exposure.

Results
Based on analytical determination of tolylfluanid in stock solutions measured values between 85 % and 88 % of nominal were found.

Based on analytical determination of tolylfluanid in test water measured values of 78 % (pH 6), 87 % (pH 7) and 85 % (pH 8) of nominal were found at test initiation. Already after 4 hours the concentration of tolylfluanid was not more than 60 % of the nominal concentration and after 24 hours only < 10 % of the nominal concentration. The acute toxicity is based on nominal initial concentrations of the WG 50 formulation.

The LC_{50}(96h) of Euparen M WG 50 to zebrafish in buffered water at pH between 6.0 and 8 ranged from 35.7 to 50 µg ai/L under static test conditions (Table B.9.2.1).

Table B.9.2.1. Acute toxicity of Tolylfluanid M WG 50 to zebrafish at different pH-values .

pH	LC_{50}(96h)		NOEC (96h)	
	µg form./L	µg ai/L	µg form./L	µg ai/L
6.0	71.4	35.7	40.6	20.3
7.0	96.2	48.1	74.1	37.1
8.0	100	50.0	74.1	37.1

Comments
The test procedure corresponded to the given guidelines. The study confirms the results of the earlier (orientating) study: the toxicity of tolylfluanid was influenced by the pH (because of the pH-dependent hydrolytic instability of tolylfluanid). The toxicity of tolylfluanid was 1.4 times higher at pH 6.0 than at pH 8.0.

B.9.11 References relied on

Annex point/ reference number	**Author(s)**	**Year**	**Title** **Source** (where different from company) **Company name, Report No., Date**, **GLP status** (where relevant), published or not	**Data protect. claimed**	**Owner**
III A, 9.2.1	Dorgerloh, M.	2004	Acute toxicity of Tolyfluanid WG 50 to fish *(Danio rerio)* at different pH-values of test water under static conditions Bayer CropScience AG, Report No. DOM 23100 Date:05.02.2004 GLP, Non Published	Yes	BAY

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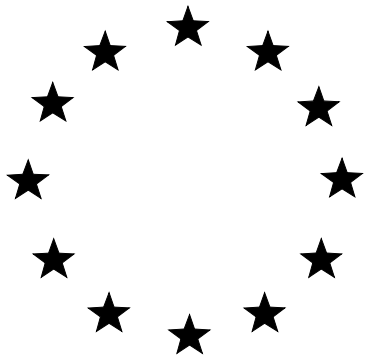

EPCO-Meetings

TOLYLFLUANID

Volume 3

ANNEX B

Summary, Scientific Evaluation and Assessment

ADDENDUM 3

Rapporteur Member State: Finland

2 June 2004

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PLANT PRODUCTION INSPECTION CENTRE
Pesticide Division
Vilhonvuorenkatu 11
P.O.Box 42 F
FIN-00501 HELSINKI, FINLAND

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B.5 Methods of analysis

B.5.3.1 Analytical methods (residue) for soil

Evaluation table rev. 0-1 (04.04.04):
Data requirement 1.3: Notifier to submit the new validation data for DFG S 19 – method.

Validation of DFG method S 19 (extended and revised version):

Outline of method for soil specimens (module E 9):

LUFA Speyer standard soil 2.2 samples were extracted with ethyl acetate/cyclohexane (1/1, v/v) using accelerated solvent extraction (ASE) under specific extraction conditions. The obtained extracts were evaporated to dryness, redissolved and the remaining solutions were cleaned up by gel permeation chromatography on Bio Beads S-X3 polystyrene gel using a mixture of ethyl acetate/cyclohexane (l/l, v/v) as eluent. Further the GPC fractions containing the target compounds were purified using silica gel columns with toluene/acetone (95/5, v/v) as eluent. The concentrated and cleaned extracts were analysed using capillary gas chromatography (DB-5 MS) with mass selective detection (MSD) using MS ions m/z 238 for quantitation and 137 and 181 for confirmation. Validation data is presented in Table 5.3.1.

(G04-0007, Lakaschus 2004)

Table 5.3.1 Validation data for the analytical methods for the determination of residues of tolylfluanid in LUFA Speyer standard soil 2.2

Type of method Developed by	m/z	Fortification level (mg/kg)	LOQ (mg/kg)	recovery (%) mean range	RSD (%)	N
Parent compound; GC-MSD; DFG S 19 (Lakaschus 2004)	m/z = 238	0.01 0.10	0.01	104 89-123* 95 75-108 overall 99	14 16 overall 15	5 5
	m/z = 137	0.01 0.10	0.01	106 91-128* 96 76-111* overall 101	14 16 overall 15	5 5
	m/z = 181	0.01 0.10	0.01	101 88-112* 94 75-106 overall 97	11 15 overall 13	5 5

* one recovery was > 110 %

Conclusion: The method is valid for the determination of residues of tolylfluanid in soil.

B.5.3.2 Analytical methods (residue) for water (including drinking water) (IIA 4.2.3)

Validation of an analytical method, 00054/E002, Weeren and Pelz 1999 in the DAR, (analogous to DFG W 5) was generated with surface water from river Alster, northern Germany, Hamburg:
pH (H_2O) 8.2,
DOC 5.2 mg C/l
TOC 20 mg C/l
Total hardness 11.0 ^{o}dH
Mud content 50 mg/l

B.5.6 References relied on

Annex point/ reference number	Author(s)	Year	Title **Source** (where different from company) **Company name, Report No., Date**, **GLP status** (where relevant), published or not	Data protect. claimed	Owner
II A, 4.2.2	Lakaschus, S.	2004	Enforcement method for the determination of residues of tolylfluanid in materials of soil – validation of DFG method S 19 (extended and revised version) (Bayer CropScience Method 00086/M064) Dr. Specht & Partner, Chemische Laboratorien GmbH, Hamburg, Germany Bayer CropScience AG, Report No.:G04-0007 Date:20.04.2004 GLP, Non Published	Yes	BAY

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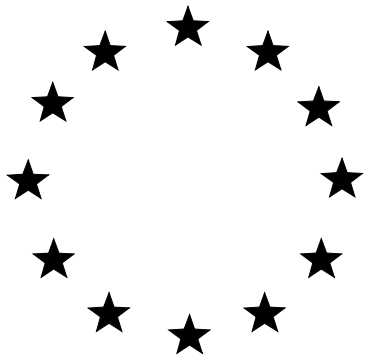

EPCO-Meetings

TOLYLFLUANID

Volume 3

ANNEX B

Summary, Scientific Evaluation and Assessment

ADDENDUM 4

Rapporteur Member State: Finland

22 June 2004

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PLANT PRODUCTION INSPECTION CENTRE
Pesticide Division
Vilhonvuorenkatu 11
P.O.Box 42 F
FIN-00501 HELSINKI, FINLAND

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B.6.3 Short-term toxicity (Annex IIA 5.3)

The results of short-term toxicity studies at oral administration are presented in Table 6.3.1. The data below is presented as basis for a discussion on the overall systemic NOAEL from oral short-term studies with tolylfluanid.

Table 6.3.1 Summary of short-term studies at oral administration

Study	Dose levels	Result, NOEL/NOAEL	Reference
Four-week oral , rat (feed)	300, 1500 and 7500 ppm	Kidney weights ↑ , T4 and T3 ↓, TSH ↑ at 7500 ppm T4 ↓ at 1500 ppm NOAEL = 300 ppm LOAEL = 1500 ppm	Bomhard (1988)
Three-month oral, rat (feed)	150, 500, 1500 and 4500 ppm (13, 46, 133 and 400 mg/kg bw/day in males and 18, 60, 175 and 524 mg/kg bw/day in fenales)	Organ weight changes starting from 500 ppm (thymus ↓, suprarenal gland ↑) or 1500 ppm (liver ↑, kidney ↑) or 4500 ppm (lungs ↓) NOAEL = 150 ppm (13 mg/kg bw/day) LOAEL = 500 ppm (46 mg/kg bw/day)	Bomhard and Schilde (1976)
13-week oral, rat (feed)	300, 1650 and 9000 ppm (20, 108 and 639 mg/kg bw/day in males, and 23, 131 and 736 mg/kg bw/day in females)	ASAT, ALAT and AP ↓ at 1650 and 9000 ppm; T4 ↓, TSH ↑, blood urea ↓ and cholesterol ↑ at 9000 ppm; blood calcium ↓ at 1650 and 900 ppm; relative liver weights ↑ at 9000 ppm. NOAEL = 300 ppm (20 mg/kg bw/day) LOAEL = 1650 ppm (108 mg/kg bw/day)	Dreist (1995)
13-week oral, dog (feed)	330, 1000 and 3000 ppm 11-12, 33-34 and 93-99 mg/kg bw/day	Liver and thyroid weights ↑ at 3000 ppm NOAEL = 1000 ppm (33 mg/kg bw/day) LOAEL = 3000 ppm (93 mg/kg bw/day)	Hoffmann and Mirea (1974)
12-month oral, dog (gelatin capsule)	2.5, 12.5 and 62.5/125 mg /kg bw/day (62.5 mg/kg bw/day on weeks 1-33, thereafter 125 mg/kg bw/day during weeks 34-52)	ALAT and GLDH ↑, AP ↓; urea and creatinine ↑; cortical tubulus alterations in kidneys at 62.5-125 mg/kg bw/day NOAEL = 12.5 mg/kg bw/day LOAEL = 63/125 mg/kg bw/day	von Keutz and Nash (1986)
52-week oral, dog (gelatin capsule)	0, 5, 20 and 80 mg/kg bw/day	No clearly treatment-related effects, except increased levels of fluoride in bone at 80 mg/kg bw/day NOAEL = 80 mg/kg bw/day The NOEL for fluoride incorporation in bones is 20 mg/kg bw/day	Wetzig and Schilde (1997)

↑ = increase, ↓ = decrease, TLF = tolylfluanid

In feeding studies with **rats**, functional disturbance of the thyroid glands, demonstrated as consistently lowered levels of T4, a less pronounced reduction in T3, and corresponding increases in TSH levels, were observed mainly at the high dose level of 7500 ppm, but T4 was also decreased in 1500 ppm males in the 28 study by Bomhard (1988). Necropsies showed a paleness of the thyroids in high dose animals, but no histopathological changes were observed (Bomhard, 1988). The function of the thyroids was also affected at a dose of 9000 ppm (639 – 736 mg/kg bw/day) in both sexes in the 13-week rat study by Dreist (1995); levels of TSH and thyroxin-binding capacity were increased and levels of T4 were reduced. Increased liver weights were observed in both sexes in the 90-day rat feeding study by Bomhard and Schilde (1976), but without changes in liver enzyme levels.

Increased relative liver weights were noted in the study by Dreist (1995) at 9000 ppm in males, and decreased liver enzyme levels were observed in either sex at 1650 ppm (108 – 131 mg/kg bw/day) and 9000 ppm (639 – 736 mg/kg bw/day). Reduced blood urea and increased cholesterol levels in 9000 ppm rats of both sexes also indicated impaired liver metabolism (Dreist, 1995). Relative kidney weights were increased in both sexes in the study by Bomhard (1988) at 7500 ppm, and in females at 1500 ppm (133 – 175 mg/kg bw/day) and 4500 ppm

(400 – 514 mg/kg bw/day) in the study by Bomhard and Schilde (1976). The overall NOAEL in short-term feeding studies in rat is 20 – 23 mg/kg bw/day (Dreist, 1995), based mainly on changes in clinical chemistry parameters indicating functional/metabolic impairment of the liver without correlating effects on organ weights and histopathological investigations.

In **dog**, absolute and relative thyroid weights were increased in males in one 13-week feeding study at 3000 ppm (93 – 99 mg/kg bw/day), but no examination of pituitary-thyroidal-axis enzyme (T4, T3, TSH) levels were performed (Hoffmann and Mirea, 1974). In the same study, increased relative liver weights were observed at 3000 ppm, and histopathology of the liver revealed an increase in slight intracytoplasmic fine to coarse PAS-positive droplets (centrilobular or diffuse). In a 12-month feeding study in dog by von Keutz and Nash (1986), increases in ALAT and GLDH levels and a decrease in AP levels was noted, but no histological findings in the livers were observed. Kidney toleration by the PSP test could not be done, but urea and creatinine concentrations were increased and histological examination revealed slight cortical tubulus alterations in kidneys of high dose animals (62.5 – 125 mg/kg bw/day). In the 52 week dog study by Wetzig and Schilde (1997), a slight increase in male liver weights was observed at 80 mg/kg bw/day, but no liver enzyme or histopathological changes were seen. The concentration of fluoride in bone and teeth was increased at 80 mg/kg bw/day in the study by Wetzig and Schilde. The lowest relevant NOAEL in short-term dog studies is 1000 ppm (33 mg/kg bw/day) in the 13-week dog study by Hoffmann and Mirea (1974).

Effects on the liver, thyroids and the kidneys were seen in oral short-term studies in both rats and dogs. Thyroidal effects were more pronounced in rats than in dogs, but at fairly high doses in both species (rat 1500 – 9000 ppm, dog 3000 ppm). Kidney weights were increased starting from 1500 ppm (133 – 177 mg/kg bw/day) in rat (Bomhard and Schilde, 1976), and histopathological findings (slight cortical tubulus alterations) in kidneys were observed in dogs at 63 – 125 mg/kg bw/day (von Keutz and Nash, 1986). The most consistent effects in rats involved the liver, for which an overall NOAEL of 20 mg/kg bw/day can be set (Dreist, 1995). The overall NOAEL in dogs based on liver effects is 33 mg/kg bw/day (Hoffmann and Mirea, 1974). Determination of fluoride content in bone and teeth was done only in the 52 week dog study by Wetzig and Schilde (1997). The overall NOAEL for a clear increase of fluoride levels in canine bone and teeth in both sexes at administration of tolylfluanid in dog for 52 weeks was 20 mg/kg bw/day. No other significant adverse effects were observed in dog at doses up to 80 mg/kg bw/day.

The same treatment related effects were observed in both rats and dogs at oral administration of tolylfluanid. The sensitivities to these effects were about the same, so an overall NOAEL for systemic short-term effects may be chosen from either species. Fluoride levels in bone and teeth start to increase clearly in dog above 20 mg/kg bw/day, and it may be noted that no clinical signs of fluorosis were observed in this 52 week dog study.

The overall NOAEL is proposed to be set based on slight treatment related effects on the liver and kidneys in both species. Comparing NOAEL:s and LOAEL:s in both rat and dog, the NOAEL of 33 mg/kg bw/day in the 13-week oral dog study by Hoffmann and Mirea (1974) is still supported as an overall no-adverse-effect-level for short-term toxicity of tolylfluanid. It is further suggested that this value is to be used for setting the AOEL.

B.6.4.2 *In vivo* genotoxicity testing (Annex IIA 5.4.2)

B.6.4.2.1 KUE 13183B: *In vivo* bone marrow cytogenetic study using male mice (Herbold, 2004)

Test guideline and GLP

The study was performed in compliance with GLP and according to OECD guideline No. 475 (July 21, 1997) and Directive 67/548/EEC, Annex V, Method B.11.

Materials and methods

Tolylfluanid (purity 96.2%) was tested for clastogenic effects in the bone marrow of male Hsd/Win:NMRI mice using single intraperitoneal dosing. A pilot test was performed using three male and three female mice per group treated intraperitoneally with 10 or 25 mg/kg tolylfluanid. Clinical sings (apathy, roughened fur, spasms, twitching, periodically stretching the body, difficulty in breathing and slitted eyes) were recorded in both sexes at both doses during a followup period of at least 120 hours. Two out of three males in the 25 mg/kg group died, but all females survived. The report concludes that no substantial differences were found between the sexes in toxicity. Therefore, only males were used. The MTD chosen for males was 16 mg/kg, which was selected as the (only) dose level in the genotoxicity test. The following testing scheme was applied:

Group	Dose in mg/kg	Route of application	Sacrifice time
Negative control	0	i.p.	12 h
Tolylfluanid	16	i.p.	12 h
Negative control	0	i.p.	24 h
Tolylfluanid	16	i.p.	24 h
Cyclophosphamide *)	20	i.p.	24 h
Negative control	0	i.p.	48 h
Tolylfluanid	16	i.p.	48 h

*) Positive control

Each group contained 5 male mice. Sacrifice times were 12, 24 and 48 h after the single intraperitoneal administration of tolylfluanid. The effects of the positive control cyclophosphamide were examined 24 h after administration. Tolylfluanid was suspended in 0.5% aqueous Cremophor emulsion, and cyclophosphamide was dissolved in deionized water before administration. The negative controls received 0.5% aqueous Cremophor emulsion intraperitoneally. The administered volume was 10 ml/kg in all groups. Colcemide (4 mg/kg) was injected intraperitoneally two hours before sacrifice to arrest the mitoses in the metaphase stage. The mitotic index was was determined by counting 1000 bone marrow cells per animal. Chromosomes of 100 metaphases per animal were examined for structural aberrations (gaps, breaks, fragments, deletions, exchanges and multiple aberrations). The examinations included also numerical aberrations (polyploid metaphases). Metaphases showing chromosome disintegration as indication of cytotoxicity were also recorded. The one-sided Chi-square test was used for statistical evaluation of test group differences. A difference was considered significant if the probability of error was below 5%.

Results

The following clinical signs were observed in the treated males: apathy, roughened fur, loss of weight, spasms, periodically stretching of body, difficulty in breathing and diarrhoea. The symptomes persisted until sacrifice. No mortalities were reported in either treated animals or controls. Mitotic indices in groups of tolylfluanid treated animals did not appreciably differ from controls. The mean mitotic index was reduced about 35% in the positive control group.

The results of the aberration analyses are summarised in Table 6.4-1.

Table 6.4.-1. Summary of results of bone marrow cytogenetic test with tolylfluanid. 100 metaphases were examined per animal. Each test group consisted of 5 male mice.

Substance	Dose (mg/kg)	Sacrifice time (Hours)	Metaphases with aberrations (%)		
			Including gaps	Excluding gaps	Exchanges only
Negative control	0	12	0.8 ± 0.4	0.6 ± 0.5	0 ± 0
Tolylfluanid	**16**	**12**	**1.2 ± 0.8**	**1.0 ± 0.7**	**0 ± 0**
Negative control	0	24	2.0 ± 2.3	0.8 ± 0.8	0 ± 0
Tolylfluanid	**16**	**24**	**1.4 ± 0.5**	**1.2 ± 0.4**	**0 ± 0**
Cyclophosphamide	20	24	45.2 ± 11.9 *	41.0 ± 11.9 *	6.6 ± 1.7 *
Negative control	0	48	1.0 ± 1.2	0.6 ± 0.9	0 ± 0
Tolylfluanid	**16**	**48**	**1.8 ± 1.5**	**1.8 ± 1.5**	**0 ± 0**

* $p < 0.01$ (Chi-square test)

No statistically significant changes in frequencies of cells with aberrations were observed with the tested dose of 16 mg/kg tolylfluanid at any of the sacrifice times of 12, 24 and 48 h after administration of the test substance. The positive control, cyclophosphamide, had a clear clastogenic effect. No treatment related increases in polyploid metaphases were observed. The historical vehicle control data (4 studies from 1995, 2000 and 2001) showed that percentages of metaphases with aberrations including gaps ranged in these earlier studies from 0.1 to 1.2 and without gaps from 0 to 0.4. The vehicle controls in this study were generally only slightly higher than the historical values. The positive control values in this study were also slightly higher than in the historical positive control data with cyclophosphamide from the 4 previous studies (8.6 – 33.8 % metaphases with gaps, 1.7 – 33.6% without gaps).

Summary

Only one intraperitoneally administered dose of 16 mg/kg tolylfluanid in male mice was used. The dose was selected based on a pilot study where mortality was observed in male mice at 25 mg/kg. The selected dose level of 16 mg/kg also caused clear treatment related signs of toxicity in the test and it can therefore be considered as the MTD. The MTD dose level in mice in this study is in line with the LD_{50} –value of about 15 mg/kg in rat at intraperitoneal administration (DAR, B.6.2.4.1). No cytotoxicity or suppression of mitogenic activity was observed at any sacrifice time with tolylfluanid, based on examinations of mitotic indices. No statistically significant differences in metaphases with aberrations between tolylfluanid treated male mice and controls at different sacrifice times were observed, gaps included or excluded. Tolylfluanid was not clastogenic in bone marrow cells of male mice at an intraperitoneally administered dose dose of 16 mg/kg, which is considered as an MTD in this study. The study is acceptable.

B.6.4.3 Summary of genotoxicity tests

The results from genotoxicity tests *in vitro* and *in vivo* are presented in Table 6.4-2.

A clearly positive test result was observed in the *in vitro* chromosome aberration assay with human lymphocytes, both with and without S9 mix. The other *in vitro* chromosome aberration test in the chinese hamster V79 lung fibroblast cell line is not acceptable because the tested doses were too low. The TK +/- gene mutation test with mouse lymphoma L5187Y cells was also positive both with and without metabolic activation. The HGPRT gene mutation test in chinese hamster V79 cells was negative, whereas the chinese hamster ovary cell test gave some indications of gene mutations (the result is rated as equivocal). The Ames/*Salmonella* tests, the gene mutation (reversion) test in *Saccharomyces cerevisiae*, and the UDS test in primary hepatocytes were all negative. Many of the *in vitro* studies were of poor quality with deficiencies in reporting. The studies do, however, indicate that tolylfluanid has some weak mutagenic potential in *in vitro* studies, which is exhibited as clastogenicity and partly positive test results in mammalian gene mutation tests.

Table 6.4-2. Summary of genotoxicity studies *in vitro* and *in vivo* (ammended with a new study).

Assay	Purity of a.s.	Activation	Result	Reference
***In vitro* Assays**				
Salmonella typhimurium Reverse mutation assay	100%	+S9 mix, rat	Negative	Herbold, 1979
		-S9 mix	Negative	
Salmonella typhimurium Reverse mutation assay	98.5%	+S9 mix, rat	Negative	Herbold, 1994
		-S9 mix	Negative	
Saccharomyces cerevisiae Reverse mutation assay	99.1%	+S9 mix, rat	Negative	Hoorn, 1984
		-S9 mix	Negative	
Chromosome aberration assay in human lymphocytes	99.2%	+S9 mix	Positive	Herbold, 1984a
		-S9 mix	Positive	
Chromosome aberration assay in Chinese hamster V79 cells	97.1-98.9%	+S9 mix, rat	Study not acceptable, too low dose levels	Herbold, 1996
		-S9 mix		
TK+/- locus mutation test in mouse lymphoma L5187Y cells	99.1%	+S9 mix, rat	Positive	Hoorn and Heidemann, 1985
		-S9 mix	Positive	
HGPRT locus mutation test in Chinese hamster V79 cells	98.5%	+S9 mix, rat	Negative	Heidemann and Miltenburger, 1987
		-S9 mix	Negative	
HGPRT locus mutation test in Chinese hamster ovary cells	98.5%	+S9 mix, rat	Equivocal	den Boer, 1987
		-S9 mix	Equivocal	
Unscheduled DNA synthesis for DNA damage	98.7%	Not applicable	Negative	Brendler-Schwaab, 1995
***In vivo* Assays**				
Bone marrow cell micronucleus test in NMRI mice	94.3%	Not applicable	Negative	Herbold, 1980
Chinese hamster bone marrow chromosomal aberration test	99.7%	Not applicable	Positive, study of poor quality	Herbold, 1983
Chinese hamster bone marrow chromosomal aberration test	97.9%	Not applicable	Negative, study of poor quality	Voelkner, 1990
KUE13183B: *In vivo* bone marrow cytogenetic study using male mice	**96.2%**	**Not applicable**	**Negative**	**Herbold, 2004**
Sister chromatid exchanges in bone marrow cells of NMRI mice	97.9%	Not applicable	Negative	Voelkner, 1988a
Spot test in mice	98.4%	Not applicable	Negative	Herbold, 1988
Chromosome aberration assay in Chinese hamster spermatogonial cells	93.1%	Not applicable	Negative	Herbold, 1984b
Chromosome aberration assay in NMRI mouse spermatogonial cells	97.9%	Not applicable	Negative	Voelkner, 1988b
Dominant lethal test in mice	98.8%	Not applicable	Negative	Herbold, 1986
^{32}P-postlabeling assay in rats	100.5%	Not applicable	Negative	Calcagnotto *et al.*, 1997

Most of the *in vivo* tests with assays of somatic cells were negative. There was, however, weak clastogenic activity in one of the chromosome aberration assays in chinese hamster bone marrow cells (Herbold, 1983). The other *in vivo* aberration assay in chinese hamster (Voelkner, 1990) was negative, but the study is not acceptable since chromosome damage was examined only once 12 h after dosage. No indications of mutagenic effects on germ cells were observed (chromosome aberration assays of mouse and chinese hamster spermatogonial cells and the dominant lethal test in mice).

Overall, there were weak indications of mutagenicity both in *in vitro* studies with mammalian cells and in one *in vivo* study for chromosomal aberrations in chinese hamster bone marrow cells. The overall assessment of the mutagenic potential of tolylfluanid is complicated by the generally poor quality of the studies.

- As chromosome damage was indicated in both *in vitro* and *in vivo* studies, a new chromosome aberration study *in vivo* in rodents was required at relevant dose levels and with three sampling times between 6 and 48 h after dosage. A new study was supplied by the notifier (Herbold, 2004), in which male mice were administered tolylfluanid intraperitoneally at an MTD level of 16 mg/kg, including examination of chromosomal aberrations at three sacrifice times: 12, 24 and 48 h after administration. Tolylfluanid did not induce chromosomal aberrations in bone marrow cells compared to controls at any sacrifice time. The new study is considered acceptable.

The overall conclusion of genotoxicity testing of tolylfluanid is that the active substance can not be classified as mutagenic, based on the fact that the overall *in vivo* test data points towards negative results, although some clear or equivocal genotoxicity test results were encountered in the sole acceptable *in vitro* chromosome aberration test and in some of the tests for gene mutations in mammalian cells.

B.6.6 Reproduction toxicity (Annex IIA 5.6)

Summary of two-generation reproduction toxicity studies (Amended with a new study)

The reproduction toxicity of KUE 13183b was investigated in three acceptable two-generation reproduction studies (Holzum and Kaliner, 1989, Pickel and Rinke, 1995, Young and Fickbohm, 2004) and one supplementary study (Holzum1991c). One study was considered to be acceptable to give additional information (Löser, 1980). The NOAELs and LOAELs determined from these studies are expressed in Table 6.6-1.

Table 6.6-1 Summary of two-generation reproduction toxicity studies conducted in rats.

Species Strain	Test material	Application dates: day of gestation	Doses tested/ Route	NOAELs/LOAELs	Reference
Rat Long-Evans	KUE 13183b 98.8%	Two-generation study	0, 300, 1500, 7500 ppm Dietary	**Adults:** NOAEL 1500 ppm, based on decreased maternal body weight **Reproduction:** NOAEL 1500 ppm based on decreased survival index, lactation index and decreased fetal body weight	Löser, 1980
Rat Wistar	KUE 13183b, premix, 89.1-91.5%	Two-generation study	0, 300, 1200, 4 800 ppm Dietary	**Adults**: No NOAEL. LOAEL 300 ppm equal to approx. 23 mg/kg bw/day, based on decreased body weight **Reproduction**: No NOAEL. LOAEL 300 ppm based on decreased viability and lactation indices	Holzum and Kaliner, 1989
Rat Wistar	KUE 13183b, premix, 89.7-91.0%	Two-generation	0, 180 ppm Dietary	**Supplementary study** **Adults:** No effects at 180 ppm, equal to approx. 19 mg/kg bw/day **Reproduction**: Lactation index was reduced at 180 ppm in F2B pups only	Holzum, 1991c
Rat Wistar	KUE 13183b 95.7-97.9%	Two-generation	0, 100, 700, 4 900 ppm Dietary	**Adults:** NOAEL 100 ppm, equal to approx. 9 mg/kg bw/day based on decreased body weight **Reproduction:** NOAEL 100 ppm, based on decreased survival rate	Pickel and Rinke, 1995
Rat Wistar	KUE 13183b 96.6-99.1%	Two-generation	0, 100, 200, 800, 4 000 ppm Dietary	**Adults:** NOAEL 800 ppm**,** equal to approx. 46.8 mg/kg bw/day based on decreased body weight and alterations in food consumption in adults **Reproduction**: NOAEL **200 ppm**, equal to 31.5 mg/kg bw/day in lactating females, based on decreased pup body weight gains and decreased pup spleen weights	Young and Fickbohm, 2004

In the new two-generation toxicity study (Young and Fickbohm, 2004), the NOAEL for reproduction was 200 ppm, corresponding to approximately 31.5 mg/kg bw/day in lactating females, based on reductions in pup body weights and decreased pup spleen weights. The NOAEL for adults was 800 ppm (46.8/57.2 mg/kg bw/day) for premating males and females.

The NOAELs for reproduction and adults are not consistent in different studies. The NOAELs for pup mortality (decreased viability index, survival index and/or lactation index) were 100<180/<300/4000 ppm (LOAELs 180/300/700/>4000) depending on the study (Table 6.6-2). Decreased viability index, survival index and/or lactation index was observed at 300, 1200 and 4800 ppm (Holzum and Kaliner, 1989), and at 700 and 4900 ppm (Pickel and Rinke, 1995), and at 180 ppm (Holzum, 1991c), but were not observed by Young and Fickbohm (2004). According to Young and Fickbohm (2004), pup mortality did not increase at dose levels up to and including 4000 ppm, but body weights of pups were reduced at 800 ppm (F1 and F2 pups) and at 4000 ppm (F2

pups) (NOAEL 200 ppm). The number of stillborn pups was also slightly increased. The NOAELs for adults were 100/180/<300//800 ppm based on decreased body weight in different studies (LOAELs >180/300/700/4000).

Table 6.6-2 NOAELs and LOAELs in two-generation reproduction toxicity studies in rats.

Dose level (ppm / mg/kg bw/day)	Adult body weight ↓	Pup body weight ↓	Pup mortality ↑	Reference
100 / 8-10	NOAEL	NOAEL	NOAEL	Pickel and Rinke, 1995
100 / 6-7, 16[a]	No effect	No effect	No effect	Young and Fickbohm, 2004
180 / 19	No effect	No effect	**F2B**	Holzum, 1991c
200 /12-15, 32[a]	No effect	NOAEL	No effect	Young and Fickbohm, 2004
300	No effect	No effect	No effect/NOAEL?	Löser, 1980
300 / 20-26	**LOAEL**	No effect	**LOAEL**	Holzum and Kaliner, 1989
700 / 58-78	**LOAEL**	**LOAEL**	**LOAEL**	Pickel and Rinke, 1995
800 / 47-57, 124[a]	NOAEL	**LOAEL**	No effect **(stillborn ↑?)**	Young and Fickbohm, 2004
1200 / 83-109	**Effect**	**Effect**	**Effect**	Holzum and Kaliner, 1989
1500	NOAEL	NOAEL	NOAEL **/LOAEL?**	Löser, 1980
4000 / 237-281, 592[a]	**LOAEL**	**Effect**	No effect **(stillborn ↑?)**	Young and Fickbohm, 2004
4800 /336 -485	**Effect**	**Effect**	**Effect**	Holzum and Kaliner, 1989
4900 / 449-619	**Effect**	**Effect**	**Effect**	Pickel and Rinke, 1995
7500	**LOAEL**	**LOAEL**	**LOAEL**	Löser, 1980

[a]during lactation

The differences in NOAELs may be caused by coprophagia which was reduced in the study by Young and Fickbohm (2004), leading to decreased compound/metabolite intake, or microbial infections in test animal colonies (Pickel and Rinke, 1995), batch or strain differences, etc. Kilham rat virus positive animals were reported by Pickel and Rinke (1995), but KV-infections are often subclinical, and related pup mortalities are uncommon. The test animals could, however, have been suffering from other infections which, although not reported, might have caused pup mortality during lactation.

Table 6.6-2 shows that pup body weights decreased at 700/800 ppm and above (Pickel and Rinke, 1995; Young and Fickbohm, 2004), and that no effecst were observed at 300 ppm and below (Pickel and Rinke, 1995; Young and Fickbohm, 2004; Holzum 1991c; Löser, 1980; Holzum and Kaliner, 1989). The only contradictory finding is the no observed effect at 1500 ppm by Löser (1980). The effect on pup mortality is more complicated. Between exposure levels of 100 ppm and 300 ppm, there was usually no effect (Pickel and Rinke, 1995; Young and Fickbohm, 2004; Löser, 1980) with one exception (Holzum, 1991c). Thus, the new study with a NOAEL of 200 ppm based on reduced pup body weight, may be appropriate considering pup mortality also. In adults, body weight decrease was observed at 300 ppm and above, except at 800 ppm (Young and Fickbohm, 2004) and at 300 and 1500 ppm (Löser, 1980).

Based on the study by Young and Fickbohm (2004), pup body weights and spleen weight decreased at the non maternotoxic dose level of 800 ppm. **The NOAEL was 200 ppm (32 mg/kg bw/day in lactating females), which is also considered to be the overall NOAEL for effects on reproduction by tolylfluanid.**

B.6.6.1 Two generation reproductive toxicity in the rat (Annex IIA 5.6.1)

- *KUE 13183b (Tolylfluanid) – A Two-Generation Rreproductive Toxicity Study in the Wistar Rat.* ***Young, A.D. and Fickbohm, B.L., 2004***

Cross reference New study

Guidelines:
The design and conduct is in compliance with EU Guidelines on Reproductive Toxicity Studies, in the Official Journal of the European Communities, 91/414/EEC, February, 1995 and OECD Guideline 416, Two-Generation Reproduction Toxicity Study, January, 2001. The study complies also with the following guidelines: US EPA Health Effects Test guideline, OPPTS 870.3800 Reproduction and Fertility Effects, August, 1998; Japan, Ministry of Agriculture, Forestry, and Fisheries (JMAFF), Guideline on the Compiling of the Test Results on Toxicity, 12 Nousan No. 8147, April, 2001, and Health Canada, Guidelines on Reproduction Toxicity Studies, Canada Gazette, Part II, Vol 122 no 2, 1988.

GLP:
OECD Principles of Good Laboratory Practice (GLP), ENV/MC/CHEM(98)17; FIFRA Good Laboratory Practice Standards, 40 CFR Part 160; the TSCA Good Laboratory Practice Standards, 40 CFR Part 792, and the Japanese Ministry of Agriculture, Forestry, and Fisheries (JMAFF), The Standards of Good Laboratory Practice for Agricultural Chemicals, 11-Nousan-6283 (October 1, 1999).

The study is acceptable

Materials and methods

KUE 13183 B (batch no 231082198; purity: 96.6-99.1% measured for samples) was administered to groups of 30 male and 30 female Wistar rats (Crl:WI(HAN)) at nominal dietary concentrations of 0, 100, 200, 800 or 4 000 ppm relative to the percentage of purity of the test substance in a two generation study with one litter per generation. The compound was dry-mixed directly with the feed.

The P parents were mated to produce F1 litters. Litters were reduced to eight pups (as close as possible four males and four females) four days after birth. Following weaning of the F1 generation pups (21-days of age) approximately 30 pups/sex/group were randomly selected as parents of the F2 generation. Mating was accomplished by co-housing one female with one male for up to 14 consecutive days. Mating was confirmed by presence of sperm in vaginal smear and/or internal vaginal plug. Estrous cycle was determined for all P- and F1-generations females, over a three-week period prior to mating, and the estrous cycle stage was determined prior to termination.

Following weaning of their respective litters (lactation day 21) each dam (both P and F1 generations) was killed and a gross external examination was performed. For all P-and F1-generation males at termination, sperm was collected from one testes and one epididymis for enumeration of homogenization-resistant spermatids and cauda epididymal sperm reserves, respectively. In addition, an evaluation of the morphology and motility was performed on sperm sampled from the distal portion of the vas deferens. Morphology and counts were conducted on the control and highest group only.

The testes, epididymides, seminal vesicles with coagulating glands, prostate, uterus, brain, pituitary, thymus, liver, kidneys, adrenal glands, thyroids, and spleen were removed, weighed, and fixed. The following tissues were also collected and fixed: vagina, oviduct and cervix, physical identifier, gross lesions, and skullcap (adults). The ovaries and the testicle were fixed in Bouin´s fixative. A gross necropsy was performed also for non-pregnant animals as described, including a term body weight, estrous cycle, organ weights and organ preservation. The patency of the cervical/uterine os was also evaluated.

The following organs were examined histopathologically from adult animals (P and F1 generations): skullcap, liver, pituitary, adrenal glands, vagina, uterus, cervix, ovaries, oviducts, epididymis (caput, corpus, and cauda), seminal vesicles/coagulating gland, prostate, testis, gross lesions. A quantitative evaluation of the primordial ovarian follicles was conducted on 10 randomly assigned F1 dams per dose level. Histopathological evaluations and evaluations of the primordial ovarian follicles were conducted on the control and highest dose groups, with one exception. The reproducrtive organs were evaluated in any animal demonstrating affected fertility.

The time to preputial separation and vaginal opening were measures in the first generation (F1 pups). Anogenital distance was measured in F2 pups. F1 pups not selected to become parents of the next generation and all F2 pups were sacrificed and examined macroscopically for any structural abnormalities or pathological changes. From pups sacrificed on day 21, the brain, spleen, thymus, and vagina were weighed with some exceptions. One pup/sex/litter from each generation had the following reproductive tissues collected for microscopic exam: uterus, ovaries, vagina, cervix, oviduct, testes, epididymides, prostate, coagulating gland, and seminal vesicles.

The group means of test compound intakes were 0, 5.8, 12.0, 46.8 and 237.0 mg/kg bw/day for males and 0, 9.0, 18.4, 72.3 and 352.7 mg/kg bw/day for females at the corresponding diet levels of 0, 100, 200, 800 and 4 000 ppm, respectively.

The dose levels for females were 0, 7.0, 14.7, 57.2 and 281.0 mg/kg bw/day during the premating period, 0, 6.6, 13.5, 54.1, and 272.1 mg/kg bw/day during gestation, and 0, 15.9, 31.5, 123.7, and 592.4 mg/kg bw/day during lactation.

Results

No treatment-related mortality was observed in parent animals. One high dose female died delivering and one low dose female was found dead. One female at 200 ppm was sacrificed moribund.

Mean body weight was significantly reduced at 4 000 ppm; for P-generation males during premating and for pups during the lactation period on days 7-21 (F1 generation) or on day 21 (F2 generation) (Table 6.6-3). At 800 ppm, mean body weight was reduced in F1 pups. Food consumption decreased or increased in males depending on the time period, and decreased in females at 4 000 ppm during premating (P generation) and during lactation days 7-21 in both generations. There were no compound-related clinical signs, effects on mating, fertility, or gestation indices, days to insemination, gestation length, estrous cycle length or the number of cycles or the median number of implants in either generation.

Some stillborn pups were observed in the F2 generation both at the 800- and 4000-ppm dose levels. At 800 ppm, 5 out of the 6 stillborn were from one dam (Dam HO3605). At 4 000 ppm, 12 stillborn pups were delivered by four dams. The number of stillborn pups was outside of the laboratory's historical control, but this was not observed in two other two-generation reproduction studies (Holzum and Kaliner, 1989; Pickel and Rinke, 1995). Some pups were missing, found dead or cannibalized, but these findings were not dose-related.

A delay in preputial separation and in vaginal opening was observed in F1 pups at 4 000 ppm and was considered to be a secondary effect to the reduced pup growth. The anogenital distance measures in the F2 pups did not show any changes compared to controls.

There was an increase in the means for epididymal sperm counts in both generations but since the reproductive performance was unaffected there appears to be no biological significance. No significant differences in the means were observed on either motility or morphology.

Increased liver weights were observed in females of the 4 000 ppm dose group in both generations, and increased kidney weights were found in males and females of the F1 generation (Table 6.6-3). Variations in organ weights relative to controls may be a secondary response to alterations in body weight gain observed in both sexes at the highest dose tested. No microscopic changes were observed in these organs.

Table 6.6-3 Main observations in the two-generation toxicity study (Young and Fickbohm, 2004)

Parameters	100 ppm	200 ppm	800 ppm	4 000 ppm
P generation				
- Food consumption - Mean body weight			↓up to**(males)[a]	↓↑up to** (males) ↓ up to**(females) ↓ up to ** (males)
- Liver weight				↑*(abs+rel,females)
- Kidney weight				↑*(abs, females; rel males)
Testes - Reduced - Enlarged - Abnormal consistency			 2 1 2	 1
Epididymides - Abcess - Reduced in size	 1	 1	 1 1	 2
F1-generation, adults				
- Food consumption				↑ up to* (males) ↓ up to*(females)
- Liver				↑* (abs, females)
- Kidney				↑*(abs, both sexes, rel, males)
Testes -Reduced in size			 1	
Epididymides/Prostate/Seminal vesicle - Abcess - Reduced in size		 1	 3	
F1 generation, pups				
- Mean body weight			↓ **	↓ **
- Mean body weight gain			↓ **	↓ **
- Preputial separation - Vaginal opening			 	Delayed** Delayed**
- Reduced testicles			2	1
F2 generation, pups				
- Stillborn pups			↑ (6)	↑ (12)
- Mean body weight				↓ **
- Mean body weight gain				↓ **

[a]change observed only in indicated sex and/or generation
* $p<0.05$, ** $p<0.01$ (statistics: Dunnett's test)

Declines in absolute and/or relative spleen, thymus, and brain weights for pups were observed at 4 000 ppm in both generations and declines in spleen weights at and above 800 ppm in F1 pups (Table 6.6-4). Decreased organ weights relative to controls may be secondary to decreased body weights in pups.

There were no dose-related histopathological changes observed in any of the tissues examined (Table 6.6-5) nor were there any effects on the quantitative evaluation of ovarian follicle and corpora lutea distribution in the F1 generation. Tubular basophilia was observed in kidneys of P-generation (7/30) and F1-generation males (6/30) at 4 000 ppm. Lower doses were not examined.

Table 6.6-4 Organ weights in pups (g) (Young and Fickbohm, 2004)

Parameters	Control	100 ppm	200 ppm	800 ppm	4 000 ppm
F1 generation, pups					
Brain (male/female) -relative to body weight	1.500/1.447 3.058/3.039	1.495/1.454 3.058/3.087	1.486/1.428 3.093/3.139	1.495/1.444 **3.251*/3.275****	**1.451***/1.413 **3.584**/3.619****
Thymus (male/female)	0.240/0.228	0.228/0.239	0.218/0.217	0.208/0.213	**0.181*/0.184****
Spleen (male/female) -relative to body weight	0.240/0.245 0.496/0.488	0.232/0.231 0.467/0.489	0.223/0.216 0.458/0.472	**0.206**/0.200**** **0.443*/0.449***	**0.153**/0.151**** **0.376**/0.386****
F2 generation, pups					
Brain (male/female) -relative to body weight	1.495/1.467 2.997/3.101	1.477/1.443 3.124/3.148	1.477/1.446 2.974/3.012	1.512/1.455 **3.198***/3.159	1.469/1.441 **3.313**/3.327***
Thymus (male/female)	0.228/0.231	0.206/0.212	0.211/0.215	0.208/0.216	**0.191****/0.199
Spleen (male/female) -relative to body weight	0.240/0.229 0.478/0.478	0.232/0.231 0.476/0.493	0.247/0.234 0.492/0.483	0.224/0.222 0.467/0.476	**0.185**/0.181**** **0.408**/0.412****

*p<0.05, **p>0.01 (statistics: Dunnet's test)

Table 6.6-5 Histopathological findings (Young and Fickbohm, 2004)

Parameters	Control	100 ppm	200 ppm	800 ppm	4 000 ppm
P-generation					
Testes (examined) - atrophy/hypoplasia	30				30 2
Epididymis (examined) - abscesses - atrophy/hypoplasia - inflammation	30 1	1 1	1 1	1 1 1	30 1 2
Prostate (examined) - inflammation	30 1				30 3
Kidneys (examined) - **tubular basophilia** - dilatation - hemorrhage - inflammation - mineralization	58 7 10 5	1 1	2 2	1 1	59 **7 (males)** 4 1 12 5
Liver (examined) - inflammation - other findings	58 20 1				59 20 1
F1-generation, adults					
Testes (examined) - atrophy/hypoplasia - inflammation	30 1 1			1 1	30
Epididymis (examined) - abscesses - aspermia - inflammation	30 1		1 1	1 1	30 1
Prostate (examined) - inflammation - decreased secretion	30 1			1 1	29
Kidneys (examined) - **tubular basophilia** - cyst/(pelvic)dilatation - **fibrosis** - inflammation - other findings	54 **3** 4 4 5		2 1 1	1 1 **1** 1 2	57 **7 (6 males)** 1 **7** 6 2

Liver (examined) - inflammation - other findings	54 17		1 1	1	57 17 2

Conclusion

The NOAEL for reproduction was 200 ppm, corresponding to approximately 31.5 mg/kg bw/day in lactating females, based on the reductions in pup body weights and decreased pup spleen weights (Young and Fickbohm, 2004). The NOAEL for adults was 800 ppm, corresponding to 46.8 and 57.2 mg/kg bw/day for premating males and females, respectively, and 123.7 mg/kg bw/day for lactating females based on reduced body weights and food consumption.

Comments

Because only one mating per generation was made, it remains unclear whether similar or different effects would have been observed in the second litter. Coprophagia may increase the intake of the test compound and its metabolites. Coprophagia was prohibited by using wire bottom cages (except during pregnancy and lactation).

B.6.8 Further toxicological studies (Annex IIA 5.8)

B.6.8.1 The toxicological relevance of fluoride uptake after repeated administration of tolylfluanid

B.6.8.1.1 Subacute and subchronic studies

The only short-term repeated dose dose study with tolylfluanid where determinations of fluoride in bone and teeth were performed was a 52 week study in dogs with administration by the oral route. The results from the fluoride determinations are presented in Tables 6.8-1 and 6.8-2.

Table 6.8-1. Determination of fluoride in ashes from canine bone sections of dogs in a 52 week subchronic study by the oral route (Wetzig and Schilde, 1997).

Tolylfluanid (mg/kg bw/day)	Milligram fluoride / g ash	
	Male dogs	Female dogs
0	0.974 ± 0.245	0.879 ± 0.092
5	1.062 ± 0.229	0.955 ± 0.169
20	1.133 ± 0.075	1.111 ± 0.154 *
80	1.838 ± 0.162 *	1.587 ± 0.191 *

* $p < 0.05$ (Mann-Whitney U test)

Table 6.8-2. Determination of fluoride in ashes from canine teeth of dogs in a 52 week subchronic study by the oral route (Wetzig and Schilde, 1997).

Tolylfluanid (mg/kg bw/day)	Milligram fluoride / g ash	
	Male dogs	Female dogs
0	0.444 ± 0.076	0.358 ± 0.091
5	0.464 ± 0.082	0.589 ± 0.155 *
20	0.519 ± 0.027	0.517 ± 0.085
80	0.771 ± 0.068 *	0.670 ± 0.099 *

* $p < 0.05$ (Mann-Whitney U test)

No signs of fluorosis were observed at gross necropsy or histopathological examination in the 52 week dietary study in dog by Wetzig and Schilde (1997). Statistically significant increases in fluoride levels in bone were observed at the high dose of 80 mg/kg bw/day in males and at 20 and 80 mg/kg bw/day in females. Increased fluoride levels were determined in teeth of male dogs at 80 mg/kg bw/day, and in females at the low dose (5 mg/kg bw/day) and the high dose. Substantial variation between individuals was observed: the significant average increase in teeth fluoride in female dogs of the 5 mg/kg bw/day group is caused by two exceptionally high individual fluoride values of 0.745 and 0.700 mg/g ash. **The overall NOAEL for a clear increase of fluoride levels in canine bone and teeth in both sexes at administration of tolylfluanid in dog for 52 weeks is 20 mg/kg bw/day.**

B.6.8.1.2 Chronic studies

Determination of fluoride in bone and teeth was performed in one chronic study in rats (Leser *et al.*, 1996) and one 2-year study in mice (Leser and Ruehl-Fehlert, 1996). The results from determinations of fluoride levels in bone and teeth of rats are presented in Tables 6.8-3 and 6.8-4, and in mice in Tables 6.8-7 and 6.8-8. Histopathological findings probably related to release of fluoride from tolylfluanid in rats is presented in Tables 6.8-5 and 6.8-6, and in mice in Tables 6.8-9 and 6.8-10.

2-year rat study (Leser *et al.*, 1996)

Table 6.8-3. Determination of fluoride in ashes from bone and teeth of rats in a 2-year chronic study by dietary administration (Leser *et al.* , 1996). Results after 53 weeks of administration of tolylfluanid.

Tolylfluanid (ppm)	Milligram fluoride / g ash in bone	
	Males	Females
0	0.414	0.648
60	0.529	0.761
300	0.886	1.223
1500	2.389*	3.148*
7500	4.721*	7.693*
	Milligram fluoride / g ash in teeth	
	Males	Females
0	0.123	0.146
60	0.168	0.192
300	0.335*	0.393
1500	0.745*	0.952*
7500	2.706*	3.557*

* $p < 0.05$

Table 6.8-4. Determination of fluoride in ashes from bone and teeth of rats in a 2-year chronic study by dietary administration (Leser *et al.* , 1996). Results after 105 - 107 weeks of administration of tolylfluanid.

Tolylfluanid (ppm and mg/kg bw/day)	Milligram fluoride / g ash in bone	
	Males	Females
0	0.683	0.805
60 (3.6)	0.833	0.935
300 (18.1)	1.326*	1.360*
1500 (90.1)	3.289*	3.506*
7500 (504.2)	9.698*	10.899*
	Milligram fluoride / g ash in teeth	
	Males	Females
0	0.309	0.328
60 (4.2)	0.252	0.277
300 (21.1)	0.450	0.430
1500 (105.2)	1.097*	1.098*
7500 (584.4)	3.456*	3.822*

* $p < 0.05$

The results of fluoride determinations in teeth and bones of rats after 53 weeks and at the end of the 2-year study are presented in Tables 6.8-3 and 6.8-4. After 53 weeks the fluoride levels in teeth and bone start to rise usually at 1500 ppm, although a significant increase (2.7-times the control level) was also seen in teeth of males at 300 ppm. At the end of the study, fluoride levels in bone started to rise at 300 ppm (1.6 – 1.9-times the control level) and the levels in teeth were elevated starting from 1500 ppm (3.3 – 3.6-times the control level). The overall NOAEL for increased bone and teeth fluoride levels is 60 ppm (3.6 – 4.2 mg/kg bw/day).

Table 6.8-5. Incidences of gross pathological findings related to release of fluoride in main study groups (all animals: m= male, f = female) (Leser *et al.* , 1996).

Incidence of gross pathological findings in main groups										
Dose (ppm)	0	60	300	1500	7500	0	60	300	1500	7500
Sex	m	m	m	m	m	f	f	f	f	f
No. of animals	50	50	50	50	50	50	50	50	50	50
Skull discoloration	0	0	1	0	21	0	0	0	0	15
Teeth discoloration	0	0	2	3	7	0	0	0	0	8

Table 6.8-6. Conspicuous non-neoplastic findings related to release of fluoride in satellite groups and main study groups (Leser *et al.* , 1996).

Satellite groups										
Dose (ppm) Sex	0 m	60 m	300 m	1500 m	7500 m	0 f	60 f	300 f	1500 f	7500 f
SKULLCAP Altered bone matrix Focal hyperostosis	10 0 0	10 0 0	10 0 0	10 0 0	10 3 1	10 0 0	10 0 0	10 0 0	10 0 2	10 2 4
Main study groups										
Dose (ppm) Sex	0 m	60 m	300 m	1500 m	7500 m	0 f	60 f	300 f	1500 f	7500 f
STERNUM Osteopetrosis	50 0	49 0	50 0	49 0	50 41	49 0	50 0	49 0	50 0	48 29
SKULLCAP Focal hyperostosis	50 0	48 2	49 0	48 1	50 31	49 0	48 0	45 1	48 0	46 25

m= male, f = female

Histopathological examination of the rats showed increased hyperostosis of the skullcap and osteopetrosis of the sternum mainly at the highest dose (7500 ppm), but a few females also had hyperostosis of the skullcap at 1500 ppm. Discoloration of the skull and teeth was observed mainly at 7500 ppm, but a few cases of teeth discoloration were also observed at 300 and 1500 ppm. Effects on liver (hepatocellular changes), kidneys (papillary mineralisation) and the thyroids (follicular cell hyperplasia) were seen at 7500 ppm. The overall NOAEL in this 2-year rat study, taking also into account effects probably related with the release of fluoride from tolylfluanid, is 300 ppm (18.1 – 21.1 mg/kg bw/day). The overall LOAEL is 1500 ppm (91.1 – 105.2 mg/kg bw/day).

2-year mouse study (Leser and Ruehl-Fehlert, 1996)

Table 6.8-7. Determination of fluoride in ashes from bone and teeth of mice in a 2-year chronic study by dietary administration (Leser and Ruehl-Fehlert, 1996). Results after 54 weeks of administration of tolylfluanid.

Tolylfluanid (ppm)	**Milligram fluoride / g ash in bone**	
	Males	**Females**
0	1.107	0.926
60	1.200	1.089
300	1.777*	1.702*
1500	3.971*	3.167*
7500	9.936*	9.398*
	Milligram fluoride / g ash in teeth	
	Males	**Females**
0	0.258	0.250
60	0.312	0.292
300	0.517*	0.515
1500	1.205*	1.131*
7500	3.275*	3.595*

* $p < 0.05$

Table 6.8-8. Determination of fluoride in ashes from bone and teeth of mice in a 2-year chronic study by dietary administration (Leser and Ruehl-Fehlert, 1996). Results after 106 weeks of administration of tolylfluanid.

Tolylfluanid (ppm and mg/kg bw/day)	Milligram fluoride / g ash in bone	
	Males	**Females**
0	1.421	1.244
60 (15.3)	1.708	1.529*
300 (76.3)	2.465	2.427*
1500 (375.8)	5.492*	5.630*
7500 (2307.6)	10.862*	12.599*
	Milligram fluoride / g ash in teeth	
	Males	**Females**
0	0.398	0.452
60 (24.5)	0.513	0.498
300 (123.9)	1.004*	0.699
1500 (610.8)	1.860*	1.731*
7500 (2962.8)	5.192*	6.159*

* $p < 0.05$

The results of fluoride determinations in teeth and bones of mice after 54 weeks and at the end of the 2-year study are presented in Tables 6.8-7 and 6.8-8. After 54 weeks the fluoride levels in teeth and bone of mice start to rise at 300 ppm (1.6 – 2.1-times the control level). At the end of the study, fluoride levels in bone started to rise generally at 300 (2.5-times the control) and 1500 ppm (3.8 – 4.7-times the control), but fluoride levels in bones of females were slightly (1.2-times) elevated alredy at 60 ppm. The overall NOAEL for increased bone fluoride levels was 60 ppm (15.3 – 24.5 mg/kg bw/day) in males, whereas in females a slight increase in fluoride levels was observed already at the lowest dose of 60 ppm.

Table 6.8-9. Incidence of histological findings in satellite group mice probably related to release of fluoride from tolylfluanid (Leser and Ruehl-Fehlert, 1996).

Satellite groups										
Dose (ppm) Sex	0 m	60 m	300 m	1500 m	7500 m	0 f	60 f	300 f	1500 f	7500 f
No. of animals	10	10	9	10	10	10	10	11*	10	10
SKULLCAP Hyperostosis	10 0	10 0	9 0	10 0	10 0	10 0	10 0	11* 0	10 1	10 4
STERNUM Hyperostosis	10 0	10 0	9 0	10 0	10 0	10 0	10 0	11* 2	10 5	10 10

* = one female misplaced in the 300 ppm male group was removed and added to the 300 ppm female group at day 58

Histopathological findings in mice at dietary administration for 2 years probably related to the release of fluoride from tolylfluanid are presented in Tables 6.8-9 and 6.8-10. In the satellite and main study groups, skeletal changes in the skullcap, femur and nose were seen most clearly at the two highest doses of 1500 and 7500 ppm. These effects were more pronounced in females. Small increases in skeletal changes were, however, also seen at 300 ppm in both the satellite and main groups. For other effects, the most conspicuous findings were related to liver effects mainly in males at 1500 and 7500 ppm (hypertrophy of hepatocytes). The overall NOAEL, taking also account skeletal changes probably related to the release of fluoride from tolylfluanid, is 60 ppm (15.3 – 24.5 mg/kg bw/day). The LOAEL is 300 ppm (76.3 – 123.9 mg/kg bw/day).

Table 6.8-10. Incidence of histological non-neoplastic findings in main study group mice probably related to release of fluoride from tolylfluanid (Leser and Ruehl-Fehlert, 1996).

Main study groups										
Dose (ppm)	0	60	300	1500	7500	0	60	300	1500	7500
Sex	m	m	m	m	m	f	f	f	f	f
SPINAL CHORD	50	49	49	49	50	49	50	50	50	50
Fibroosseus lesion						29	33	38	39	5
hyperostotic lesion						4	1	3	8	44
STERNUM	50	49	49	50	49	49	50	50	50	50
hyperostosis	3	1	1	1	2	4			1	1
fibroosseus lesion	1					39	41	38	38	1
hyperostotic lesion			2			4	5	9	8	48
synchondric body tissue degeneration						11	5	6	14	25
cartilage	20	17	13	12	9	10	7	11	11	6
congestion, marrow			1		1	4	1			1
SKULLCAP	48	48	49	50	47	49	50	50	50	50
hyperostosis		1	1	5	17					
fibroosseus lesion						7	3	10	7	
hyperostotic lesion						2	4	6	23	44
FEMUR	50	49	49	50	50	49	50	50	50	50
fibroosseus lesion	1					28	38	36	42	41
hyperostosis femur epi	8	7	12	6	5	8	13	3	13	17
tibia	5	2	7	2	6	5	7	3	7	7
diameter						2	1		1	8
focal spongiosa	2	4	1	3	4	5	5	8	12	37
increased adipocytes		2	2	5	2	1	9	8	7	8
NOSE	50	49	49	50	50	49	50	50	50	49
hyperostosis					9					
fibroosseus lesion		1			1	10	21	21	29	1
hyperostotic lesion							2	1	6	43

m = male, f = female

Intake of fluoride at exposure to tolylfluanid

Tolylfluanid contains about 6% fluorine as part of the molecule. If the ADI is set at 0.2 mg/kg bw/day, based on the 2-year dietary study in rat with a NOAEL of 18.1 – 21.1 mg/kg bw/day (SF = 100), then the highest acceptable amount of fluoride released from the molecule is about 0.012 mg/kg bw/day. Table 6.8-11 presents a calculation of the intake of tolylfluanid based on the currently supported MRL:s for commodities in the European diet (Heimann, 2002).

Table 6.8-11. Calculation of the Theoretical Maximum Daily Intake (TMDI) of tolylfluanid according to WHO guideline (revised, 1997). The ADI is set at 0.2 mg/kg bw/day. Calculations are based on the European diet (FAO/WHO, 1998). The body weight of the consumer is assumed to be 60 kg (adapted from Heymann, 2002).

Commodity	MRL proposals (mg/kg)	Food consumption (g/person/day)	TMDI (mg/person/day)	TMDI (mg/kg bw/day)	% of ADI
Pome fruit	5	51.3	0.256500	0.004275	
Grapes	5	16.1	0.080500	0.001342	
Strawberries	3	5.3	0.015900	0.000265	
Cane fruit	5	0.5	0.002500	0.000042	
Other small fruit and berries	2	1.5	0.003000	0.000050	
Tomatoes and eggplants	2	68.3	0.136600	0.002277	
Peppers	2	10.4	0.020800	0.000347	
Cucumbers and courgettes	1	9.0	0.009000	0.000150	
Melons	0.2	18.3	0.003660	0.000061	
Lettuce and similar	15	24.5	0.367500	0.006125	
Leeks	2	2.0	0.004000	0.000067	
Hops	30	4.9 [a)]	0.147000	0.002450	
Meat	0.05*	208.5	0.010425	0.000174	
Edible offals	0.05*	12.6	0.000630	0.000011	
Fat	0.05*	8.0	0.000400	0.000007	
Milks	0.01*	294.0	0.002940	0.000049	
Eggs	0.05*	37.5	0.001875	0.000031	
Total			**1.063230**	**0.017721**	**8.9**

[a)] Value taken from German food consumption data (BBA Guideline Part IV, 3 – 7; 1993)
* Limit of quantification

The TMDI for tolylfluanid in the european diet is 0.017721 mg/kg bw/day. Assuming that the release of fluoride is 6% of the mass of tolylfluanid, then the expected intake of fluoride from tolylfluanid treated food commodities is about 0.0011 mg/kg bw/day.

In assessing the extent of exposure to fluoride released from tolylfluanid in consumers, all possible exposure sources must be considered. The main source for fluoride in most countries is direct consumption of drinking water. Food commodities are also a major source for fluoride intake in consumers. The WHO guideline for a maximum level of fluoride in water is 1.5 mg/litre (WHO, 1994). The UK Medical Research Council (MRC, 2002) has concluded that there is a risk for dental fluorosis in children at drinking water fluoride levels ≥2 mg/l. In areas where the natural levels of fluoride in water are low, the recommended maximum addition of fluoride in the form of tablets to prevent dental caries is 1.5 mg per day. Provided that the maximum allowable daily intake of fluoride from all sources should not exceed 1.5 mg per person, to avoid fluorosis, the allowable intakes as mg/kg bw/day for different age groups (addults 70 kg and children 20 kg bw) vary between 0.02 and 0.08 mg/kg bw/day.

If the total recommendable intake of fluoride in humans from all sources should not exceed 0.02 mg/kg bw/day, the addition of fluoride from tolylfluanid in the diet would contribute at most to about 5% of the total amount fluoride that can be safely ingested per day.

Summary of possible health effects of fluoride released from tolylfluanid

In rats, at life-time ingestion of tolylfluanid, fluoride levels in bone increased from 0.683 – 0.805 mg/g ash in controls to about 1.3 mg/g ash at a dose of about 20 mg/kg bw/day of tolylfluanid. In mice fluoride levels in bone increased from 1.244 – 1.421 mg/g ash in controls to 1.529 – 1.708 mg/g ash at a dose of >15 mg/kg bw/day. There is surprisingly little information about levels of fluoride in bones of humans in relation to ingested amounts, considering that the controversy over the benefits of fluoride supplementation of the diet has been

going on now for at least 40 years. Weatherell (1966) reported that the amount of fluoride in bones of humans, in areas where drinking water contains less than 0.5 mg/l fluoride, increases with age. In the age group 20 – 30 years the range of fluoride concentrations in bone varied between 0.2 and 0.8 mg/g ash, and in the age group 70 – 80 years from 1.0 to 2.5 mg/g ash. A direct comparison with animal data is difficult, but at the highest recommended level of fluoride in water (1.5 mg/l) the concentrations of fluoride in bones of humans in these aereas may expected to be higher than 0.6 mg/g ash and even higher than 5.0 mg/g ash in different age groups. Skeletal anomalies in rats and mice occurred clearly at feeding levels higher than 100 mg/kg bw/day tolylfluanid, when concentrations of fluoride in bones were usually over 3.0 mg/g ash. The dietary intake assessment for tolylfluanid and the fluoride released from it show that the tolylfluanid residues in food contributes little to the total amount of fluoride ingested per day.

Based on the animal studies and what is known about effects of fluoride in humans, the overall NOAEL:s for the 2-year rat study (about 20 mg/kg bw/day) and the 2-year mouse study (about 15 mg/kg bw/day) are approporiate also from the point of view of fluoride release from tolylfluanid and the likelyhood of fluorosis in humans at intake levels close to the ADI:s possibly set from these values.

B.6.8.2 Relevance of metabolites formed in plants for re-entry activities (Schöfer, 2003)

In plant metabolism studies of tolylfluanid performed with strawberries and grapes besides the parent compound and DMST (II) two further metabolites including their glucosides and several conjugates were detected and identified: 4-hydroxymethyl-DMST (III) and 2-hydroxyphenyl-DMST (V). The chemical structures of metabolites are shown in Table 6.8-14. Workers could be exposed to these metabolites by re-entry activities, especially at harvest. Therefore, exposure concentrations possibly occurring by re-entry activities were estimated for the metabolites 4-hydroxymethyl-DMST (III) (WAK5818), 4-hydroxy-methyl-DMST-glucoside (IV) (WAK6550), 2-hydroxyphenyl-DMST (V) (WAK6698), and 2-hydroxyphenyl-DMST-glucoside (VI) (WAK6676), and toxicological data were generated which allow a rough risk assessment for re-entry activities.

Risk assessment for re-entry activities: Toxicity of metabolites

Acute oral toxicity was tested for 4-hydroxymethyl-DMST (III) (WAK 5818), 4-hydroxymethyl-DMST-glucoside (IV) (WAK6550), 2-hydroxyphenyl-DMST (V) (WAK6698), and 2-hydroxyphenyl-DMST-glucoside (VI) (WAK6676). In addition, Ames tests were performed with all metabolites and WAK6698 was also tested in the mouse lymphoma test to evalute the mutagenic potential. All tested metabolites were negative in genotoxicity tests. The acute oral LD_{50} values were >5000 mg/kg bw for all compounds. Therefore, it can be concluded that the toxicities of the tested metabolites are lower or comparable to the toxicity of the parent compound tolylfluanid.

Exposure assessment

The exposure assessment of the metabolites in question is done by comparing possible exposure data of metabolites and the parent compound.

The exposure assessment for re-entry activities for the parent compound and DMST was performed on the basis of a.s. concentrations detected directly after the last application. To compare the exposure for re-entry activities performed for the parent compound with the potential exposure to metabolites, following findings have to be taken into consideration:

Time of exposure: Comparison of metabolic profiles of grapes and strawberries show that the intensity of metabolism probably depends on the PHI. In strawberries, 14 days after application only very low amounts of the metabolites in question were detected in and on fruits (sum total 11.5% of total recovered radioactivity (TRR)). In grapes, 35 days post-treatment, the amounts of metabolites were considerably higher, accounting for 77.4 % of the TRR (see Table 6.8-12). The metabolic degradation of tolylfluanid seems to be relatively slow, so

that considerably higher amounts of metabolites other than DMST are only formed when the time between application and harvest is relatively long. Accordingly, exposure to metabolites III, IV, V and VI via re-entry activities can only occur at the time of harvest.

Distribution in the plant: For re-entry activities only residues on the surface of fruits or leaves are to be considered. The metabolism study in strawberries showed that the amounts of 4-hydroxymethyl-DMST and 4-hydroxymethyl-DMST-glucoside as well as 2-hydroxyphenyl-DMST-glucoside or 3-hydroxyphenyl-DMST were significantly higher within the fruit than on the fruit surface. About 20 % of the 4-hydroxymethyl-DMST-derivates and 2-hydroxyphenyl-DMST-glucoside or 2-hydroxyphenyl-DMST were detected on the fruit surface while about 80 % were detected within the fruit (see Table 6.8-12).

Unfortunately, in the metabolism study with grapes where the highest amounts of the metabolites were found, surface rinse was not separately analysed. However, it can be assumed that the distribution between fruit surface and pulp is similar for different fruits with high water content and that the findings described in strawberry metabolism are also applicable for grapes.

Maximum concentrations of metabolites: Total residues determined in the metabolism study in grapes declined by a factor of 0.45 from 4.0 mg/kg TRR (total recovered radioactivity) immediately after application to 1.83 mg/kg TRR in the fruits at time of harvest. The main metabolite at the date of harvest in grapes was 4-hydroxymethyl-DMST-glucoside which accounted for 46% of the total recovered radioactivity (TRR). 2-Hydroxyphenyl-DMST-glucoside amounted to 13% of TRR, while the aglycons 4-hydroxymethyl-DMST and 2-hydroxyphenyl-DMST as well as other conjugates of these aglycons occurred in significantly lower amounts of up to 1.3% for the aglycons and up to 7.3% for mixtures of conjugates (see Table 6.8-12).

Table 6.8-12. Results of metabolism studies on [phenyl-UL-^{14}C]tolylfluanid in strawberries and grapes

		Grapes PHI = 35 days	Strawberries PHI = 14 days		
		in/on fruit [% of TRR]	surface rinse [% of TRR]	fruit [% of TRR]	% on surface
Tolylfluanid	I	13.1	63.0	2.7	
DMST	II	1.9	6.2	8.7	
4-Hydroxymethyl-DMST	III	1.3	0.8	2.1	28 %
4-Hydroxymethyl-DMST-glucoside	IV	46.0	1.0	5.6	15 %
4-Hydroxymethyl-DMST-conjugates		7.3			
Sum 4-Hydroxymethyl-DMST-derivates		54.6	1.8	7.7	19 %
3-Hydroxyphenyl-DMST-glucoside	VII	1.8			
3-Hydroxyphenyl-DMST-conjugates		1.7			
Sum 3-Hydroxyphenyl-DMST-derivates		3.5			
2-Hydroxyphenyl-DMST	V	0.2	0.3*	1.5*	17 %*
2-Hydroxyphenyl-DMST-glucuoside	VI	13.1			
2-Hydroxyphenyl-DMST-conjugates		6.0			
Sum 2-Hydroxyphenyl-DMST-derivates		19.3			

* 2-Hydroxyphenyl-DMST-glucoside or 3-Hydroxyphenyl-DMST

Calculation of maximum expected concentrations: Based on these considerations described above maximum expected exposure concentrations of metabolites at harvest compared to concentrations of the parent compound immediately after application were calculated. Compared to the concentration of the parent compound metabolite concentrations are reduced by different factors summarised below. Resulting maximum exposure concentrations are given in Table 6.8-13.

Decline of TRR between application and harvest:	45 % of initial TRR is detected at harvest
Part of the total amount of a metabolite detected on the fruit surface:	20 % on surface
Maximum amounts (in % of the TRR) of the metabolites found in grapes:	46% 4-hydroxymethyl-DMST-glucoside 13% 2-hydroxyphenyl-DMST-glucoside 1.3% 4-hydroxymethyl-DMST 0.2% 2-hydroxyphenyl-DMST 7.3% 4-hydroxymethyl-DMST-conjugates 6.0% 2-hydroxyphenyl-DMST-conjugates

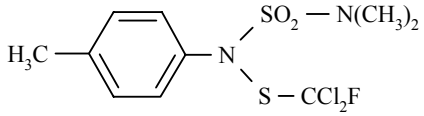
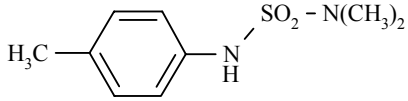
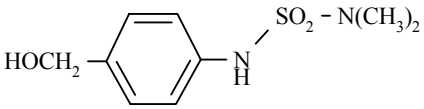
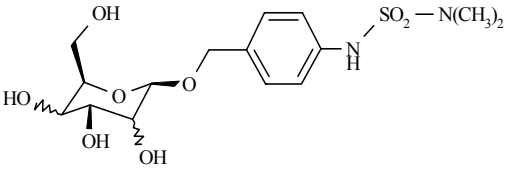
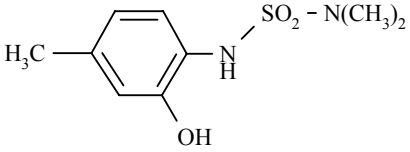
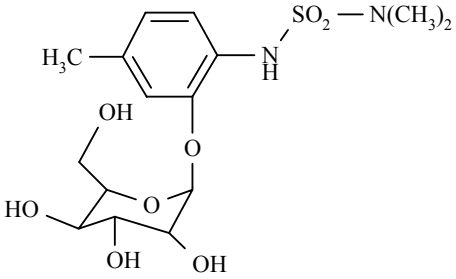
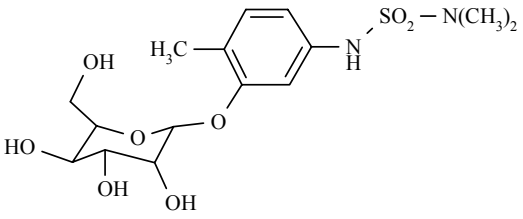
Table 6.8-13. Maximum exposure concentration (in % of maximum exposure concentration of tolylfluanid immediately after application)

Compound		Maximum exposure concentration [% of tolylfluanid]
4-hydroxymethyl-DMST-glucoside	IV	4 %
2-hydroxyphenyl-DMST-glucoside	VI	1 %
4-hydroxymethyl-DMST	III	0.1 %
2-hydroxyphenyl-DMST	V	<<0.1 %
4-hydroxymethyl-DMST–conjugates		< 0.5 %
2-hydroxyphenyl-DMST–conjugates		< 0.5 %

Conclusions

Based on the very low exposure compared to the parent compound and the lower or at most equal toxicity compared to the parent compound, it can be concluded that these metabolites can be considered as toxicologically non-relevant in terms of exposure by re-entry. The assessed metabolites include the plant specific metabolites WAK6550 (4-hydroxymethyl-DMST-glucoside), WAK6676 (2-hydroxyphenyl-DMST-glucoside) and WAK6698 (2-hydroxyphenyl-DMST).

Table 6.8-14. List of metabolites: Chemical structures of metabolites discussed in section 6.8.2.

No.	Formula	Name used in summaries Code used in toxicological reports and summaries
a.s.		**Tolylfluanid**
II		**DMST** Dimethylaminosulf-P-toluidid
III		**4-Hydroxymethyl-DMST** WAK 5818
IV		**4-Hydroxymethyl-DMST-glucoside** WAK 6550
V		**2-Hydroxyphenyl-DMST** WAK 6698
VI		**2-Hydroxyphenyl-DMST-glucoside** WAK 6676
VII		**3-Hydroxyphenyl-DMST-glucoside** WAK 6567

B.6.9. Medical data

B.6.9.1. Tolylfluanid – Assessement of literature research in various databases (Heimann, 2004)

In the DAR for tolylfluanid, Volume 1, Level 4 (Data requirements) more data on possible reports of clinical cases, poisoning incidents, exposure of the general population and epidemiological studies was required from the notifier. The notifier was asked to do extensive literature searches and report on the results. The data bases and search words used in the searches was also asked to be reported by the notifier.

The data bases used in the literature searches are presented in Table 6.9-1.

Table 6.9-1. The databases used for searches of reports on clinical cases, poisoning incidents, exposure of the general population and epidemiological studies linked to the use of plant protection products containing tolylfluanid.

Data base name or abbreviation	Full name of the data base
Biosis	
CCRIS	Chemical Carcinogenesis Research Information System
Chemical Abstracts	
Chemlist	
Chemtox	
CIVS	Chemikalieninformationssystem verbraucherrelevante Stoffe
Crop Protection File	
CSNB	Chemical Safety News Base
Current Contents/Scisearch	
Derwent Drug File/Ringdoc	
DOSE	Royal Society of Chemistry
Embase	
HSDB	Hazardous Substances Data Bank
IPA	International Pharmaceutical Abstracts
IRIS	Integrated Risk Information System
ISTPB	Index to Scientific and Technical Proceedings and Books
Medline	
MSDS	Material Safety Data Sheets
NIOSHTIC	National Institute for Occupational Safety and Health, Techbical Information Center
RTECS	Registry of Toxic Effects of Chemical Substances
Somed	SozialMedizin und Public Health
Toxbio	
Toxline	
Ulidat	Umwelt-Literaturdatenbank

The following search terms were used:

- CAS No: 731-27-1
- KUE 13183B
- Tolylfluanid
- Euparen M
- Medical data
- Medical experiences with humans
- Poisoning cases".

Results

The summary from the notifier, Bayer CropScience, states that no adverse effects could be detected related to human.

B.6.12. Dermal absorption (Annex IIIA 7.3)

In the DAR of tolylfluanid, the estimation of dermal absorption for the undiluted product and 1:10 and 1:100 dilutions of the a.s. was based only on the *in vivo* dermal absorption study in rat by Weber (2001). Below, a re-estimation of the expected dermal absorption in humans is presented, based on the data presented in the *in vivo* study, and taking into account the difference in dermal penetration between rat and humans (*in vitro* comparison of dermal penetration through rat and human skin by van de Sandt, 2001)

B.12.1 [Phenyl-UL-14C]tolylfluanid 50 WG (Euparen M): percutaneous absorption study in the rat (7.3/01; Weber, 2001)

Test guideline and GLP

The study was performed according to GLP and the method complied with draft OECD guideline 427 for the testing of chemicals - Skin absorption: *in vivo* method.

Materials and methods

The purpose of the study was to investigate the percutaneous absorption of the preparation related radioactivity, its penetration through the skin and its elimination via excretion after different exposure periods. Three groups of 4 male Wistar rats were treated with uniformly 14-C labeled tolylfluanid aqueous suspensions of the formulation on a skin area of l0 cm² to give target dose levels related to the active substance of 7.5, 0.75 and 0.075 mg per animal, corresponding to l5, l.5, and 0.15% of the product. The animals were exposed under non-occlusive conditions for periods of 8 and 24 hours. In an additional test serious the application site was washed after a contact time of 8 hours and the animals were sacrificed l68 hours after application in order to study the absorption kinetics and to follow the bioavailability of the residues remaining on the skin after washing.

Results

After an exposure period of 24 hours the percutaneously absorbed radioactivity amounted for the formulated product in aqueous suspension to l.9% of the recovered radioactivity after application of 7.5 mg (l5% Euparen M 50 WG), to 12% of the recovered radioactivity after application of 0.75 mg (l.5% Euparen M 50 WG), and to 32% of the recovered radioactivity after application of 0.075 mg (0.l5% Euparen M 50 WG). In other terms, the absorbed amount of radioactive tolylfluanid accounted for the formulated product in aqueous suspension to14 µg/cm^2 of the recovered radioactivity after application of 7.5 mg, to 9.3 µg/cm^2 of the recovered radioactivity after application of 0.75 mg, and to 2.6 µg/cm^2 of the recovered radioactivity after application of 0.075 mg. The radioactivity remaining in the washed skin at the application side after 24 hours amounted for 7.0%, 8.2% and 13% of the recovered dose for the high, intermediate and low dose, respectively. The fraction not absorbed after the 24 h exposure, calculated from the radioactivity determined in the rinsing of all material that was in contact with the skin, amounted to 91%, 80% and 55% of the recovered dose for the high, intermediate and low dose, respectively (Table 6.12-1).

After an exposure period of 8 hours the respective values are given in Table 6.12-1.

During the l60 h post-exposure period, the radioactivity fraction remaining in the washed skin at the application site was bioavailable to further absorption, yielding absorption of 3.8%, 7.0% and 22% of the recovered radioactivity, for the high, intermediate and low dose, respectively.

The radioactivity entering the body was not extensively retained in the tissues but was rapidly eliminated from the body and excreted mainly via the urine: The excretion ratio renal to fecal after l68 h was about 8:l. The compound-related residue in the sum of the tissues and organs excluding the skin at the application site, obtained for the three dose groups was low ranging between 0.2 and 0.6% of the recovered radioactivity.

Table 6.12-1. Percutaneos absorption of ^{14}C-Tolylfluanid 50 WG in aqueous formulations in the male rat (mean values, normalised for 100% recovery)

Applied amount of ^{14}C-Tolylfluanid [mg/ l0 cm² of rat skin]	7.5			0.75			0.075		
Time of sacrifice [n=4, each group]	8	24	168*	8	24	168*	8	24	168*
Radioactivity absorbed [%]	1.3	1.9	3.8	3.8	12	7.0	13	32	22
Radioactivity absorbed [µg/cm^2]	9.5	14	29	2.9	9.3	5.3	1.1	2.6	1.7
Radioactivity remaining in the washed skin [%]	6.7	7.0	0.2	3.0	8.2	0.5	14	13	2.9
Radioactivity remaining in the washed skin [µg/cm^2]	49	52	1.2	2.3	6.4	0.4	1.1	1.0	0.2
Radioactivity not absorbed [%]	92	91	96	93	80	93	73	55	75
Recovery [% of applied dose]	90-100	90-100	99-102	105-109	102-115	101-104	92-110	102-105	90-111

* 8h exposure followed by 160 h observation period

Conclusion

Absorption of tolylfluanid related radioactivity in rats during 8 hours continuous exposure to formulations of 7.5, 0.75 or 0.075 mg of ^{14}C-tolylfluanid per animal and 10 cm^2 skin area ranged between 1.3% and 13% of the recovered dose. Taking into account the radioactivity remaining in the skin as a potential reservoir for systemically available tolylfluanid, the total available amounts of a.s. after 8 h of exposure are 8%, 7% and 27% for the undiluted product, 1:10 and 1:100 dilutions, respectively. For the undiluted product and the different dilutions, the amounts absorbed within 8-168 h ranged between 0.02 and 0.29 mg / 10 cm^2 of skin; i.e. after treatment with amounts of tolylfluanid ranging over two orders of magnitude, a difference of amounts absorbed of one order of magnitude was observed. The study is acceptable.

B.6.12.2 In vitro percutaneous absorption study with [phenyl-UL-14C]tolylfluanid (Euparen M 50 WG) using human and rat epidermal membranes (7.3/02; van de Sandt, 2001)

Test guideline and GLP

The study was performed according to GLP and the method complied in general with draft OECD guideline 428 for the testing of chemicals - Skin absorption: *in vitro* method. However, the exposure system differed from the diffusion cell application mentioned in OECD guideline 428, but is considered as acceptable.

Materials and methods

The purpose of the study was to investigate the in vitro percutaneous absorption of the preparation related radioactivity through rat and human epidermal membranes.

Tolylfluanid was examined as formulation in three aqueous suspensions (l.707 [15% Euparen M 50 WG], 0.082 [1.5% Euparen M 50 WG] and 0.0073 [0.15% Euparen M 50 WG] mg/cm²) and as pure compound (0.638, 0.071and 0.0068 mg/cm²). Human skin samples from one female Caucasian donor and skin from 4 male Sprague Dawley rats were prepared to obtain epidermal membranes after chemical separation from the dermis. Membrane integrity was tested by determining the permeability coefficient (k_p) for tritiated water. A testosterone

application served as reference (historical control). The formulations were applied to the skin membranes with the aid of glass rings glued to the epidermis. Skin samples were transferred into well plates allowing contact to the receptor fluid (physiological saline) to the dermal side while stratum corneum remained in air contact. The plates were incubated at 32º C. The epidermis surface (0.64 cm^2) was exposed to the chemicals dissolved in various matrices in volumes of predominantly 6.4 µl and left unoccluded for 24 h. Samples of the receptor fluid were taken at 1, 2, 4, 6, 8, 10, 20, 22 and 24 h after application for analysis of penetrated radioactivity.

Results

For tolylfluanid as an ingredient of Euparen M 50 WG, the relative skin absorption through human epidermis after 24 hours was 0.23 % (15 % aqueous suspension), 2.l9 % (1.5 % aqueous suspension) and 8.50 % (0.15 % aqueous suspension) of the applied dose. In rat epidermis, the relative skin absorption was 0.35 %, 3.82 % and 3l.2 %, respectively. In other terms, the absorbed amount of radioactive tolylfluanid accounted for human epidermis to 4.04 µg/cm^2 (15 % aqueous suspension), 1.80 µg/cm^2 (1.5 % aqueous suspension) and 0.62 µg/cm^2 (0.15 % aqueous suspension). Through rat epidermis, the absorption was 6.0 µg/cm^2, 3.14 µg/cm^2 and 2.27 µg/cm^2, respectively (Table 6.12-2).

For tolylfluanid as pure compound, the relative skin absorption through human epidermis after 24 hours was l.60 % (0.638 mg/cm², high dose), 5.98 % (0.071 mg/cm², intermediate dose) and 5.42 % (0.0068 mg/cm², low dose) of the applied dose. In rat epidermal membranes, the relative skin absorption was l.20 %, l2.2 % and 7.25 %, respectively. In other terms, the absorbed amount of radioactive tolylfluanid accounted for human epidermis to 10.2 µg/cm^2 (0.638 mg/cm², high dose), 4.22 µg/cm^2 (0.071 mg/cm², intermediate dose) and 0.37 µg/cm^2 (0.0068 mg/cm², low dose). Through rat epidermis, the absorption was 7.63 µg/cm^2, 8.61 µg/cm^2 and 0.50 µg/cm^2, respectively (Table 6.12.3).

After an exposure period of 8 hours the respective values are given in Table 6.12-2 for tolylfluanid as an ingredient of Euparen M 50 WG and Table 6.12-3 for tolylfluanid as pure substance.

The substance's penetration rates (flux) are given in Table 6.12-2 for tolylfluanid as an ingredient of Euparen M 50 WG and in Table 6.12-3 for tolylfluanid as pure substance. The fluxes for human and rat epidermal membranes range for the respective dose within the same order of magnitude. Fluxes arising from penetration of tolylfluanid as an ingredient of Euparen M 50 WG were in the same order of magnitude as the ones obtained from the pure substance determinations. A tendency towards higher permeability of rat skin compared to human skin was reported. Based on fluxes, rat epidermal membranes were 2 to 4 times more permeable than the human epidermis to tolylfluanid when applied as an ingredient of Euparen M 50 WG. When tolylfluanid was applied as pure compound, no clear species ranking concerning permeability was possible. However, the comparison is based on epidermal membrane samples of one human donor only.

Table 6.12-2. *In vitro* percutaneous absorption of tolylfluanid <u>as an ingredient of EUPAREN M 50 WG</u> through human and rat epidermal membranes (mean values)

Applied amount of ^{14}C-Tolylfluanid [mg/cm² of skin]	1.707 (≈15% Euparen M 50 WG)				0.082 (≈1.5% Euparen M 50 WG)				0.0073 (≈0.15% Euparen M 50 WG)			
Radioactivity absorbed	of applied dose [%]		amount [µg/cm²]		of applied dose [%]		amount [µg/cm²]		of applied dose [%]		amount [µg/cm²]	
	Human [n=1*]	Rat [n=4]	Human [n=1*]	Rat [n=4]	Human [n=1*]	Rat [n=3]	Human [n=1*]	Rat [n=3]	Human [n=1*]	Rat [n=4]	Human [n=1*]	Rat [n=4]
Time of exposure [h]												
8	0.09	0.17	1.60	2.87	0.60	1.29	0.49	1.06	2.18	7.91	0.16	0.58
24	0.23	0.35	4.04	6.00	2.19	3.82	1.80	3.14	8.50	31.2	0.62	2.27
Flux [µg/cm^2/h]	0.21	0.35			0.08	0.13			0.03	0.11		
Recovery [% of applied dose]	31-98	94-147			88-173	87-140			78-105	87-107		

* 4-fold determination

Table 6.12-3. *In vitro* percutaneous absorption of Tolylfluanid as pure substance through human and rat epidermal membranes (mean values)

Applied amount of ^{14}C-Tolylfluanid [mg/cm² of skin]	0.638				0.071				0.0068			
Radioactivity absorbed	of applied dose [%]		amount [µg/cm²]		of applied dose [%]		amount [µg/cm²]		of applied dose [%]		amount [µg/cm²]	
	Human [n=1*]	Rat [n=4]	Human [n=1*]	Rat [n=4]	Human [n=1*]	Rat [n=4]	Human [n=1*]	Rat [n=3]	Human [n=1*]	Rat [n=4]	Human [n=1*]	Rat [n=4]
Time of exposure [h]												
8	0.44	0.47	2.83	2.97	1.61	4.35	1.13	3.07	1.79	4.44	0.12	0.30
24	1.60	1.20	10.2	7.63	5.98	12.2	4.22	8.61	5.42	7.25	0.37	0.50
Flux [µg/cm²/h]	0.46	0.31			0.19	0.39			0.02	0.05		
Recovery [% of applied dose]	101-117	66-101			86-99	88-98			77-93	80-90		

* 4-fold determination

Conclusion

The *in vitro* penetration of tolylfluanid through human epidermal membranes during 24 hours continuous exposure to l.707 (15% Euparen M 50 WG), 0.082 (1.5% Euparen M 50 WG) or 0.0073 (0.15% Euparen M 50 WG) mg/cm² ranged between 0.23% and 8.50 % or between 1.60% and 5.98 % (as pure compound, exposure to 0.638, 0.071 or 0.0068 mg/cm²) of the applied dose. Based on the penetration rates (flux), rat epidermis showed a tendency towards higher permeability compared to human epidermis. The differences in flux rates (rat/human) for tolylfluanid as ingredient of Euparen M50 WG were 1.67, 1.63 and 3.67 for the undiluted formulation and 1.10 and 1:100 dilutions thereof, respectively. However, the comparison is based on epidermal membrane samples of one human donor only. The study is acceptable.

B.6.12.4 Summary of dermal absorption

The studies on dermal absorption of ^{14}C-tolylfluanid *in vivo* and *in vitro* showed a good correlation in the rat; i.e. the penetration values obtained were comparable. On a mass basis, similar initial doses resulted in similar penetration after 24 h exposure. A slight tendency towards lower penetration *in vitro* could be assessed (flux rate rat/human: 1.67, 1.63 and 3.67 using undiluted Euparen M50 WG and 1:10 and 1:100 dilutions), however the values were within the same order of magnitude (Table 6.12-4). The species comparisons are based on one human skin sample only.

Table 6.12-4. *In vitro* and *in vivo* absorption of ^{14}C-Tolylfluanid through rat skin after 24 h exposure (mean values)

Dose	High			Intermediate			Low		
	in vivo	***in vitro***		***in vivo***	***in vitro***		***in vivo***	***in vitro***	
	As ingredient of Euparen M 50 WG		As pure substance	As ingredient of Euparen M 50 WG		As pure substance	As ingredient of Euparen M 50 WG		As pure substance
Applied amount of ^{14}C-Tolylfluanid [mg/cm² of skin]	0.75	1.707	0.638	0.075	0.082	0.071	0.0075	0.0073	0.0068
Radioactivity absorbed [µg/cm^2]	14	6.0	7.6	9.3	3.1	8.6	2.6	2.3	0.5

Based on the *in vivo* dermal absorption study in rat, the proposed skin absorption figures to be used in occupational exposure risk assessment are 5, 4 and 7% for the undiluted product and 1:10 and 1:100 dilutions of the product, respectively. The absorption figures are based on the percentage of radioactivity absorbed after 8 hours of dermal exposure added with the percentage of radioactivity remaining with the skin in the *in vivo* dermal absorption study in rat, corrected with the differences in fluxes of dermal penetration between rat and human skin *in vitro* of the formulated product.

B.6.14. Re-entry exposure

Re-entry exposure may occur if the worker enters the sprayed area relatively shortly after application. For post application exposures the dermal absorption is in general considered to be the most important exposure route, while inhalation exposure is less important, especially in outdoor scenarios. In this addendum estimations of re-entry exposure through the dermal and inhalation routes are calculated based on EUROPOEM II final report recommendations (Europoem II Project FAIR3-CT96-1406, December 2002).

Re-entry exposure to tolylfluanid in the DAR was estimated after single application. In this addendum estimations are also made by taking into account the possibility of tolylfluanid accumulation on the leaves after consecutive applications.

The accumulation calculations are based on the following parameters: Tolylfluanid mass deposition on the leaves after single application, the decline rate between applications and the number of applications (Table 6.14-1). The mass loading on the leaves directly after the final application represents a worst case scenario and probably overestimates the situation after the pre-harvest interval (PHI). The notifier has submitted the decline rate estimates based on residue studies. The decline rate estimates were determined from the time periods that reflected mean or minimum application intervals (Table 6.14-2). Since no specific DFR data are available, the DFR values were calculated from the application rate (AR) values and the leaf area index (LAI) estimates that were introduced in the EUROPOEM II report (DFR = AR / LAI). The LAI value in DRF calculations was assumed to be 2 (both sides of the leaves are sprayed). A dermal absorption value of 7 % was used (spray solution 1:100) in the calculations. The model input parameters are shown in Table 6.14-3.

Table 6.14-1. The number of applications and intervals between applications.

Crop	Max no. of applications	Application interval (days)	Time period where the decline rate was determined (field study) (days)
Strawberries	3	7-10	7
Grapes	8	8-19	14
Apples	7	7-14	7
Cucumber	6	***	3

*** no data available

Table 6.14-2. Tolylfluanid mass on the surface of the leaves after single and consecutive applications.

			DFR cumulative (µg/cm^2)							
Crop	DFR[a] single spray µg/cm^2	Decline %	1.spray	2. spray	3. spray	4.spray	5. spray	6. spray	7.spray	8.spray
Strawberries	**1.25**	80	1.25	2.25	**3.05**	***	***	***	***	***
Grapes	**1.00**	70	1.00	1.70	2.19	2.53	2.77	2.94	3.06	**3.14**
Apples	**0.75**	50	0.75	1.13	1.32	1.41	1.46	1.48	**1.49**	***
Cucumber	**0.75**	50	0.75	1.13	1.32	1.41	1.45	**1.48**	***	***

DFR = dislogdeable foliar residue, [a] DFR_{single} = application rate / LAI (=2), *** no spraying

Dermal re-entry exposure is estimated by the algorithm (results in Table 6.14-4):

$$\mathbf{E_{systemic} = DFR \times TF \times T \times AR \times DA / BW}$$

where: E_{Total} = Estimated potential exposure, mg/ kg bw/day
DFR = Dislodgeable foliar residue, µg/cm^2
TF = Transfer coefficient factor, cm^2/person x h
T = Work rate, h/day
AR = Application rate
DA = Dermal absorption percentage of spray solution, 7 %
BW= Body weight, 60 kg

Inhalation exposure for the glasshouse scenario is estimated by the algorithm (results in Table 6.14-5):

mg as / h inhaled = kg as / ha applied x task specific factor

where: task specific factor = 0.03 (low-volume mist application)
Time of exposure= 6 h
Inhalation absorption= 100%
Body weight = 60 kg

Table 6.14-3. The model input parameters.

Scenario	Transfer coeff. bare hands + coverall (cm^2/person x h)	Transfer coeff.[b] gloves + coverall (cm^2/person x h)	AR (kg/ha)	DFR single (µg/cm^2)	DFR cumulated (µg/cm^2)	Work rate (h/day)
Strawberries	3 000	750	2.5	1.25	3.05	6
Grapes	4 500	2250	2.0	1.00	3.14	6
Apples	4 500	2250	1.5	0.75	1.49	6
Cucumber	5 000	500	1.5	0.75	1.48	6

[b] 10 % penetration trough gloves is assumed, AR = application rate, DFR = dislogdeable foliar residue

Results

Table 6.14-4. Re-entry exposure and comparison to the AOEL (0.3 mg/ kg bw/day).

Crop	EXPOSURE FOR SINGLE SPRAY				EXPOSURE FOR CONSEQUTIVE SPRAYS			
	Systemic exposure (no Gloves) mg/kg/day	Systemic exposure (with Gloves) mg/kg/day	% AOEL (no Gloves)	% AOEL (with Gloves)	Systemic exposure (no Gloves) mg/kg/day	Systemic exposure (with Gloves) mg/kg/day	% AOEL (no Gloves)	% AOEL (with Gloves)
Strawberries	0.0656	0.0164	**22**	**5**	0.1601	0.0400	**53**	**13**
Grapes	0.0630	0.0315	**21**	**11**	0.1978	0.0989	**66**	**33**
Apples	0.0354	0.0177	**12**	**5.9**	0.0704	0.0352	**23**	**12**
Cucumber	0.0394	0.0039	**13**	**1.3**	0.0777	0.0078	**26**	**2.6**

Table 6.14-5. Re-entry exposure in glasshouse scenario and comparison to the AOEL (0.3 mg/ kg bw/day).

Crop	Dermal exposure (no Gloves) mg/kg/day	Inhalation exposure (no RPE) mg/kg/day	Systemic exposure (no PPE) mg/kg/day	% AOEL (no PPE)	Dermal exposure (with Gloves) mg/kg/day	Inhalation exposure (with RPE) mg/kg/day	Systemic exposure (with PPE) mg/kg/day	% AOEL (with Gloves)
Cucumber Glasshouse	0.0777	0.0225	**0.100**	**33**	0.0078	0.00225	**0.010**	**3**

RPE = Respirator, protection efficiency 90 %

Conclusions

The model predictions indicate that re-entry exposure after single application as well as after consecutive applications in outdoor and indoor scenarios stays below the AOEL when appropriate PPE are worn (gloves and garments).

B.6.15 References relied on

Author(s)	Annex point/ reference number	Year	Title **Source** (where different from company) **Company name, Report No., Date,** **GLP status** (where relevant)**, published or not**	Data protect. claimed	Owner
Boer, W. C. den	II A, 5.4.1/06	1987	Mutagenicity test on KUE 13183b in the CHO/HGPRT forward mutation assay Hazleton Biotechnologies Laboratory, Veenendaal, Netherlands Bayer AG, ReportNo.:R4204, Date:1987-08-24 GLP, Non Published	Yes	BAY
Bomhard, E.	II A, 5.3.1/01	1988	KUE 13183 b - Subacute toxicological study on the question of an effect on the thyroid in rats (four-week feeding test) Bayer AG, ReportNo.:17183, Date:1988-09-28 GLP, Non Published	Yes	BAY
Bomhard, E.; Schilde, B.	II A, 5.3.2.1/01	1976	KUE 13183B - Subchronic toxicological experiments on rats (feeding experiment over 3 months) Bayer AG, ReportNo.:5929, Date:1976-02-20 Non GLP, Non Published	Yes	BAY
Brendler-Schwaab, S.	II A, 5.4.1/08	1995	KUE 13183B - Test on unscheduled DNA synthesis in rat liver primary cell cultures in vitro Bayer AG, ReportNo.:24436, Date:1995-10-31 GLP, Non Published	Yes	BAY
Calcagnottto, A. M.; Jeffry, A. M.; Luo, F. Q.	II A, 5.4.2/09	1997	32P-postabeling assay for detection of adduct formation by tolylfluanid (TF) in rat lung, thyroid and liver DNA American Health Foundation, Valhalla, NY, USA Bayer AG, ReportNo.:R6933, Date:1997-08-25 GLP, Non Published	Yes	BAY
Dreist, M.	II A, 5.3.2.1/02	1995a	KUE 13183B (common name: Tolylfluanid) - Subchronic toxicity study in wistar rats (thirteen-week administration in the diet with a four-week recovery period) Bayer AG, ReportNo.:24334, Date:1995-09-27, Amended:2000-10-04 GLP, Non Published *CONFIDENTIAL*	Yes	BAY
Heidemann, A.; Miltenburger, H. G.	II A, 5.4.1/05	1987	KUE 13183b - Detection of gene mutations in somatic mammalian cells in culture: HGPRT-test with V79 cells - Test report of study LMP 260 Laboratorium fuer Mutagenizitaetspruefung, Darmstadt, Germany Bayer AG, ReportNo.:R4103, Date:1987-05-08 GLP, Non Published	Yes	BAY

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Heimann, K.G.	II A, 5.8	2002	Assessment of fluoride uptake after prolonged administration of tolylfluanid Bayer AG Date: 2002-07-17 Non GLP, Non Published	-	BAY
Heimann, K.G.	II A, 5.9	2004	Tolylfluanid - Assessment of literature research in various databases Bayer CropScience AG, Report No.: MO-04-004642 Date: 2004-05-04 Non GLP, Non Published	Yes	BAY
Herbold, B.	II A, 5.4.1/01	1979	KUE 13183b - Salmonella/microsome test for point mutagenic effects Bayer AG, ReportNo.:8265, Date:1979-03-30 Non GLP, Non Published	Yes	BAY
Herbold, B.	II A, 5.4.2/01	1980	KUE 13183 b (Tolylfluanid) - Micronucleus test on the mouse to evaluate for mutagenic effect Bayer AG, ReportNo.:9149, Date:1980-05-13 Non GLP, Non Published	Yes	BAY
Herbold, B.	II A, 5.4.2/02	1983	KUE 13183 b (tolylfluanid, Euparen M, Preventol VP OC 3017) - Cytogenetic study of the chinese hamsters bone marrow in vivo to evaluate for mutagenic effect Bayer AG, ReportNo.:11792, Date:1983-05-10, Amended:2000-10-13 Non GLP, Non Published	Yes	BAY
Herbold, B.	II A, 5.4.1/02	1984a	KUE 13183b (c.n. tolylfluanid) - Cytogenetic study with human lymphocyte cultures in vitro to evaluate for harmful effect on chromosomes Bayer AG, ReportNo.:12836, Date:1984-08-06, Amended:2000-10-13 Non GLP, Non Published	Yes	BAY
Herbold, B.	II A, 5.4.203	1984b	KUE 13183b - Cytogenetic study of the spermatogonia of the chinese hamster in vivo to evaluate for mutagenic effect Bayer AG, ReportNo.:12739, Date:1984-06-08 Non GLP, Non Published	Yes	BAY
Herbold, B.	II A, 5.4.2/04	1986	KUE 13183b C. N. tolylfluanid - Dominant lethal test on the male mouse to evaluate for mutagenic effect Bayer AG, ReportNo.:15017, Date:1986-08-26 GLP, Non Published	Yes	BAY

Author(s)	**Annex point/ reference number**	**Year**	**Title** **Source** (where different from company) **Company name, Report No., Date,** **GLP status** (where relevant)**, published or not**	**Data protect. claimed**	**Owner**
Herbold, B. A.	II A, 5.4.2/06	1988	KUE 13183b (c.n. tolylfluanid) - Spot test on cross-bred C57B1/6J x T stock mouse fetuses to evaluate for induced somatic changes in the genes of the coat pigment cells Bayer AG, ReportNo.:16752, Date:1988-05-31 GLP, Non Published	Yes	BAY
Herbold, B. A.	II A, 5.4.1/07	1994	KUE 13183b - Salmonella/microsome test Bayer AG, ReportNo.:22843, Date:1994-01-27 GLP, Non Published	Yes	BAY
Herbold, B.	II A, 5.4.1/09	1996	KUE 13183b - In vitro mammalian chromosome aberration test with chinese hamster V79 cells Bayer AG, ReportNo.:24581, Date:1996-01-02 GLP, Non Published	Yes	BAY
Herbold, B.	IIA, 5.4.2	2004	KUE 13183B *In vivo* bone marrow cytogenetic study using male mice Bayer HealthCare AG Report No: AT01134 Date: 2004-04-08 GLP, Non Published	Yes	BAY
Hoffmann, K.; Mirea, D.	II A, 5.3.2.3/01	1974	KUE 13183 b (tolylfluanide, Euparen M) - Subchronic toxicity study on dogs (thirteen-week feeding experiment) Bayer AG, ReportNo.:4957, Date:1974-09-12 Non GLP, Non Published	Yes	BAY
Holzum, B.	II A, 5.6.1/03	1991c	KUE 13183 b (c.n. Tolylfluanid) - Two-generation study on rats (supplement to study T1007392) Bayer AG, ReportNo.:20583, Date:1991-08-30, Amended:1995-04-10 GLP, Non Published	Yes	BAY
Holzum, B.; Kaliner, G.	II A, 5.6.1/02	1989	KUE 13183 b (c.n. Tolylfluanide) - 2 generation study on rats Bayer AG, ReportNo.:17788, Date:1989-03-03 GLP, Non Published	Yes	BAY
Hoorn, A. J. W.	II A, 5.4.1/03	1984	Mutagenicity evaluation of KUE 13 183b (c.n. Tolylfluanid) in the reverse mutation induction assay with saccharomyces serevisiae strains S 138 and S 211 Litton Bionetics, Veenendaal, Netherlands Bayer AG, ReportNo.:R3060, Date:1984-08-29 GLP, Non Published	Yes	BAY

Author(s)	**Annex point/ reference number**	**Year**	**Title** **Source** (where different from company) **Company name, Report No., Date,** **GLP status** (where relevant)**, published or not**	**Data protect. claimed**	**Owner**
Hoorn, A. J. W. G.; Heidemann, A.	II A, 5.4.1/04	1985	Mutagenicity evalulation of KUE 13183B (c.n. Tolylfluanid) in the mouse lymphoma forward mutation assay Litton Bionetics, Veenendaal, Netherlands Bayer AG, ReportNo.:R3192, Date:1985-02-01 GLP, Non Published	Yes	BAY
Keutz, E. von; Nash, G.	II A, 5.5.3/01	1986	KUE 13183b (Tolylfluanid) - Chronic toxicity to dogs after oral administration (12-month capsule study) Bayer AG, ReportNo.:12999, Date:1986-07-22 Non GLP, Non Published	Yes	BAY
Leser, K. H.; Rosenbruch, M.; Rinke, M.	II A, 5.5.1/02	1996	KUE 13183b (c.n. Tolylfluanid) - Study on Chronic Toxicity and Carcinogenicity in Wistar rats (administration in food over 2 years) Bayer AG, ReportNo.:25426, Date:1996-09-13, Amended:2000-10-04 GLP, Non Published *CONFIDENTIAL*	Yes	BAY
Leser, K. H.; Ruehl-Fehlert, C.	II A, 5.5.2/02	1996	KUE 13183b (c.n. Tolylfluanid) - Oncogenicity study in B6C3F1 mice (administration in food over 2 years) Bayer AG, ReportNo.:25548, Date:1996-10-17, Amended:2000-10-04 GLP, Non Published *CONFIDENTIAL*	Yes	BAY
Loeser, E.	II A, 5.6.1/01	1980	KUE 13183b (Euparen M-active ingredient) - Generation study with rats Bayer AG, ReportNo.:9419, Date:1980-08-29 Non GLP, Non Published	Yes	BAY
MRC	II A, 5.8.	2002	Medical Research Council working group report: Water fluoridation and Health. Medical Research Council, 20 Prk Crescent, London, W1B 1AL, September 2002. GLP, Published	-	-
Pickel, M. ; Rinke, M.	II A, 5.6.1/04	1995	KUE 13183 B - Two-generation study in rats Bayer AG, ReportNo.:23921, Date:1995-04-10, Amended:2000-10-04 GLP, Non Published *CONFIDENTIAL*	Yes	BAY

Author(s)	**Annex point/ reference number**	**Year**	**Title** **Source** (where different from company) **Company name, Report No., Date,** **GLP status** (where relevant)**, published or not**	**Data protect. claimed**	**Owner**
Sandt, van de, J. J. M.	III A, 7.3/02	2001	In vitro percutaneous absorption study with [phenyl-UL-14C]tolylfluanid (Euparen M 50 WG) using human and rat epidermal membranes TNO Nutrition and Food Research Institute, Zeist, Netherlands Bayer AG, ReportNo.:V3263, Date:2001-03-14 GLP, Non Published	Yes	BAY
Schoefer, S.	II A, 5.8	2003	Tolylfluanid - Statement: Relevance of metabolites formed in plants for re-entry activities Bayer CropScience AG, Report No.: MEF-416/03 Date: 2003-12-10 Non GLP, Non Published	Yes	BAY
Voelkner, W.	II A, 5.4.2/05	1988a	Sister chromatid exchange assay in bone marrow cells of the mouse with KUE 13183B Cytotest Cell Research GmbH & Co. KG, Darmstadt, Germany Bayer AG, ReportNo.:R4422, Date:1988-05-02 GLP, Non Published	Yes	BAY
Voelkner, W.	II A, 5.4.2/07	1988b	Mouse germ-cell cytogenetic assay with KUE 13 183b Cytotest Cell Research GmbH & Co. KG, Darmstadt, Germany Bayer AG, ReportNo.:R4485, Date:1988-07-01 GLP, Non Published	Yes	BAY
Voelkner, W.	II A, 5.4.2/08	1990	Chromosome aberration assay in bone marrow cells of the chinese hamster with KUE 13183b CCR, Rossdorf, Germany Bayer AG, ReportNo.:R5153, Date:1990-09-20 GLP, Non Published	Yes	BAY
Weatherell, J.A.	II A, 5.8.	1966	Fluoride and the skeletal and dental tissues. In: Eichler, O., Farah, A., Herksen, H., Welch, A.D. and Smith F.A., ed. Handbook of experimental pharmacology, New York, Springer-Verlag, Vol 20, part 1, pp. 141 – 172. Non GLP, Published	-	-
Weber, H.	III A, 7.3/01	2001	(phenyl-UL-14C) tolylfluanid 50 WG (Euparen M): percutaneous absorption study in the rat Bayer AG, ReportNo.:MR-130/01, Date:2001-03-29 GLP, Non Published	Yes	BAY

Author(s)	**Annex point/ reference number**	**Year**	**Title** **Source** (where different from company) **Company name, Report No., Date,** **GLP status** (where relevant)**, published or not**	**Data protect. claimed**	**Owner**
Wetzig, H.; Schilde, B.	II A, 5.5.3/02	1997	KUE 13183 b (c.n. Tolylfluanid) - Chronic (52 week) oral toxicity study in dogs Bayer AG, ReportNo.:26664, Date:1997-09-24, Amended:2000-10-04 GLP, Non Published *CONFIDENTIAL*	Yes	BAY
WHO	II A, 5.8.	1994	Fluorides and Oral Health: report of a WHO Expert Committee on Oral Health Status and Fluoride Use (Technical Report series 846), Geneva, World Health Organisation Non GLP, Published	-	-
Young, A.D.; Fickbohm, B.L.	II A, 5.6.1	2004	KUE 13183b (Tolylfluanid): A two-generation reproductive toxicity study in the Wistar rat Bayer CropScience AG, Report No.: 200770 Date: 2004-01-30 amended: 2004-04-06 GLP, Non Published	Yes	BAY

B.7 Residue data

B.7.9 Livestock feeding studies (Annex IIA 6.4)

Studies on the metabolism, distribution and expression of residues in livestock were done in goat (Ecker and Weber, 1995) and in hens (Weber and Ecker, 1996). The only feed item for goats in which residues of tolylfluanid may occur is apple pomace. None of the crops which are treated with tolylfluanid are in any significant amount fed to poultry. Below, the relevance of the metabolite DMST in edible products from goat , and the necessity to perform livestock feeding studies, is assessed.

B.7.9.1 Relevance of DMST as residue in animal products

B.7.9.1.1 Summary of the goat metabolism study (Ecker and Weber, 1995)

In a metabolism study on lactating goat [phenyl-UL-^{14}C]tolylfluanid was administered to the animal on three consecutive days at a dose level of 10 mg/kg body weight, which is equivalent to 250 ppm in feed (DAR on tolylfluanid point B.7.2.1). Due to the overall favourable elimination kinetics, the total radioactive residue at sacrifice accounted for only 2.8 % of the total dose. Thus, the resultant residue levels in most tissues and organs as well as in milk were low; the highest levels were always found in the excretory organs kidney and liver (Table 7.9.1).

No parent compound was detected in any of the tissues, organs or milk. DMST, 4-(dimethylaminosulfonylamino) benzoic acid (XI) and 4-(dimethylaminosulfonylamino) hippuric acid (XIII) represent the major biodegradation products (see DAR on tolylfluanid Figure 7.2.1).

DMST occurred mainly in the fat of the treated goat. The fat samples of the study were prepared for the extraction procedures as composite of perirenal, subcutaneous and omental fat. The mean concentration value of these three different types of fat was 1.473 mg/kg total recovered radioactivity (parent compound equivalents, see Table 7.9.1), which corresponds to about 0.54 % of the totally administered radioactivity. In three analyses, 14.68%, 16.74%, and 17.68 % of the recovered radioactivity from the composite fat samples were identified as DMST. Based on the above given mean concentration value, this corresponds to 0.22 mg/kg, 0.25 mg/kg and 0.26 mg/kg and, respectively. Thus the highest observed DMST residue in fat was 0.26 mg/kg.

The highest amounts of 4-(dimethylaminosulfonylamino) benzoic acid (XI) and 4-(dimethylaminosulfonylamino) hippuric acid (XIII) were found in liver and kidney of the goat. In these organs the total radioactive residue amounted to 37 mg/kg in kidney and to 20.58 mg/kg in liver. In three analyses, the following results were obtained for these metabolites:

a) 4-(dimethylaminosulfonylamino) benzoic acid
   kidney: 36.82%, 37.41%, and 43.30% corresponding to 13.62 mg/kg, 13.84 mg/kg, and 16.02 mg/kg,
   liver: 14.26%, 14.74%, and 15.11% corresponding to 2.94 mg/kg, 3.03 mg/kg, and 3.11 mg/kg

b) 4-(dimethylaminosulfonylamino) hippuric acid
   kidney: 35.17%, 45.2%, and 45.86 % corresponding to 13.01 mg/kg, 16.72 mg/kg, 16.97 mg/kg and
   liver: 57.67%, 57.77% and 59.11 % corresponding to 11.87 mg/kg, 11.89 mg/kg, and 12.17 mg/kg

Thus the highest observed residue was 16.97 mg/kg of 4-(dimethylaminosulfonylamino) hippuric acid in kidney.

Table 7.9.1 Equivalent concentrations in edible tissues and milk of one lactating goat after repeated (3 times) oral administration of 10 mg [phenyl U-^{14}C] tolylfluanid/kg bw 50 hours after first administration

Tissue	Equivalent concentration referring to parent compound (mg/kg)
Kidney	37
Liver	21
Perirenal fat	2.3
Omental fat	1.3
Subcutaneous fat	0.85
Flank muscle	0.65
Loin muscle	0.49
Thigh muscle	0.44
Milk	0.24 (mg/L)

Calculation of the dietary burden based on residue data

The only feed item in which residues of tolylfluanid may occur is apple pomace[1]. Table 7.9.2 provides the calculated burden of tolylfluanid residues for cattle. The STMR-values represent the sum of tolylfluanid and DMST expressed in parent compound equivalents.

Table 7.9.2 Calculation of residue intake of tolylfluanid by cattle

Feeding item (dry matter)	Percent of crop in diet (%)	Intake of		Residue in crop (STMR) (mg/kg)	Transfer factor	Residue in feeding item (mg/kg)	Residue intake via feed item		
		Dry matter (kg/animal /day)	Fresh material (kg/animal /day)				(kg/animal/ day)	mg/kg feed (dry matter)	(mg/kg bw´/day)
Dairy cattle:	daily maximum intake of feed in dry matter: 20 kg					body weight: 550 kg			
Apple, pomace, wet (23%)	10	2	8.7	1.0	3.9	3.9	33.93	1.7	0.06
Beef cattle:	daily maximum intake of feed in dry matter: 15 kg					body weight: 350 kg			
Apple, pomace, wet (23%)	20	4.5	19.6	1.0	3.9	3.9	76.4	5.1	0.22

The values indicate that beef cattle are potentially more exposed to tolylfluanid and DMST residues than dairy cattle are. Therefore, all further considerations are focused on beef cattle.

Adaptation of the metabolism data

As mentioned above, the metabolism study on a lactating goat was conducted at a dose level of 10 mg/kg body weight, which is equivalent to 250 ppm in feed. Compared to the actually expected dietary burden, this is a highly exaggerated dose rate. The reason for using such a high rate lies in the purpose of the study. The major purpose of the metabolism study was to identify the nature of the residues and to clarify the metabolic pathway of tolylfluanid in farm animals. Therefore, the study was deliberately designed in such a way as to result in maximised residue levels, which would allow easy identification of metabolites. This was done by:

a) using a highly exaggerated dose level, and
b) choosing an unusual early time for sacrifice, when residues in plasma and tissues were at a maximum level.

Thus, the obtained residue results are exaggerated in regard to their magnitude. Appropriate adjustments need to be made in order to realistically estimate, whether measurable residues are likely to occur in edible animal tissues.

The respective calculations are given below as well as a justification as to why they are considered to be acceptable.

The metabolism study was overdosed by a factor of about 45 (10 mg/kg bw ÷ 0.22 mg/kg bw). The highest residue value for DMST in fat determined in the metabolism study is 0.26 mg/kg. Divided by the factor of 45 the values is about 0.006 mg/kg. The highest residue value of the two other major metabolites was 16.97 mg/kg of 4-(dimethylaminosulfonylamino) hippuric acid in kidney. Divided by the factor of 45 the value is about 0.38 mg/kg.

[1] Commission of the European Communities, Directorate-General for Agriculture, 1997: Working document on guidelines for the generation of data concerning residues as provided in Annex II part A, section 6 and Annex III, part A, section 8 of Directive 91/414/EEC concerning the placing of plant protection products on the market, 1607/VI/97 rev.1 of 22/7/1997, Appendix G on livestock feeding studies, page 4

Feasibility of extrapolating data / linearity

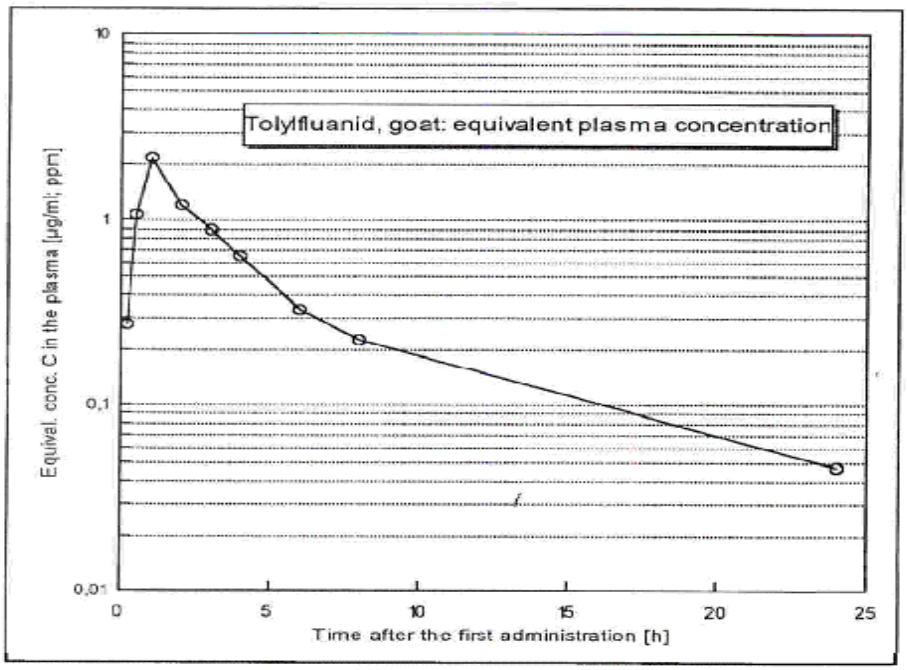
Use of a factor described above is considered permissible when linearity between dosage and residue values can be expected. Linearity can generally be assumed for the range of dosages, which are below the level at which "saturation" occurs. Once the point of saturation has been reached, the biokinetic behaviour is known to change, i.e. processes are known to decline in rate. Before that point occurs however, a linear dose related behaviour at different dosages can generally be expected.

In regard to tolylfluanid and the metabolism study on goat, the results indicate that the point of "saturation" has not been reached at the administered dose level of 10 mg / kg bw of [Phenyl U-^{14}C] tolylfluanid, because the radioactivity was absorbed rapidly as can be deduced from the maximum equivalent concentration in plasma which was reached after about 1 h (t_{max}) after dosing, corresponding to an absorption half-life of 17 min (Figure 7.9.1). Due to the study design (no complete radioactivity retracement in the whole body, GIT and exhaled air), no exact absorption ratio could be calculated. However, from the relatively high proportion excreted via urine in conjunction with the relatively high concentrations of radioactivity in kidney and liver (Table 7.9.1), a quite complete absorption could be assumed in analogy to the rodent experiments. This kinetic behaviour indicates a rapid absorption, distribution and excretion. Thus it may be assumed that a point of saturation has not been reached for tolylfluanid and linear extrapolation is allowed down to any dosage lower than 10 mg/kg bw.

The given line of reasoning is further supported by the findings of rat metabolism studies (DAR on tolylfluanid B.6.1). Tolylfluanid was administered to rats at dose levels of 2, 20 and 100 mg/kg body weight. A comparison of the plasma curves shows, that they are similar for the dose levels of 2 and 20 mg/kg bw. In both cases the peak is quickly reached, and the slope is relatively steep. In contrast, peak and slope are flattened out for the curve obtained for the dose level of 100 mg/kg bw. Again this indicates linearity for a dose range of up to at least 20 mg/kg body weight, whereas the point of saturation appears to be reached for a dose level of 100 mg/kg bw.

Figure 7.9.1. Equivalent plasma concentrations in goat (from Ecker and Weber, 1995)

Figure 2: [^{14}C]Tolylfluanid: equivalent concentrations C [µg/ml] in the plasma of a lactating goat after the first oral administration of 10 mg/kg body weight



Time of sacrifice

Furthermore, in order to obtain a complete understanding on the metabolism of tolylfluanid in ruminant farm animals the goat was sacrificed at a time when the highest amount of residues was to be expected in the organs and tissues. This is when the peak level in the plasma has been reached for tolylfluanid; i.e. the goat was sacrificed 2 hours after the final administration. Under practical conditions however, animals are rarely sacrificed immediately after they have been fed. Accordingly the guideline on feeding studies recommends sacrificing animals 24 hours after the final administration, i.e. after feeding. Based on the favourable biokinetic behaviour of tolylfluanid, residues will have been eliminated to a great extent within 24 hours after administration, and thus the magnitude will be considerably lower than after 2 hours. This is demonstrated by equivalent concentrations in the plasma (determined after adminstration of the first dose to the goat), which were

1.217 µg/ml - 2 hours after final administration and
0.047 µg/ml - 24 hours after final administration.

These values differ by a factor of about 26. For a compound with rapid distribution and excretion, concentrations in tissues can be generally regarded as proportionally related to plasma concentrations.

Applying this factor to the above given value of 4-(dimethyl-aminosulfonylamino) hippuric acid (0.38 mg/kg ÷ 26), the highest residue to be expected in farm animals is 0.015 mg/kg in kidney. This value is just above the trigger value of 0.01 mg/kg in edible animal issues and clearly below a feasible limit of quantification of an analytical method. A feasible LOQ for edible offal's would be 0.05 mg/kg.

In regard to the DMST residues in fat however, this factor cannot fully be applied as fat is a storage tissue. But even though elimination from fat is slower than e.g. from muscle and excretory organs, it will still occur to some degree. Therefore the above-mentioned residue level of 0.006 mg/kg may be considered to represent a maximum value for DMST. This value is below the trigger value of 0.01 mg/kg in edible animal tissues and below a feasible limit of quantification of an analytical method for fat (0.05 mg/kg). Furthermore, even though DMST is the least polar tolylfluanid metabolite, no risk of DMST accumulation in organs and DMST is to be expected, due to the reasons given below.

Potential accumulation of DMST in organs and tissues

In the goat metabolism study about 20% of the total radioactive residue (TRR) in fat was formed by the metabolite DMST. DMST was also detected in other organs and tissues but with a lower percentage. From this difference in the constitution of residues a potential accumulation of DMST residues in fat may be concluded.

The relatively higher percentage of DMST in fat is not surprising because DMST is the least polar of all metabolites detected in organs and tissues of the goat. However DMST can not be regarded as a lipophilic compound as it has a rather low partition coefficient (log P_{OW}) of 1.99. In environmental test guidelines (e.g. OECD 305, Bioconcentration: Flow-through Fish Test) a compound is considered to have an accumulation potential if it has a log P_{OW} value >3. The lipophilicity of DMST is clearly below this trigger value. An accumulation risk may also exist for a compound if it cannot be metabolised by living systems. This also is obviously not the case for DMST.

DMST is the first intermediate formed by metabolisation of tolylfluanid. It may also be formed by hydrolysis of tolylfluanid in the alkaline environment of the intestine and directly absorbed from the intestine. Therefore DMST is detected in the organs and tissues of the goat 2 hours after oral administration of tolylfluanid. It has to be emphasised that after such a short delay only a transient state of the metabolism and excretion of the radiolabelled tolylfluanid and of DMST is reached. But even at that point in time the predominant proportion of the first formed DMST has been further metabolised to more polar metabolites like 4-(dimethylamino-sulfonylamino) hippuric acid (XIII) and 4-(dimethylamino-sulfonylamino) benzoic acid (XI). These compounds account for the largest part of the total radioactive residue in all organs and tissues. Even in fat the percentage of each of these metabolites is higher than the percentage of DMST.

The reason why a higher percentage of DMST is detected in fat seems to be that DMST has the highest lipophilicity of all compounds in the metabolic profiles and therefore is partitioning better into fat than the more polar metabolites. But this does not indicate an accumulation risk as the lipophilicity of DMST is only moderate on an absolute scale and because the intermediately formed DMST is further metabolised to more polar compounds that are excreted.

This is also supported by the results of biokinetic, metabolism and autoradiography studies in the rat. The metabolism of tolylfluanid in the rat follows a similar pathway as in the goat with DMST as the first intermediate. In the biokinetic and autoradiography studies a fast excretion of tolylfluanid in the rat was demonstrated. Very low residues in fat were detected 48h after oral administration of 100 mg/kg [Phenyl-UL-^{14}C] tolylfluanid to male and female rats. The residues measured in fat were lower than in muscle and in most other tissues. In the autoradiography study very low residues of radioactivity were detected only in kidney and liver 24 hours after oral administration of 20 mg/kg [Phenyl-UL-^{14}C] tolylfluanid to male rats. No radioactive residues were observed in muscle and subcutaneous fat.

The presented data indicate that no measurable residue will occur in the edible products of animal origin. Furthermore, considering the issue of dietary risk, even misuse of the product would not cause any appreciable risk to the consumer.

Dietary risk assessment for DMST

The metabolism study on goat has shown significant residues only in form of DMST in fat as well as two relevant metabolites in the excretory organs kidney and liver. The considerations above show, that under realistic worst case conditions, these residues will be below an analytical limit of quantification of 0.05 mg/kg. But even if in case of misuse when residues at the LOQ or at 10 x the LOQ would occur, the impact of this residue intake via animal fat or edible offal's would be insignificant in itself as well as compared to the intake via all other relevant food items. Based on the currently proposed ADI of 0.2 mg/kg bw for tolylfluanid and on calculations according to WHO guideline (DAR on tolylfluanid B.7.16.1), the following can be calculated:
Residue intake via animal fat = 0.05 mg/kg $\Rightarrow$ ADI exhaustion = 0.0024%,
Residue intake via animal fat = 0.5 mg/kg $\Rightarrow$ ADI exhaustion = 0.024%.
Residue intake via edible offal's = 0.05 mg/kg $\Rightarrow$ ADI exhaustion = 0.0004%,
Residue intake via edible offal's = 0.5 mg/kg $\Rightarrow$ ADI exhaustion = 0.004%.

Conclusions

The available data are deemed sufficient to show that measurable tolylfluanid residues, including DMST in fat, are not likely to occur in products of animal origin. Even misuse of the product would not result in any appreciable risk to the consumer. Further feeding studies in cattle are not considered necessary.

B.7.18 References relied on

Author(s)	Annex point/ reference number	Year	Title **Source** (where different from company) **Company name, Report No., Date,** **GLP status** (where relevant)**, published or not**	Data protect. claimed	Owner
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Weber, H.; Ecker, W.	II A, 6.2.3 /01	1996	[Phenyl-UL-14C] tolylfluanid Absorption, distribution, excretion and metabolism in laying hens Bayer AG, ReportNo.:PF4170, Date:15.11.1996, Amended:27.09.2000 GLP, Non Published	Yes	BAY

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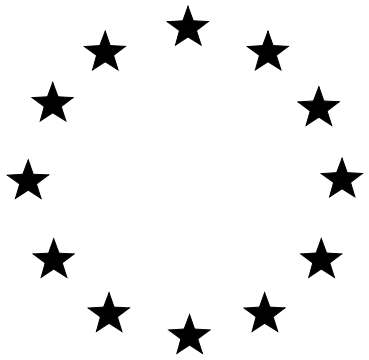

EPCO-Meetings

TOLYLFLUANID

Volume 3

ANNEX B

Summary, Scientific Evaluation and Assessment

ADDENDUM 5

Rapporteur Member State Finland

08.11.2004

This document has not been peer reviewed and does not represent the opinion of the other Member States nor the European Commission

KTTK
KASVINTUOTANNON TARKASTUSKESKUS

PLANT PRODUCTION INSPECTION CENTRE
Pesticide Division
Vilhonvuorenkatu 11
P.O.Box 42
FI-00501 HELSINKI, FINLAND

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B.5 Methods of analysis

B.5.1 Analytical methods for technical active substance and formulation analysis (IIA 4.1, IIIA 5.1)

B.5.1.1 Technical active substance (IIA 4.1)

Evaluation table rev. 0-3 (21.09.04):

Data requirement 1.1: Notifier to submit new study on analytical profile of batches (taking into account specification and validation of analytical methods for impurities)

Reference: Hake, G. (2004a): Tolylfluanid (KUE13183B) Assay of Technical Grade Active Ingredient HPLC – External Standard. Bayer CropScience AG, Unpublished Analytical method No.: AM002004MP1
Hake, G. (2004b): Validation of HPLC-method AM002004MP1 KUE 13183B Assay of Technical Grade Active Ingredient. Bayer CropScience AG, Report No.: VB1-AM002004MP1

Guideline: Directive 96/46/EC

GLP: No

Principle of the method:

Sample was homogenized thoroughly in an agate mortar. Approx. 100 mg of this accurately weighed material was transfered to a 100 ml flask and made up to the mark with acetonitrile. The samples were analysed by reverse phase HPLC (Spherisorb ODS 2, 125 mm x 4.0 mm, 3 µm) with gradient elution and using external standardisation and DAD detector. Validation data is presented in Table 5.1.1.

Table 5.1.1 Summary of method validation (active substance)

Substrate	Linearity (linear between)	Precision – repeatability (% RSD)	Accuracy (%)	Specificity – interference %
Technical active substance (Hake 2004)	1 x 6 conc. corr. coeff. = 0.9991	0.32 N = 6	102 N = 6	No interference. Linear in the operating range.

Conclusion: The UV-spectra from reference substance and sample showed no spectral difference, retention times were identical. Chromatograms of blank, reference substance and sample were checked and found to be free of interfering compounds. Linearity was confirmed by six concentrations with double measurements in the range 80 – 120 % of recommended weight.
In 5-batch analysis identity of active substance was additionally confirmed by ^{1}H-NMR-spectra.
The method is acceptable for the determination of active ingredient in technical active substance.

B.5.1.2 Impurities (IIA 4.1)

Reference: Hake, G. (2004c): Tolylfluanid byproducts HPLC – external standard. Bayer CropScience AG, Unpublished Analytical method No.: AM002104MP1.

Guideline: Directive 96/46/EC

GLP: No

Principle of the method:

Sample was homogenized thoroughly in an agate mortar. Approx. 100 mg of this accurately weighed material was transfered to a 100 ml flask and made up to the mark with acetonitrile. The samples were analysed by reverse phase HPLC (Spherisorb ODS 2, 125 mm x 4.0 mm, 3 µm) with gradient elution and using external standardisation and DAD detector. Confirmatory method is not necessary (HPLC-DAD). Validation data is presented in Annex C, Confidential Information, point C.1.4.1 / B.5.1.2 Impurities (IIA 4.1) in Table C.3.

Conclusion: The method is acceptable for the determination of organic impurities in technical active substance.

B.5.3.1 Analytical methods (residue) for soil

Evaluation table rev. 0-3 (21.09.04):
Data requirement 1.3: Notifier to submit the new validation data (of DMST) metabolite for DFG S 19 – method.

Reference: Lakaschus, S. (2004b): Validation of enforcement method DFG S 19(extended and revised version) (Bayer CropScience Method 00086/M065) for the determination of residues of DMST in soil. Bayer CropScience AG, Unpublished Report No.: G04-0082

Guideline: Directive 96/46/EC

GLP: Yes

Principle of the method:

LUFA Speyer standard soil 2.2 samples were extracted with ethyl acetate/cyclohexane (1/1, v/v) using accelerated solvent extraction (ASE) under specific extraction conditions. The obtained extracts were evaporated to dryness, redissolved and the remaining solutions were cleaned up by gel permeation chromatography on Bio Beads S-X3 polystyrene gel using a mixture of ethyl acetate/cyclohexane (l/l, v/v) as eluent. The concentrated extracts were analysed using capillary gas chromatography (DB-5 MS) with mass selective detection (MSD) using MS ion m/z 214 for quantitation and m/z 106 for confirmation. Because only two fragment ions with mass to charge ratios above m/z 100 were available for the GC-MSD, LC-MS/MS was additionally used for confirmation with m/z 106. The concentrated extracts for GC-MSD analyses were acidified with 0.1 % acetic acid, evaporated nearly to dryness and dissolved in 0.1 % acetic acid/methanol (l/l, v/v) and analysed with LC-MS/MS. Validation data is presented in Table 5.3.1.

Table 5.3.1 Validation data for the analytical methods for the determination of residues of DMST in LUFA Speyer standard soil 2.2

Type of method Developed by	m/z	Fortification level (mg/kg)	LOQ (mg/kg)	recovery (%) mean range	RSD (%)	N
DMST; GC-MSD; DFG S 19 (Lakaschus 2004b)	m/z = 214	0.01 0.10	0.01	77 61-86 75 68-83 overall 76	13 8 overall 10	5 5 10

Type of method Developed by	m/z	Fortification level (mg/kg)	LOQ (mg/kg)	recovery (%) mean range	RSD (%)	N
DMST; GC-MSD;	m/z = 106	0.01 0.10	0.01	87 79-97 73 69-80 overall 80	8 6 overall 12	5 5 10
LC-MS/MS DFG S 19 (Lakaschus 2004b)	m/z = 106	0.01 0.10	0.01	94 91-97 86 85-93 overall 90	3 7 overall 7	3 3 6

Conclusion: The linearity of the GC-MSD detector response was confirmed by injecting 5 standard solutions covering the working range of 0.0067 - 1.00 µg/ml DMST (m/z = 214 for routine analysis and m/z = 106 for confirmation).
The linearity of the LC-MS/MS detector response was confirmed by injecting 5 standard solutions covering the working range of 0.0005 - 0.050 µg/ml DMST (MRM 215 => 106 for confirmation).. The correlation coefficients (r) were found to be r = 0.9998 for m/z = 214 (GC-MSD) and r = 1.0000 for MRM 215 => 106 (LC-MS/MS). Representative chromatograms were included in the study. The method is valid for the determination of residues of DMST in soil.

B.5.3.2 Analytical methods (residue) for water (including drinking water) (IIA 4.2.3)

Evaluation table rev. 0-3 (21.09.04):
Data requirement 1.4: A study for the determination of residues of tolylfluanid in drinking water (taking the potential problems of the analysis of tolylfluanid into concideration).

Reference: Brumhard, B. (2004): Analytical method 00904 for the determination of tolylfluanid and DMST in drinking and surface water by HPLC-MS/MS. Bayer CropScience AG,, Unpublished Report No.: MR-132/04

Guideline: Directive 96/46/EC

GLP: Yes

Principle of the method:

Prior to analysis formic acid is added to the drinking and surface water samples to a final concentration of 1 ml/l. Acidified samples are directly injected into the HPLC-MS/MS. Residues of tolylfluanid and DMST were determined by HPLC (Phenomenex Aqua®, 150 mm x 2 mm, 5 µm column; gradient eluation) using turbo-ionspray interface and mass selective detector (MS/MS). The method was validated for two mass transitions of tolylfluanid (m/z 346.9 → 237.8 and m/z 346.9 → 137.0) as well as DMST (m/z 214.9 → 106.0 and m/z 214.9 → 79.0). Because HPLC-MS/MS method is highly specific, an additional confirmatory method is not necessary. Validation data is presented in Table 5.3.2

Table 5.3.2 Summary of method validation for the determination of residues of flutolanil in water

Type of method Developed by	Substrate	Fortification level (µg/l)	LOQ (µg/l)	Recovery (%) mean	range	RSD (%)	N
Tolylfluanid	Surface water (m/z 346.9/237.8)	0.05	0.05	100	94-104	3	10
		0.5		100	98-104	2	9
	Surface water (m/z 346.9/137.0)	0.05	0.05	100	93-108	5	10
		0.5		100	92-108	5	10
	Drinking water (m/z 346.9/237.8)	0.05	0.05	100	96-106	3	10
		0.5		100	93-116	7	10
	Drinking water (m/z 346.9/137.0)	0.05	0.05	100	92-109	5	10
		0.5		100	89-107	6	10
DMST	Surface water (m/z 214.9/106.0)	0.05	0.05	100	96-103	2	10
		0.5		100	93-102	3	10
	Surface water (m/z 214.9/79.0)	0.05	0.05	100	94-105	3	10
		0.5		100	91-102	3	10
	Drinking water (m/z 214.9/106.0)	0.05	0.05	100	99-101	1	10
		0.5		100	94-103	3	10
HPLC-MS/MS Brumhard 2004 (MR-132/04)	Drinking water (m/z 214.9/79.0)	0.05	0.05	100	96-103	2	10
		0.5		100	95-103	3	10

The blank values of all control samples were below the limit of detection (0.3 x LOQ). The linearity of MS/MS-detection of tolylfluanid and DMST was determined in surface water / formic acid (1000/1, v/v) in the range of

0.04 µg/l to 10 µg/l. The correlation coefficient for tolylfluanid was 0.9997 (mz 346.9 / 237.8) and 1.0000 (mz 346.9 / 137.0), respectively. The correlation coefficient for DMST was 1.0000 (mz 214.9 / 106.0) and 1.0000 (mz 214.9 / 79.0), respectively. Representative chromatograms were included in the study.

For method validation, surface water from the river Rhine sampled in Leverkusen-Hitdorf and tap water sampled in building 6610 of the Agricultural Centre, Bayer CropScience AG, D-40789 Monheim were used. Characteristics of the surface water and tap water are listed in the study.

Because of the direct measurement of fortified samples without separate extraction and clean-up steps it is not possible to determine recovery rate. An estimation of the accuracy of the analytical technique was obtained by an assessment of the linearity of matrix calibration and by determination of the repeatability of sample analysis.

Conclusion: The method is acceptable.

B.5.6 References relied on

Annex point/ reference number	Author(s)	Year	Title **Source** (where different from company) **Company name, Report No., Date**, **GLP status** (where relevant), published or not	Data protect. claimed	Owner
IIA 4.1	Hake, G.	2004a	Tolylfluanid (KUE13183B) Assay of Technical Grade Active Ingredient HPLC – External Standard. Bayer CropScience AG, Research, Product Technology, Monheim, Germany Bayer CropScience AG, Analytical method No.: AM002004MP1 Date:11.10.2004 Non GLP, Non Published	Yes	BAY
IIA 4.1	Hake, G.	2004b	Validation of HPLC-method AM002004MP1 KUE 13183B Assay of Technical Grade Active Ingredient. Bayer CropScience AG, Research, Product Technology Analytics, Monheim, Germany Bayer CropScience AG, Report No.: VB1-AM002004MP1 Date:12.10.2004 Non GLP, Non Published	Yes	BAY
IIA 4.1	Hake, G.	2004c	Tolylfluanid byproducts HPLC – external standard. Bayer CropScience AG, Research, Product Technology Analytics, Monheim, Germany Bayer CropScience AG, Analytical method No.: AM002104MP1 Date:04.10.2004 Non GLP, Non Published	Yes	BAY
II A, 4.2.2	Lakaschus, S.	2004b	Validation of enforcement method DFG S 19(extended and revised version) (Bayer CropScience Method 00086/M065) for the determination of residues of DMST in soil. Dr. Specht & Partner, Chemische Laboratorien GmbH, Hamburg, Germany Bayer CropScience AG, Report No.:G04-0082 Date:23.08.2004 GLP, Non Published	Yes	BAY
IIA, 4.2.3	Brumhard, B.	2004	Analytical method 00904 for the determination of tolylfluanid and DMST in drinking and surface water by HPLC-MS/MS. Bayer CropScience AG, Development-Residues, operator and consumer safety, Monheim, Germany Bayer CropScience AG, Report No.:MR-132/04 Date:12.10.2004 GLP, Non Published	Yes	BAY

B.6 Toxicology and Metabolism

B.6.14 Exposure data (Annex IIIA. 7.2)

Operator exposure to tolylfluanid was estimated by using models or model containing data. For exposure assessments during orchard spraying also field study data was utilized. The notifier has calculated the exposure using two generally accepted models, the British UK-POEM and the German model. In addition to these, operator exposure was estimated using the EUROPOEM-model and the Dutch-model. Bystander exposure was estimated by using spray-drift calculations. Worker exposure (re-entry) was estimated by using the recommendations presented in the EUROPOEM II re-entry working group report.

B.6.14.1 Operator exposure and comparison to the AOEL

Tolylfluanid is a fungicide which is used for controlling various pests on a wide variety of crops in agriculture, horticulture and viticulture. The use scenarios include ground boom spraying for low crops, broadcast air assisted sprayers for high crops and portable or hand held sprayers for field high crops and for glasshouses. The exposure assessment was based on the use of the lead formulation Euparen M 50 WG, which contains 50% tolylfluanid (500 g/kg). The product comes in 5 kg containers and it is diluted with a water rate of 400-2000 l/ha. Depending on the crop, the use rates vary from 1.5 to 2.5 kg as/ha (i.e. 3-5 kg product/ha). Between 2 to 7 sprayings are recommended. Euparen M 50 WG consists of solid, coarse particles with a small respirable size fraction (0.1 % of the particle mass has a smaller aerodynamic diameter than 75 μm).

The application parameters for model inputs are shown in TABLE 6.14-1. Dermal absorption figures of 5 % for the undiluted product and 7 % for the diluted (1:100) product were used. These values for dermal absorption were agreed upon at the EPCO 09 Expert Meeting in Braunschweig, 6.-7.7.2004. The inhalation absorption was assumed to be 100%. The exposures were calculated with and without personal protective equipment (PPE are specified in model result tables). The average body weight was assumed to be 60 kg in EUROPOEM and UK-POEM and Dutch-model calculations, and 70 kg in German model calculations. The notifier has modeled operator exposure by using spraying area sizes which reflect EU-wide averages, not the highest ones. In order to estimate exposure also in realistic worst cases (RWC), the exposures for larger spraying areas were estimated using EUROPOEM. The results from model calculations are shown in TABLES 6.14-2 – 6.14-4.

TABLE 6.14-1
GROUPED SCENARIOS FOR EXPOSURE CALCULATIONS

Application Technique	Treated Area per Working Day Grouped Crops	Maximum Recommended Use Rate [kg as/ha]	Spray Volume [L/ha] Used for Calculation	Models Used to Predict Field Operator Exposure
Low Field Crops				
Tractor mounted boom sprayer	20 ha and 30 ha Strawberries	2.5	300	German model (20 ha) UK-POEM (20 ha) EUROPOEM (20 and 30 ha)
High Field Crops				
Tractor mounted orchard sprayer	15 ha and 20 ha Apples, pears	1.5	500	UK-POEM (15 ha) (high volume) EUROPOEM (15 and 20 ha)
Tractor mounted orchard sprayer	8 ha and 15 ha Grapes	2.0	n.a.	German model EUROPOEM (8 and 15 ha)
Hand held sprayer high crops: Field	1 ha Grapes, apples, pears	2.0	n.a.	German model EUROPOEM
Greenhouse				
Hand held spray gun high crops: Greenhouse	1 ha Cucumber, Zucchini	1.5	1500	Dutch model

EUROPOEM

EUROPOEM is based on a generic database obtained from operator exposure monitoring studies during the use of plant protection products in Europe. The database contains data submitted by industry and trade associations. Depending on the size of a database, the percentile values of surrogate exposures vary from the 75th to maximum.

TABLE 6.14-2
EUROPOEM PREDICTIONS (mg/kg bw/day) OF OPERATOR EXPOSURE TO TOLYLFLUANID AND A COMPARISON TO THE SYSTEMIC AOEL VALUE (0.3 mg/kg bw /day*)

Application method	Dose kg/ha	HA	PPE	Inhalation exposure[1] mg/kg bw/day	Dermal exposure[2] mg/kg bw/day	Systemic exposure mg/kg bw/day	**% of systemic AOEL**
Tractor mounted boom sprayer	5	20	no	0.09	0.17	0.26	**87**
(strawberries)	5	20	yes	0.09	0.021	0.11	**37**
Tractor mounted boom sprayer	5	30	no	0.14	0.26	0.40	**130**
(strawberries)	5	30	yes	0.14	0.02	0.16	**53**
Tractor mounted orchard sprayer	4	8	no	0.03	0.81	0.84	**280**
(grapes)	4	8	yes	0.03	0.14	0.17	**57**
Tractor mounted orchard sprayer	4	15	no	0.07	1.51	1.58	**530**
(grapes)	4	15	yes	0.07	0.26	0.33	**110**
Tractor mounted orchard sprayer	3	15	no	0.05	1.13	1.18	**390**
(apples)	3	15	yes	0.05	0.19	0.24	**80**
Tractor mounted orchard sprayer	3	20	no	0.07	1.53	1.58	**530**
(apples)	3	20	yes	0.07	0.26	0.33	**110**
Hand held sprayer, high crops: field	4	1	no	0.04	1.43	1.47	**490**
(apples)	4	1	yes	0.04	0.27	0.31	**100**

***** AOEL value agreed upon at the EPCO 09 Expert Meeting in Braunschweig, 6.-7.7.2004
Dose = kg product per hectare
PPE = Personal protective equipment (gloves during mixing and loading ; gloves, standard protective garment and boots during application)
HA= Treated area, hectares
[1] Excluding hand held methods, inhalation exposure was calculated from the maximum surrogate exposure value. For hand held methods the 90th percentile was used
[2] Excluding hand held methods, dermal exposure was calculated from the 75th percentile. For hand held methods the 90th percentile was used.

German model

Operator exposure estimates were calculated using the German model: "*Uniform Principles for Safeguarding the Health of Applicators of Plant Protection Products (Uniform Principles for Operator Protection); Mitteilungen aus der Biologischen Bundesanstalt für Land- und Forstwirtschaft, Berlin-Dahlem, no. 277, 1992"*. The used scenarios were: "Application to field crops using tractor mounted boom sprayer", "Application to high crops using tractor mounted air blast sprayer" and " Application to high crops using hand held equipment".

The following sizes for treated areas were used in operator exposure calculations: 20 ha for low field crops using tractor mounted boom sprayers, 8 ha for high field crops using tractor mounted air blast sprayers, 1 ha for high crops (field + greenhouse) using hand held equipment (knapsack sprayer + spray gun). In German model calculations the body weight of the operator is assumed to be 70 kg.

Dutch model

The modified Dutch model was used for indoor applications in greenhouses. The Dutch model uses 90th percentiles. Recent studies during varying European conditions in glasshouses (Finland and Greece) show that there is a quite large variation in exposure between operators, in most cases probably due to technical problems with the spraying equipment and varying personal skills. This supports the use of high percentiles in glasshouse exposure estimations, especially when the database in the modified Dutch model is limited in size and

geographical distribution (Tuomainen *et al.,* 2002a and b, and Machera *et al.,* 2003). An area of 1 ha, a spray concentration of 0,2 % (i.e. 1 g/l) and a body weight of 60 kg was used in calculations.

TABLE 6.14-3
GERMAN MODEL AND DUTCH MODEL PREDICTIONS (mg/kg bw/day) OF OPERATOR EXPOSURE TO TOLYLFLUANID AND COMPARISON TO THE SYSTEMIC AOEL VALUE (0.3 mg/kg bw /day)

Application Technique	PPE	Inhalation exposure mg/kg bw/day	Dermal exposure mg/kg bw/day	Systemic exposure mg/kg bw/day	**% of systemic AOEL**
German model: Tractor mounted boom sprayer (20 ha)	no	0.006	0.17	0.18	**60**
	yes	0.006	0.04	0.03	**10**
German model: Tractor mounted orchard sprayer (8 ha)	no	0.006	0.20	0.21	**70**
	yes	0.006	0.03	0.04	**13**
German model: Hand held sprayer, high crops: Field and knapsack (1 ha)	no	0.009	0.10	0.11	**37**
	yes	0.009	0.03	0.04	**13**
Dutch Model: Hand held spray, high crops: Greenhouse	no	0.014	0.233	0.25	**83**
	yes	0.014	0.0233	0.04	**13**

ha= Treated area, hectares
PPE= For undiluted product: gloves, standard protective garment (plant protection) and sturdy footwear. For diluted product: standard protective garment (plant protection) and sturdy footwear.

UK-POEM

Operator exposure estimates were calculated using the revised UK predictive operator exposure model UK-POEM, 2002. The scenarios for solid concentrate formulations used were: "Tractor-mounted/trailed boom sprayer: hydraulic nozzles" and "Tractor-mounted/trailed broadcast air-assisted sprayer:500 l/ha".

The following assumptions were used in operator exposure calculations: the treated area was 20 ha for strawberries, the same as in the German model. For application in orchards the value of 15 ha was used (8 ha in the German model). The spray volumes used were 300 L/ha for low field crops and 500 L/ha for pome fruit. In UK-POEM calculations the body weight of the operator is assumed to be 60 kg.

TABLE 6.14-4
UK-POEM PREDICTIONS (mg/kg bw/day) OF OPERATOR EXPOSURE TO TOLYLFLUANID AND COMPARISON TO THE SYSTEMIC AOEL VALUE (0.3 mg/kg bw /day)

Application Technique	PPE	Inhalation[1] exposure mg/kg bw/day	Dermal exposure mg/kg bw/day	Systemic exposure mg/kg bw/day	**% of systemic AOEL**
Tractor mounted boom sprayer	no	0.01	0.84	0.85	**280**
	yes	0.01	0.26	0.27	**90**
Tractor mounted orchard sprayer	no	0.02	0.82	0.84	**280**
	yes	0.02	0.52	0.54	**180**

PPE= Gloves during mixing and loading and during application
[1] Inhalation exposure is calculated only during application (no mixing and loading)

Field studies

The notifier has submitted two operator exposure studies conducted under field conditions. One study was carried out by the Health and Safety Executive (HSE) during springs of 1995 and 1996 in the United Kingdom *(Technical Development Survey: Exposure to chlorpyrifos in orchard spraying; published by: Health and Safety Executive, 9/98).* In this study personal samples were collected from 63 operators during application of chlorpyrifos (insecticide). The dermal body exposure was determined by using the patch-technique and hand exposure by using the cotton glove technique (either worn under protective gloves or without gloves). Inhalation exposure was measured in the breathing zone by using filters together with Tenax-tubes. Orchard spraying was performed with tractor mounted air-assisted equipment with water rates from 55 L/ha to 1174 L/ha. About 80% of the tractors had a cab. The results were expressed mostly as potential dermal body exposure, actual hand exposure and inhalation exposure as µg active substance per day. The measurements were not fully in compliance with the current OECD guidance document (for the conduct of studies on operator exposure). Nevertheless, some general conclusions can be drawn.
The measured exposures were then compared to UK-POEM results which were calculated using the field study application parameters. The comparison revealed that UK-POEM inhalation estimates exceed measured exposures by a factor of 25 when tractors with cabs were used and by a factor of 4 when tractors without a cab were used. Only at the highest percentiles did UK-POEM results underestimate measured exposures. This degree of overestimation is, however, at an acceptable level and covers the variability and uncertainty in exposure assessments (model conservatism). Exposure by inhalation at orchard spraying is normally not that significant; the major part of the systemic exposure is due to dermal exposure. For dermal exposure (body and hands) the UK-POEM estimates exceeded measured values usually by a factor of about 200. The exception was when tractors without cabs where used; there body exposure exceeded the measured values only about 15 times. Over 93% of the UK-POEM estimates exceeded the measured exposures by a factor > 10 (up to 10000). The study indicates that operator exposure in orchard spraying may in some real life situations be lower than UK-POEM predicted exposures. In order to illustrate more realistic levels of exposure, the UK-POEM predictions were recalculated by multiplying the dermal exposure results by a factor of 0.5, which leads to an overestimation of exposure by about 100 times, instead of 200, when using UK-POEM. The model results are still quite conservative, but they indicate that also worst case exposures can be at an acceptable level when operators wear proper protective clothing (see TABLE 6.14-5). Operator exposure is expected to stay clearly below the AOEL at normal use conditions.

TABLE 6.14-5
RE-CALCULATED UK-POEM PREDICTIONS OF OPERATOR EXPOSURE TO TOLYLFLUANID AND COMPARISON TO THE SYSTEMIC AOEL VALUE (0.3 mg/kg bw /day)

Application Technique	PPE	Inhalation exposure mg/kg bw/day	Dermal exposure[1] mg/kg bw/day	Systemic exposure mg/kg bw/day	**% of systemic AOEL**
Tractor mounted boom sprayer	no	0.008	0.42	0.43	**140**
	yes	0.008	0.13	0.14	**47**
Tractor mounted orchard sprayer	no	0.015	0.40	0.42	**140**
	yes	0.015	0.25	0.27	**90**

PPE= Gloves during mixing and loading and during application
[1] Recalculated dermal exposure (multiplied by a factor of 0.5). This theoretically yields a 100-fold overestimation of exposure, compared to field data from one study

Three orchard spraying studies (pome fruit) with tolylfluanid were carried out in the Netherlands, Belgium and Germany in order to measure operator exposure to tolylfluanid during mixing/loading and application of the Euparen M 50 product. Complete personal samples were collected from twelve operators during professional orchard air blast spraying (including mixing/loading) in fruit plantations.

Potential and actual dermal exposure to tolylfluanid was measured by passive whole body dosimetry. The operators were clothed in accordance to their usual work practice. During mixing and loadind tasks the operators wore long trousers, a long-sleeved jacket, a cap and protective gloves. During application tasks the operators wore the same type of clothing as during mixing/loading. At application the operators used gloves only during maintaince operations. Hand exposure was determined by using a hands and gloves washing method. Inhalation

exposure from the breathing zone was measured using IOM samplers fitted with glass fiber filters and a Tenax tubes.
The sprayed areas ranged from 11 ha to 48 ha (mean 22 ha), which most probably covers well the orchard areas typically treated within the EU. The operators were clothed according to their usual work practices, including long sleeved jackets/shirts and long trousers. The only PPE they used were gloves during mixing and loading tasks. The systemic exposures were calculated from the normalized potential exposures by using an application rate of 4 kg as/ha, an area of 20 ha, 2.6% penetration trough gloves and 5 % penetration trough the skin.

The systemic exposures ranged from 0.002 to 0.04 mg/kg bw/day, which comprise 1 to 13 % of the AOEL value.

B.6.14.2 Conclusions on operator exposure

The UK-POEM and EUROPOEM results indicate that operator exposure to tolylfluanid may exceed the AOEL if no personal protective equipment is used. In tractor boom and glass house applications the model predictions indicate, however, that exposure can be controlled to an acceptable level when operators use personal protection. Concerning orchard spraying scenarios the Eurpoem and UK-POEM exposure predictions (with PPE) were at or slightly above the AOEL-value. The German model results, on the other hand, showed acceptable uses for all scenarios.

The field studies with 75 observations from four EU-countries (three studies with tolylfluanid and one with generic data from the use of chlorpyrifos) in orchard spraying tasks indicate that operator exposure in real life may be considerably lower compared to the UK-POEM and the Europoem model estimations, and that these models may therefore give fairly conservative estimates of exposure during orchard spraying. Some caution should therefore be exercised when interpreting exposure model results from orchard use.

Taking into account the conservatism in modeling results, as well as the field measurement data, it is safe to assume that operator exposure to tolylfluanid is at an acceptable level even in worst case scenarios when proper personal protective equipment is used. In practice, the use of gloves is the most effective way to reduce exposure. Furthermore, suitable protective clothing and a respirator is needed during hand held sprayings and during mixing and loading tasks performed indoors. In greenhouse applications a re-entry interval of 12 hours is recommended.

B.6.14.3 Bystander exposure

Currently, there are no generally accepted models for estimating bystander exposure. The exposure estimations in this monograph are therefore based on the recommendations by the EUROPOEM II bystander working group (*EUROPOEM 2 – Bystander Working Group Report, September 2001, Revised December 2002*).

Spray drift is considered to be the portion of the applied amount of active substance which is carried beyond the treated area during the application. The following simplified assumptions have been used in the calculations: bystanders stay downwind, the distance between bystanders and the source is 10 m (in the field), a one hour exposure time, a breathing rate of 1.25 m^3/h, an unprotected skin area of 1 m^2, a dermal absorption rate of 7 % and an inhalation absorption rate of 100 %. The body weight of a bystander is assumed to be 60 kg. The summary of the exposure calculations is shown in TABLE 6.14-6.

E_{dermal}= UR [kg as/m^2] * DF [%] * A_{skin} [m^2]* T [h] * dermal absorption [%] (equation 1)

$E_{inhalation}$= C_{spray} [mg/m^3] * BR [m^3/1 h] *DF [%] * T [h]* inhalation absorption [%] (equation 2)

$E_{systemic}$= E_{dermal} + $E_{inhalation}$ (equation 3)

Where,

UR= use rate [kg as /ha]
DF= spray drift factor [%]
BR= breathing rate (m^3 / h)
A_{skin} = Surface area of unprotected skin [m^2]

C_{spray} = active substance concentration in the spray mist [mg/m^3]

TABLE 6.14-6
BYSTANDER EXPOSURE AND COMPARISON TO AOEL (DF VALUES ARE ADAPTED FROM THE WORKING GROUP REPORT, TABLE: BASIC DRIFT VALUES FOR ONE APPLICATION. GROUND SEDIMENT IN % OF THE APPLICATION RATE (90th PERCENTILE)

Scenario	UR (kg as/m^2)	Cspray[1] (mg/m^3)	DF (%)	Inhalation exposure (mg/kg/1h)	Dermal exposure (mg/kg/1h)	Systemic exposure (mg/kg bw/day)	**% of systemic AOEL**
Tractor mounted boom sprayer (strawberries)	2.5^{-5}	1.5	0.3	0.0022	0.00005	0.002	**> 1**
Tractor mounted orchard sprayer	1.5^{-5}	3.7	12	0.0053	0.0025	0.008	**3**
Tractor mounted orchard sprayer	2.0^{-5}	1.3	1.2	0.0019	0.00025	0.002	**>1**
Hand held sprayer, high crops: Field	2.0^{-5}	5	3	0.0073	0.001	0.008	**3**
Hand held spray, high crops: Greenhouse	1.5^{-5}	1	3	0.0014	0.00015	0.001	**>1**

[1] Spray concentration is calculated by using the water rate and active substance use rate values (the water rate value is estimated to be 1600 l/ha for strawberries, 400 l/ha for apples, 1600 l/ha for grapes and 1500 l/ha for cucumber).

UR= use rate [kg as /ha] , DF= spray drift factor [%]

The calculations showed that bystander exposure is well below the AOEL value during all types of application.

B.7 Residue data

The residue section has been revised according to the demands of the EFSA.

The ECPO 10 meeting proposed to change the residue definition for monitoring in plant from parent compound to sum of tolylfluanid and DMST expressed as tolylfluanid. This calls for a recalculation of the MRL proposal.

However, the RMS wants still retain the original residue definition referring parent only for monitoring purposes and the sum of tolylfluanid and DMST for the dietary risk assessment. For grapes two other a metabolites were included for the risk assessment. The RMS wants to stress opinion that the described change in residue definition is considered questionable due to the following reasons:

1) The residue definition of parent compound only is in compliance with current guidelines and takes all relevant parameters into account, i.e. basic toxicology, presence in significant amounts, and suitability of analytical procedure for routine monitoring.

2) The establishment of MRLs in processed commodities has so far not been decided on within the EC and may concern commodities only for which the processing procedure requires concentration and not dilution steps.

3) In case of tolylfluanid, the residue definition for the purpose of dietary risk assessment already includes DMST. Thus, the fact that DMST may occur in some commodities at quantitatively significant amounts is already covered.

4) Concerning worldwide authorities and organisations, the residue definition for tolylfluanid and enforcement purposes is set as parent compound only by e.g. Codex Alimentarius, US EPA, Australian APVMA and others. Within Europe, the residue definition is currently also parent compound, with two exceptions only. Therefore, the parent only definition is strongly supported by the authorities.

5) DFG S 19 and DFG S 8 methods were validated only for parent compound. The DAR (See Point B.5.2) contains a multitude of methods validated for parent and DMST metabolite for various plants. However, further validation is required for most of methods (e.g. ILV and confirmation methods).

In the special case of beverages like wine, tolylfluanid would not be sufficient as analyte for enforcement purposes as it rapidly degrades to DMST. However, this is an occurrence specific to dilution and hydrolysis. The RMS propose that in the event that the setting of MRLs for processed commodities should become a requirement, the residue definition for tolylfluanid should be modified to include DMST for those commodities only for which hydrolysis is of relevance.

The RMS has re-calculated the MRL proposals referring the sum of tolylfluanid + DMST for residue definition. Statistical methods such as method I and method II have been used for calculation of the MRL-values as described in Draft Commission Guidance Document (7039/VI/95 on 22/7/1997). Residue levels expressed as < LOQ were assumed to be at the LOQ. MRLs were calculated separately for each data set (Southern Europe/Northern Europe/greenhouse). For the MRL proposal the highest calculated MRL corresponding the critical GAP of the supported use patterns was selected. The residue levels used for calculation were expressed as tolylfluanid (tolylfluanid = 347.3 g/mol, DMST = 214.3 g/mol). With the exception of hops, outliers were considered as true residue values for all crops.

The table below shows a comparison of the MRL proposals presented in the DAR to the revised MRL proposals based on the sum of tolylfluanid + DMST. Where deviations to the original MRL proposal occurred, they are marked in bold print.

Justifications for extrapolations are given in Table B.7.13-2. (No longer group tolerances are proposed for lettuce and similar, MRL is proposed only for lettuce; consequently cress and endive are eliminated from intake calculations).

Table B.7.13-1 MRL proposals in the DAR in comparison to revised MRLs based on the sum of tolylfluanid + DMST

Crop	MRL proposal of RMS (tolylfluanid only) (mg/kg)	Revised MRL proposal (tolylfluanid + DMST) (mg/kg)
Pome fruit	2	**3**
Grapes	5	5
Strawberries	3	3
Cane fruit	5	5
Other small fruit and berries	2	**3**
Tomatoes and eggplants	2	2
Peppers	2	2
Cucumber and courgettes	1	**2**
Melons	0.2	**0.3**
Lettuce and similar	15	**20**
Leeks	2	**3**
Hops	30	**50**

Table B.7.13-2 Justifications for extrapolation

Crop investigated in trials	Intended extrapolation to	Justification
Grapes (8 x N-EU field, 10 x S-EU field)	|none	-
Apples (8 x N-EU, field) 6 x apples, 3 x pears (S-EU, field)	pome fruit, whole group	A minimum of 4 apple trials allows possible extrapolation to the whole group (guideline working document 7525/VI/95 rev. 7, App. D, Table 3). As a sufficient number of trials are available and residue levels on apples and pears are comparable, extrapolation to the whole group is considered to be acceptable.
Strawberry (10 x N-EU field, 8 x S-EU field) |	none	-
4 x raspberry, 4 x blackberry (N-EU only, field)	Cane fruit, whole group	8 trials alone of two representatives (must also include a minimum of 4 raspberry trials) allows extrapolation to the whole group (guideline working document 7525/VI/95 rev. 7, App. D, Table 3). As residue trials were performed on two of the group and the required trails on raspberries are available, extrapolation to whole group is considered acceptable.
Black currant (8 x N-EU field, alone)	Other small fruits and berries, whole group (other than wild)	8 trials of blackcurrants or of two representatives must also include a minimum of 4 blackcurrant trials) allows extrapolation to the whole group (guideline working document 7525/VI/95 rev. 7, App. D, Table 3).The first prerequisite of guideline requirements is fulfilled (8 trials on blackcurrants). Therefore, it is considered acceptable to extrapolate to the whole group.
Tomato (8 x N-EU field, 8 x S-EU field, 10 x greenhouse)	Eggplants (=Aubergines)	According to the guideline document (7525/VI/95 rev. 7, App. D, Table 3) extrapolation from tomato to aubergines is possible. As a sufficient number of trials are available, extrapolation is considered acceptable.
Sweet peppers (10 x greenhouse)	Peppers (without chilli peppers)	According to the guideline document (7525/VI/95 rev. 7, App. D, Table 3) extrapolation from sweet peppers to peppers is possible. As a sufficient number of trials on peppers are available, extrapolation is considred acceptable.

Continued

Continued

Crop investigated in trials	**Intended extrapolation to**	**Justification**
Cucumber (4 x N-EU field, 8 x greenhouse)	Cucurbits, edible peel, whole group	According to the guideline document (7525/VI/95 rev. 7, App. D, Table 3) trials on cucumber or courgettes (if courgettes alone 8 trials) allows extrapolation to the whole group (comprising cucumber, gherkins, courgettes = zucchini, others). As a sufficient number of trials on cucumber are available, extrapolation is considred acceptable.
Lettuce	Lettuce	According to the guideline document (7525/VI/95 rev. 7, App. D, Table 3) trials on lettuce allows extrapolation to the whole group (concederation should be given to possible residues in lamb's lettuce and cress). No residue trials were conducted on lamb's lettuce and cress and MRL proposal is limited to lettuce.
Leeks	None	-
Hops	None	-

Detailed MRL calculations of the selected trials relevant to the revised MRL proposal are seen in the Tables B.7.13-3 - B.7.13-21 in the following pages:

Table B.7.13-3 Revised MRL Calculations: Pome fruit (Northern Europe)

Table: Apple, Northern Europe

Active substance :	tolylfluanid + DMST	Crop group :	Pomaceous fruit
Portion analysed :	fruit	Commodity :	Apple
Target value :	MRL	PHI :	7 d

No.	Crop	Days after application	Residue value (mg/kg) tolylfluanid	Residue value (mg/kg) tolylfluanid + DMST	Study-No. [1]/ Report-No.	No. of applic.	FL-Type	Product	Country
1	Apple	7	0.18	0.21	0586-95 / RA-2095/95	7	WG 50	EUPAREN M WG 50	Germany
2	Apple	7	0.19	0.22	0378-95 / RA-2095/95	7	WG 50	EUPAREN M WG 50	Nether-lands
3	Apple	7	0.24	0.29	0587-95 / RA-2095/95	7	WG 50	EUPAREN M WG 50	Germany
4	Apple	7	0.35	0.41	0380-95 / RA-2095/95	7	WG 50	EUPAREN M WG 50	Germany
5	Apple	7	0.46	0.51	0585-95 / RA-2095/95	7	WG 50	EUPAREN M WG 50	Germany
6	Apple	7	0.58	0.76	0590-95 / RA-2095/95	7	WG 50	EUPAREN M WG 50	Nether-lands
7	Apple	7	0.59	0.74	0584-95 / RA-2095/95	7	WG 50	EUPAREN M WG 50	Germany
8	Apple	7	1.7	1.86	0381-95 / RA-2095/95	7	WG 50	EUPAREN M WG 50	Germany

[1] as given in the Tier 1 summaries
value no. 8 is an outlier for t1

Results (Apple)

Method I (Weinmann/Nolting) (all values)	R	0.625
	s	0.543
	k	3.145
	Rmax=R+k*s	**2.333**
Method I (elimination of outliers)	R	0.449
	s	0.231
	k	3.355
	Rmax=R+k*s	**1.225**
Method II (Wilkening) (75 % quantile)	R (0.75)	0.755
	Rber=2*R(0.75)	**1.510**

Summary of results:

Maximum residue values for a pre-harvest interval of: 7 days

Method I (all values)	2.33 mg/kg
Method I (elimination of outliers)	1.23 mg/kg
Method II (75% quantile)	1.51 mg/kg

STMR: 0.21;0.22;0.29;0.41;**(0.46)**;0.51;0.74;0.76;1.86

Table B.7.13-4 Revised MRL Calculations: Pome fruit (Southern Europe)

Table: Apple;Pear; Southern Europe

Active substance :	tolylfluanid + DMST	Crop group :	Pomaceous fruit
Portion analysed :	fruit	Commodity :	Apple; Pear
Target value :	MRL	PHI :	3 d

No.	Crop	Days after appli-cation	Residue value (mg/kg) Tolylfluanid	Residue value (mg/kg) Tolylfluanid + DMST	Study-No. [1]/ Report-No.	No. of applic.	FL-Type	Product	Country
1	Pear	3	0.3	0.33	0266-94 / RA-2150/94	3	WG 50	EUPAREN M WG 50	Italy
2	Apple	3	0.37	0.43	0264-94 / RA-2064/94	3	WG 50	EUPAREN M WG 50	Italy
3	Apple	5	0.42	0.47	0262-94 / RA-2064/94	3	WG 50	EUPAREN M WG 50	Italy
4	Apple	3	0.66	0.72	0301-95 / RA-2096/95	3	WG 50	EUPAREN M WG 50	France
5	Apple	3	0.78	0.91	0379-95 / RA-2096/95	3	WG 50	EUPAREN M WG 50	Italy
6	Pear	3	0.78	0.86	0267-94 / RA-2150/94	3	WG 50	EUPAREN M WG 50	Italy
7	Pear	3	0.89	1.0	0268-94 / RA-2150/94	3	WG 50	EUPAREN M WG 50	Spain
8	Apple	3	0.95	1.01	0588-95 / RA-2096/95	3	WG 50	EUPAREN M WG 50	France
9	Apple	3	2.3	2.45	0265-94 / RA-2064/94	3	WG 50	EUPAREN M WG 50	Spain

[1] as given in the Tier 1 summaries
value no. 9 is an outlier for t1

Results (Apple;Pear)

Method I (Weinmann/Nolting) (all values)	R	0.909
	s	0.631
	k	2.992
	Rmax=R+k*s	**2.798**
Method I (elimination of outliers)	R	0.716
	s	0.272
	k	3.145
	Rmax=R+k*s	**1.571**
Method II (Wilkening) (75 % quantile)	R (0.75)	1.005
	Rber=2*R(0.75)	**2.010**

Summary of results:

Maximum residue values for a pre-harvest interval of: 3 days

Method I (all values)	2.80 mg/kg
Method I (elimination of outliers)	1.57 mg/kg
Method II (75% quantile)	2.01 mg/kg

STMR: 0.33;0.43;0.47;0.72;**(0.86)**;0.91;1.0;1.01;2.45

Table B.7.13-5 Revised MRL Calculations: Grapes (Northern Europe)

Table: Grape, northern Europe

Active substance :	tolylfluanid + DMST	Crop group :	Vines
Portion analysed :	bunch of grapes	Commodity :	Grape
Target value :	MRL	PHI :	35-42 d

No.	Crop	Days after appli-cation	Residue value (mg/kg) tolylfluanid	Residue value (mg/kg) tolylfluanid + DMST	Study-No. [1]/ Report-No.	No. of applic.	FL-Type	Product	Country
1	Grape	35	0.06	0.14	0212-88 / 0212-88	8	WG 50	EUPAREN M WG 50	Germany
2	Grape	42	0.25	0.35	8200-87 / 8200-87	8	WG 50	Euparen M WG 50	Germany
3	Grape	35	0.35	0.46	0211-88 / 0211-88	8	WG 50	EUPAREN M WG 50	Germany
4	Grape	42	0.49	0.67	8202-87 / 8202-87	8	WG 50	Euparen M WG 50	Germany
5	Grape	42	0.63	0.84	8201-87 / 8201-87	8	WG 50	Euparen M WG 50	Germany
6	Grape	35	0.67	0.83	0213-88 / 0213-88	8	WG 50	EUPAREN M WG 50	Germany
7	Grape	35	0.91	1.19	0210-88 / 0210-88	8	WG 50	EUPAREN M WG 50	Germany
8	Grape	35	1.7	1.94	8203-87 / 8203-87	8	WG 50	Euparen M WG 50	Germany

[1] as given in the Tier 1 summaries

Results (Grape)

Method I (Weinmann/Nolting) (all values)	R	0.803
	s	0.564
	k	3.145
	Rmax=R+k*s	**2.575**
Method II (Wilkening) (75 % quantile)	R (0.75)	1.103
	Rber=2*R(0.75)	**2.205**

Summary of results:

Maximum residue values for a pre-harvest interval of: 42 days

Method I (all values)	2.58 mg/kg
Method II (75% quantile)	2.21 mg/kg

For refined risk assessment an STMR value for the sum of tolylfluanid and DMST as well as the aglyca of 4- hydroxymethyl-DMST-glycoside and 2-hydroxyphenyl-DMST-glycoside (expressed as tolylfluanid) is used.

Table B.7.13-6 Revised MRL Calculations: Grapes (Southern Europe)

Table: Grape, southern Europe

Active substance :	tolylfluanid + DMST	Crop group :	Vines
Portion analysed :	segment of a bunch of grapes	Commodity :	Grape
Target value :	MRL	PHI :	21 d

No.	Crop	Days after appli-cation	Residue value (mg/kg) tolylfluanid	Residue value (mg/kg) tolylfluanid + DMST	Study-No. [1]/ Report-No.	No. of applic.	FL-Type	Product	Country
1	Grape	21	2.6	2.96	0015-95 / RA-2093/95	3	WG 50	EUPAREN M WG 50	France
2	Grape	21	0.46	0.61	0085-93 / RA-2049/93	3	WP 50	EUPAREN M WP 50	France
3	Grape	21	0.06	0.16	0320-93 / RA-2049/93	3	WP 50	EUPAREN M WP 50	France
4	Grape	21	2.1	2.38	0321-93 / RA-2049/93	3	WP 50	EUPAREN M WP 50	France
5	Grape	21	1.4	1.51	0322-93 / RA-2049/93	3	WP 50	EUPAREN M WP 50	France
6	Grape	21	0.36	0.42	0423-92 / RA-2007/92	5	WG 50	EUPAREN M WG 50	France
7	Grape	21	0.57	0.75	0424-92 / RA-2007/92	5	WG 50	EUPAREN M WG 50	France
8	Grape	21	0.33	0.41	0425-92 / RA-2007/92	5	WG 50	EUPAREN M WG 50	France
9	Grape	21	1.4	1.63	0426-92 / RA-2007/92	5	WG 50	EUPAREN M WG 50	France
10	Grape	21	3.5	3.82	0599-95 / RA-2093/95	3	WG 50	EUPAREN M WG 50	France

[1] as given in the Tier 1 summaries

Results (Grape)

Method I (Weinmann/Nolting) (all values)	R	1.465
	s	1.238
	k	2.875
	Rmax=R+k*s	**5.025**
Method II (Wilkening) (75 % quantile)	R (0.75)	2.525
	Rber=2*R(0.75)	**5.050**

Summary of results:

Maximum residue values for a pre-harvest interval of: 21 days

Method I (all values)	5.02 mg/kg
Method II (75% quantile)	5.05 mg/kg

For refined risk assessment an STMR value for the sum of tolylfluanid and DMST as well as the aglyca of 4- hydroxymethyl-DMST-glycoside and 2-hydroxyphenyl-DMST-glycoside (expressed as tolylfluanid) is used.

Table B.7.13-7 Revised MRL Calculations: Strawberry (Northern Europe)

Table: Strawberry, northern Europe

Active substance :	tolylfluanid + DMST	Crop group :	Small fruit
Portion analysed :	fruit	Commodity :	Strawberry
Target value :	MRL	PHI :	7 d

No.	Crop	Days after appli-cation	Residue value (mg/kg) tolylfluanid	Residue value (mg/kg) tolylfluanid + DMST	Study-No. [1]/ Report-No.	No. of applic.	FL-Type	Product	Country
1	Strawberry	10	0.07	0.15	8254-87 / 8254-87	3	WG 50	Euparen M WG 50	Germany
2	Strawberry	7	0.43	0.66	8255-87 / 8255-87	3	WG 50	Euparen M WG 50	Germany
3	Strawberry	7	0.65	1.2	8250-87 / 8250-87	3	WG 50	Euparen M WG 50	Germany
4	Strawberry	7	0.69	1.1	8251-87 / 8251-87	3	WG 50	Euparen M WG 50	Germany
5	Strawberry	7	0.73	1.12	0013-88 / 0013-88	5	WG 50	Euparen M WG 50	Nether-lands
6	Strawberry	10	0.75	0.99	0088-72 / 0088-72	3	WP 50	Euparen M WP 50	Germany
7	Strawberry	10	0.9	1.06	0087-72 / 0087-72	3	WP 50	Euparen M WP 50	Germany
8	Strawberry	7	0.93	1.3	8252-87 / 8252-87	3	WG 50	Euparen M WG 50	Germany
9	Strawberry	11	1.4	1.81	0089-72 / 0089-72	3	WP 50	Euparen M WP 50	Germany
10	Strawberry	7	1.9	2.71	8253-87 / 8253-87	3	WG 50	Euparen M WG 50	Germany

[1] as given in the Tier 1 summaries

Results (Strawberry)

Method I (Weinmann/Nolting) (all values)	R	1.210
	s	0.678
	k	2.875
	Rmax=R+k*s	**3.159**
Method II (Wilkening) (75 % quantile)	R (0.75)	1.428
	Rber=2*R(0.75)	**2.855**

Summary of results:

Maximum residue values for a pre-harvest interval of: 7 days

Method I (all values)	3.16 mg/kg
Method II (75% quantile)	2.86 mg/kg

STMR: 0.15;0.66;0.99;1.06;1.1;**(1.1)**;1.12;1.2;1.3;1.81;2.71

Table B.7.13-8 Revised MRL Calculations: Strawberry (Southern Europe)

Table: Strawberry, southern Europe

Active substance :	tolylfluanid + DMST	Crop group :	Small fruit
Portion analysed :	fruit	Commodity :	Strawberry
Target value :	MRL	PHI :	3 d

N	Crop	Days after appli-cation	Residue value (mg/kg) tolylfluanid	Residue value (mg/kg) tolylfluanid + DMST	Study-No. [1]/ Report-No.	No. of applic.	FL-Type	Product	Country
1	Strawberry	3	0.04	0.35	0592-95 / RA-2097/95	3	WG 50	EUPAREN M WG 50	France
2	Strawberry	3	0.11	0.22	0012-95 / RA-2097/95	3	WG 50	EUPAREN M WG 50	Spain
3	Strawberry	3	0.41	0.77	0285-97 / RA-2048/97	3	WP 50	EUPAREN M WP 50	France
4	Strawberry	3	0.44	0.80	0571-96 / RA-2062/96	3	WG 50	EUPAREN M WG 50	France
5	Strawberry	3	0.45	0.76	0351-94 / RA-2086/94	3	WG 50	EUPAREN M WG 50	Spain
6	Strawberry	3	0.61	1.44	0013-95 / RA-2097/95	3	WG 50	EUPAREN M WG 50	France
7	Strawberry	3	0.64	0.87	0177-96 / RA-2062/96	3	WG 50	EUPAREN M WG 50	France
8	Strawberry	3	0.71	2.31	0286-97 / RA-2048/97	3	WP 50	EUPAREN M WP 50	France

[1] as given in the Tier 1 summaries

Results (Strawberry)

Method I (Weinmann/Nolting) (all values)	R	0.940
	s	0.663
	k	3.145
	Rmax=R+k*s	**3.026**
Method II (Wilkening) (75 % quantile)	R (0.75)	1.298
	Rber=2*R(0.75)	**2.595**

Summary of results:

Maximum residue values for a pre-harvest interval of: 3 days

Method I (all values)	3.03 mg/kg
Method II (75% quantile)	2.60 mg/kg

STMR: 0.22;0.35;0.76;0.77;**(0.79)**;0.80;0.87;1.44;2.31

Table B.7.13-9 Revised MRL Calculations: Cane fruit (Northern Europe)

Table: Blackberry, Raspberry; northern Europe

Active substance :	tolylfluanid + DMST	Crop group :	Small fruit
Portion analysed :	fruit	Commodity :	Blackberry; Raspberry
Target value :	MRL	PHI :	14 d

No.	Crop	Days after appli-cation	Residue value (mg/kg) tolylfluanid	Residue value (mg/kg) tolylfluanid + DMST	Study-No. [1]/ Report-No.	No. of applic.	FL-Type	Product	Country
1	Raspberry	14	0.42	0.48	0598-95 / RA-2107/95	4	WG 50	EUPAREN M WG 50	Great Britain
2	Blackberry	14	0.61	0.72	0028-95 / RA-2107/95	4	WG 50	EUPAREN M WG 50	Great Britain
3	Raspberry	14	1.4	1.55	0006-95 / RA-2107/95	4	WG 50	EUPAREN M WG 50	Great Britain
4	Blackberry	14	1.6	1.88	0440-97 / RA-2045/97	4	WG 50	EUPAREN M WG 50	Great Britain
5	Raspberry	14	1.7	2.04	0027-95 / RA-2107/95	4	WG 50	EUPAREN M WG 50	Germany
6	Blackberry	14	1.7	2.06	0095-97 / RA-2045/97	5	WG 50	EUPAREN M WG 50	Germany
7	Blackberry	14	2.0	2.19	0533-95 / RA-2107/95	4	WG 50	EUPAREN M WG 50	Germany
8	Raspberry	14	2.4	2.87	0597-95 / RA-2107/95	4	WG 50	EUPAREN M WG 50	Germany

[1] as given in the Tier 1 summaries

Results (Blackberry;Raspberry)

Method I (Weinmann/Nolting) (all values)	R	1.724
	s	0.789
	k	3.145
	Rmax=R+k*s	**4.204**
Method II (Wilkening) (75 % quantile)	R (0.75)	2.158
	Rber=2*R(0.75)	**4.315**

Summary of results:

Maximum residue values for a pre-harvest interval of: 14 days

Method I (all values)	4.20 mg/kg
Method II (75% quantile)	4.32 mg/kg

STMR: 0.48;0.72;1.55;1.88;**(1.96)**;2.04;2.06;2.19;2.87

Table B.7.13-10 Revised MRL Calculations: Other small fruits and berries (Northern Europe)

Table: Currant, black; Northern Europe

Active substance :	tolylfluanid + DMST	Crop group :	Small fruit
Portion analysed :	fruit	Commodity :	Currant, black
Target value :	MRL	PHI :	14 d

No.	Crop	Days after appli-cation	Residue value (mg/kg) tolylfluanid	Residue value (mg/kg) tolylfluanid + DMST	Study-No. [1]/ Report-No.	No. of applic.	FL-Type	Product	Country
1	Currant, black	14	0.24	0.63	0007-95 / RA-2108/95	2	WG 50	EUPAREN M WG 50	Great Britain
2	Currant, black	14	0.24	0.37	0204-99 / RA-2007/99	2	WG 50	EUPAREN M WG 50	Great Britain
3	Currant, black	14	0.32	0.45	0203-99 / RA-2007/99	2	WG 50	EUPAREN M WG 50	Great Britain
4	Currant, black	14	0.50	0.78	0112-99 / RA-2007/99	2	WG 50	EUPAREN M WG 50	Germany
5	Currant, black	14	0.43	0.80	0591-95 / RA-2108/95	2	WG 50	EUPAREN M WG 50	Great Britain
6	Currant, black	14	0.57	0.81	0202-99 / RA-2007/99	2	WG 50	EUPAREN M WG 50	Germany
7	Currant, black	14	0.90	1.37	0412-96 / RA-2061/96	2	WG 50	EUPAREN M WG 50	Great Britain
8	Currant, black	14	1.3	1.83	0411-96 / RA-2061/96	2	WG 50	EUPAREN M WG 50	Germany

[1] as given in the Tier 1 summaries

Results (Currant, black)

Method I (Weinmann/Nolting) (all values)	R	0.880
	s	0.489
	k	3.145
	Rmax=R+k*s	**2.417**
Method II (Wilkening) (75 % quantile)	R (0.75)	1.230
	Rber=2*R(0.75)	**2.460**

Summary of results:

Maximum residue values for a pre-harvest interval of: 14 days

Method I (all values)	2.42 mg/kg
Method II (75% quantile)	2.46 mg/kg

STMR: 0.37;0.45;0.63;0.78;**(0.79)**;0.80;0.81;1.37;1.83

Table B.7.13-11 Revised MRL Calculations: Tomato and eggplant (Northern Europe)

Table: Tomato and eggplant; northern Europe

Active substance :	tolylfluanid + DMST	Crop group :	Fruit vegetables
Portion analysed :	fruit	Commodity :	Tomato
Target value :	MRL	PHI :	3 d

No.	Crop	Days after appli-cation	Residue value (mg/kg) tolylfluanid	Residue value (mg/kg) tolylfluanid + DMST	Study-No. [1]/ Report-No.	No. of applic.	FL-Type	Product	Country
1	Tomato	5	0.15	0.34	0219-88 / 0219-88	6	WG 50	EUPAREN M WG 50	Germany
2	Tomato	3	0.15	0.30	8206-87 / 8206-87	6	WG 50	Euparen M WG 50	Germany
3	Tomato	3	0.18	0.26	0222-88 / 0222-88	6	WG 50	EUPAREN M WG 50	Germany
4	Tomato	3	0.20	0.35	8207-87 / 8207-87	6	WG 50	Euparen M WG 50	Germany
5	Tomato	3	0.27	0.40	0221-88 / 0221-88	6	WG 50	EUPAREN M WG 50	Germany
6	Tomato	3	0.34	0.49	8205-87 / 8205-87	4	WG 50	Euparen M WG 50	Germany
7	Tomato	3	0.47	0.55	0220-88 / 0220-88	6	WG 50	EUPAREN M WG 50	Germany
8	Tomato	3	0.99	1.27	8204-87 / 8204-87	6	WG 50	Euparen M WG 50	Germany

[1] as given in the Tier 1 summaries
value no. 8 is an outlier for t1

Results (Tomato)

Method I (Weinmann/Nolting) (all values)	R	0.495
	s	0.328
	k	3.145
	Rmax=R+k*s	**1.525**
Method I (elimination of outliers)	R	0.384
	s	0.104
	k	3.355
	Rmax=R+k*s	**0.732**
Method II (Wilkening) (75 % quantile)	R (0.75)	0.535
	Rber=2*R(0.75)	**1.070**

Summary of results:

Maximum residue values for a pre-harvest interval of: 3 days

Method I (all values)	1.52 mg/kg
Method I (elimination of outliers)	0.73 mg/kg
Method II (75% quantile)	1.07 mg/kg

STMR: 0.26;0.30;0.34;0.35;**(0.38)**;0.40;0.49;0.55;1.27

Table B.7.13-12 Revised MRL Calculations: Tomato and eggplant (Southern Europe)

Table: Tomato and eggplant, Southern Europe

Active substance :	tolylfluanid + DMST	Crop group :	Fruit vegetables
Portion analysed :	fruit	Commodity :	Tomato
Target value :	MRL	PHI :	3 d

No.	Crop	Days after appli-cation	Residue value (mg/kg) tolylfluanid	Residue value (mg/kg) tolylfluanid + DMST	Study-No. [1]/ Report-No.	No. of applic.	FL-Type	Product	Country
1	Tomato	3	0.04	0.07	0583-95 / RA-2100/95	3	WG 50	EUPAREN M WG 50	Italy
2	Tomato	3	0.07	0.10	0678-95 / RA-2100/95	3	WG 50	EUPAREN M WG 50	Italy
3	Tomato	3	0.19	0.24	0581-95 / RA-2100/95	3	WG 50	EUPAREN M WG 50	Italy
4	Tomato	3	0.21	0.27	0681-95 / RA-2100/95	3	WG 50	EUPAREN M WG 50	Italy
5	Tomato	3	0.23	0.29	0259-94 / RA-2063/94	3	WG 50	EUPAREN M WG 50	Italy
6	Tomato	3	0.42	0.58	0260-94 / RA-2063/94	3	WG 50	EUPAREN M WG 50	Italy
7	Tomato	3	0.47	0.60	0682-95 / RA-2100/95	3	WG 50	EUPAREN M WG 50	Spain
8	Tomato	3	0.54	0.69	0679-95 / RA-2100/95	3	WG 50	EUPAREN M WG 50	Spain

[1] as given in the Tier 1 summaries

Results (Tomato)

Method I (Weinmann/Nolting) (all values)	R	0.355
	s	0.237
	k	3.145
	Rmax=R+k*s	**1.101**
Method II (Wilkening) (75 % quantile)	R (0.75)	0.595
	Rber=2*R(0.75)	**1.190**

Summary of results:

Maximum residue values for a pre-harvest interval of: 3 days

Method I (all values)	1.10 mg/kg
Method II (75% quantile)	1.19 mg/kg

STMR: 0.07;0.10;0.24;0.27;**(0.28)**;0.29;0.58;0.60;0.69

Table B.7.13-13 Revised MRL Calculations: Tomato and eggplant (greenhouse)

Table: Tomato and eggplant, greenhouse

Active substance :	tolylfluanid + DMST	Crop group :	Fruit vegetables
Portion analysed :	fruit	Commodity :	Tomato
Target value :	MRL	PHI :	3 d

No.	Crop	Days after appli-cation	Residue value (mg/kg) tolylfluanid	Residue value (mg/kg) tolylfluanid + DMST	Study-No. [1]/ Report-No.	No. of applic.	FL-Type	Product	Country
1	Tomato	3	0.08	0.14	0608-95 / RA-2101/95	6	WG 50	EUPAREN M WG 50	Germany
2	Tomato	3	0.16	0.22	0609-95 / RA-2101/95	6	WG 50	EUPAREN M WG 50	Germany
3	Tomato	3	0.26	0.37	0261-94 / RA-2063/94	3	WG 50	EUPAREN M WG 50	Italy
4	Tomato	3	0.24	0.40	0035-95 / RA-2101/95	6	WG 50	EUPAREN M WG 50	Germany
5	Tomato	3	0.42	0.47	0500-00 / RA-2097/00	6	WG 50	EUPAREN M WG 50	Germany
6	Tomato	3	0.49	0.67	0352-93 / RA-2048/93	3	WP 50	EUPAREN M WP 50	Spain
7	Tomato	3	0.59	0.70	0607-95 / RA-2101/95	6	WG 50	EUPAREN M WG 50	Germany
8	Tomato	3	0.72	0.77	0502-00 / RA-2097/00	6	WG 50	EUPAREN M WG 50	Belgium
9	Tomato	3	1.4	1.5	0501-00 / RA-2097/00	6	WG 50	EUPAREN M WG 50	Italy
10	Tomato	3	1.4	1.56	0503-00 / RA-2097/00	6	WG 50	EUPAREN M WG 50	Italy

[1] as given in the Tier 1 summaries

Results (Tomato)

Method I (Weinmann/Nolting) (all values)	R	0.680
	s	0.492
	k	2.875
	Rmax=R+k*s	**2.094**
Method II (Wilkening) (75 % quantile)	R (0.75)	0.953
	Rber=2*R(0.75)	**1.905**

Summary of results:

Maximum residue values for a pre-harvest interval of: 3 days

Method I (all values)	2.09 mg/kg
Method II (75% quantile)	1.91 mg/kg

STMR: 0.14;0.22;0.37;0.40;0.47;**(0.57)**;0.67;0.70;0.77;1.5;1.56

Table B.7.13-14 Revised MRL Calculations: Tomato and eggplant (greenhouse, tolylfluanid in mixture with iprovalicarb)

Table: Tomato and eggplant, greenhouse (trials in combination with iprovalicarb)

Active substance :	tolylfluanid + DMST	Crop group :	Fruit vegetables
Portion analysed :	fruit	Commodity :	Tomato
Target value :	MRL	PHI :	7 d

No.	Crop	Days after appli-cation	Residue value (mg/kg) tolylfluanid	Residue value (mg/kg) tolylfluanid + DMST	Study-No. [1]/ Report-No.	No. of applic.	FL-Type	Product	Country
1	Tomato	7	0.36	0.47	0213-97 / RA-2126/97	5	WG 43.5	SZX 0722 & Tolylfluanid WG 43.5	Germany
2	Tomato	7	0.52	0.76	1619-98 / RA-2135/98	8	WG 43.5	SZX 0722 & Tolylfluanid WG 43.5	Belgium
3	Tomato	7	0.74	0.98	0697-97 / RA-2126/97	5	WG 43.5	SZX 0722 & Tolylfluanid WG 43.5	Belgium
4	Tomato	7	0.79	1.02	1308-98 / RA-2135/98	8	WG 43.5	SZX 0722 & Tolylfluanid WG 43.5	Germany
5	Tomato	7	0.82	1.06	0700-97 / RA-2126/97	5	WG 43.5	SZX 0722 & Tolylfluanid WG 43.5	France
6	Tomato	7	0.63	1.07	1620-98 / RA-2135/98	8	WG 43.5	SZX 0722 & Tolylfluanid WG 43.5	Italy
7	Tomato	7	0.83	1.07	1073-98 / RA-2135/98	8	WG 43.5	SZX 0722 & Tolylfluanid WG 43.5	Spain
8	Tomato	7	0.86	1.07	1621-98 / RA-2135/98	8	WG 43.5	SZX 0722 & Tolylfluanid WG 43.5	Germany
9	Tomato	7	1.2	1.96	0698-97 / RA-2126/97	5	WG 43.5	SZX 0722 & Tolylfluanid WG 43.5	Italy

[1] as given in the Tier 1 summaries; value no. 9 is an outlier for t1

Results (Tomato)

Method I (Weinmann/Nolting) (all values)	R	1.051
	s	0.396
	k	2.992
	Rmax=R+k*s	**2.236**
Method I (elimination of outliers)	R	0.938
	s	0.216
	k	3.145
	Rmax=R+k*s	**1.616**
Method II (Wilkening) (75 % quantile)	R (0.75)	1.070
	Rber=2*R(0.75)	**2.140**

Summary of results:

Maximum residue values for a pre-harvest interval of: 7 days

Method I (all values)	2.24 mg/kg
Method I (elimination of outliers)	1.62 mg/kg
Method II (75% quantile)	2.14 mg/kg

STMR: 0.47;0.76;0.98;1.02;**(1.06)**;1.07;1.07;1.07;1.96

Table B.7.13-15 Revised MRL Calculations: Pepper (greenhouse)

Table: Pepper, sweet; greenhouse

Active substance :	tolylfluanid + DMST	Crop group :	Fruit vegetables
Portion analysed :	fruit	Commodity :	Pepper, sweet
Target value :	MRL	PHI :	3-5 d

No.	Crop	Days after appli-cation	Residue value (mg/kg) tolylfluanid	Residue value (mg/kg) tolylfluanid + DMST	Study-No. [1]/ Report-No.	No. of applic.	FL-Type	Product	Country
1	Pepper, sweet	5	0.08	0.13	0256-94 / RA-2028/94	3	WG 50	EUPAREN M WG 50	Italy
2	Pepper, sweet	3	0.28	0.34	0257-94 / RA-2028/94	3	WG 50	EUPAREN M WG 50	Italy
3	Pepper, sweet	3	0.20	0.44	0442-00 / RA-2094/00	3	WG 50	EUPAREN M WG 50	Nether-lands
4	Pepper, sweet	5	0.36	0.44	0357-94 / RA-2028/94	3	WG 50	EUPAREN M WG 50	Spain
5	Pepper, sweet	3	0.26	0.62	0441-00 / RA-2094/00	3	WG 50	EUPAREN M WG 50	Nether-lands
6	Pepper, sweet	3	0.49	0.72	0665-94 / RA-2028/94	3	WG 50	EUPAREN M WG 50	Italy
7	Pepper, sweet	3	0.66	0.85	0356-94 / RA-2028/94	3	WG 50	EUPAREN M WG 50	Spain
8	Pepper, sweet	3	0.61	0.95	0258-94 / RA-2028/94	3	WG 50	EUPAREN M WG 50	Italy
9	Pepper, sweet	5	1.2	1.41	0359-94 / RA-2028/94	3	WG 50	EUPAREN M WG 50	Spain
10	Pepper, sweet	3	1.3	1.64	0667-94 / RA-2028/94	3	WG 50	EUPAREN M WG 50	Spain

[1] as given in the Tier 1 summaries

Results (Pepper, sweet)

Method I (Weinmann/Nolting) (all values)	R	0.754
	s	0.476
	k	2.875
	Rmax=R+k*s	**2.123**
Method II (Wilkening) (75 % quantile)	R (0.75)	1.065
	Rber=2*R(0.75)	**2.130**

Summary of results:

Maximum residue values for a pre-harvest interval of: 3 days

Method I (all values)	2.12 mg/kg
Method II (75% quantile)	2.13 mg/kg

STMR: 0.13;0.34;0.44;0.44;0.62;**(0.67)**;0.72;0.85;0.95;1.41;1.64

Table B.7.13-16 Revised MRL Calculations: Cucumbers and courgettes (Northern Europe)

Table: Cucumber, northern Europe

Active substance :	tolylfluanid + DMST	Crop group :	Fruit vegetables
Portion analysed :	fruit	Commodity :	Cucumber
Target value :	MRL	PHI :	3 d

No.	Crop	Days after appli-cation	Residue value (mg/kg) tolylfluanid	Residue value (mg/kg) tolylfluanid + DMST	Study-No. [1]/ Report-No.	No. of applic.	FL-Type	Product	Country
1	Cucumber	3	0.02	0.05	0096-95 / RA-2103/95	6	WG 50	EUPAREN M WG 50	Germany
2	Cucumber	3	<0.02	0.05	0604-95 / RA-2103/95	6	WG 50	EUPAREN M WG 50	Germany
3	Cucumber	3	0.02	0.05	0605-95 / RA-2103/95	5	WG 50	EUPAREN M WG 50	Germany
4	Cucumber	3	0.02	0.05	0606-95 / RA-2103/95	5	WG 50	EUPAREN M WG 50	Germany

[1] as given in the Tier 1 summaries

Results (Cucumber)

Method I (Weinmann/Nolting)	R	0.050
(all values)	s	0.000
	k	4.210
	Rmax=R+k*s	**0.050**
Method II (Wilkening)	R (0.75)	0.050
(75 % quantile)	**Rber=2*R(0.75)**	**0.100**

Summary of results:

Maximum residue values for a pre-harvest interval of: 3 days

Method I (all values)	0.05 mg/kg
Method II (75% quantile)	0.10 mg/kg

STMR: 0.05;0.05;**(0.05)**;0.05;0.05

Table B.7.13-17 Revised MRL Calculations: Cucumbers and courgettes (greenhouse)

Table: Cucumber and courgettes, greenhouse

Active substance :	tolylfluanid + DMST	Crop group :	Fruit vegetables
Portion analysed :	fruit	Commodity :	Cucumber
Target value :	MRL	PHI :	3 d

No.	Crop	Days after appli-cation	Residue value (mg/kg) tolylfluanid	Residue value (mg/kg) tolylfluanid + DMST	Study-No. [1]/ Report-No.	No. of applic.	FL-Type	Product	Country
1	Cucumber	3	0.05	0.08	0600-95 / RA-2104/95	6	WG 50	EUPAREN M WG 50	Germany
2	Cucumber	3	0.11	0.16	0602-95 / RA-2104/95	6	WG 50	EUPAREN M WG 50	Germany
3	Cucumber	3	0.18	0.31	0303-95 / RA-2104/95	6	WG 50	EUPAREN M WG 50	Italy
4	Cucumber	3	0.18	0.34	0026-95 / RA-2104/95	6	WG 50	EUPAREN M WG 50	Germany
5	Cucumber	3	0.30	0.40	0302-95 / RA-2104/95	6	WG 50	EUPAREN M WG 50	Spain
6	Cucumber	3	0.57	0.67	0603-95 / RA-2104/95	6	WG 50	EUPAREN M WG 50	Germany
7	Cucumber	3	0.55	0.68	0179-96 / RA-2063/96	6	WG 50	EUPAREN M WG 50	Spain
8	Cucumber	3	0.64	0.96	0419-96 / RA-2063/96	6	WG 50	EUPAREN M WG 50	Italy

[1] as given in the Tier 1 summaries

Results (Cucumber)

Method I (Weinmann/Nolting)	R	0.450
(all values)	s	0.297
	k	3.145
	Rmax=R+k*s	**1.383**
Method II (Wilkening)	R (0.75)	0.678
(75 % quantile)	**Rber=2*R(0.75)**	**1.355**

Summary of results:

Maximum residue values for a pre-harvest interval of: 3 days

Method I (all values)	1.38 mg/kg
Method II (75% quantile)	1.36 mg/kg

STMR: 0.08;0.16;0.31;0.34;**(0.37)**;0.40;0.67;0.68;0.96

Table B.7.13-18 Revised MRL Calculations: Melon (Northern + Southern Europe)

Table: Melon, northern + southern Europe

Active substance :	tolylfluanid + DMST	Crop group :	Fruit vegetables
Portion analysed :	whole fruit	Commodity :	Melon
Target value :	MRL	PHI :	14 d

No.	Crop	Days after appli-cation	Residue value (mg/kg) tolylfluanid	Residue value (mg/kg) tolylfluanid + DMST	Study-No. [1]/ Report-No.	No. of applic.	FL-Type	Product	Country
1	Melon	14	<0.02	0.05	0086-93 / RA-2045/93	3	WG 50	EUPAREN M WG 50	France
2	Melon	14	<0.02	0.05	0313-93 / RA-2045/93	3	WG 50	EUPAREN M WG 50	France
3	Melon	14	<0.02	0.05	0314-93 / RA-2045/93	3	WG 50	EUPAREN M WG 50	France
4	Melon	14	<0.02	0.08	0315-93 / RA-2045/93	3	WG 50	EUPAREN M WG 50	France
5	Melon	14	<0.02	0.05	0202-94 / RA-2052/94	3	WG 50	EUPAREN M WG 50	Greece
6	Melon	14	<0.02	0.05	0199-94 / RA-2052/94	3	WG 50	EUPAREN M WG 50	France
7	Melon	14	<0.02	0.08	0097-97 / RA-2046/97	3	WG 50	EUPAREN M WG 50	France
8	Melon	14	<0.02	0.07	0200-94 / RA-2052/94	3	WG 50	EUPAREN M WG 50	France
9	Melon	13	0.02	0.08	0415-96 / RA-2064/96	3	WG 50	EUPAREN M WG 50	France
10	Melon	14	0.08	0.16	0203-94 / RA-2052/94	3	WG 50	EUPAREN M WG 50	Greece
11	Melon	14	0.04	0.17	0096-97 / RA-2046/97	3	WG 50	EUPAREN M WG 50	France
12	Melon	14	0.10	0.25	0417-96 / RA-2064/96	3	WG 50	EUPAREN M WG 50	France

[1] as given in the Tier 1 summaries

Results (Melon)

Method I (Weinmann/Nolting) (all values)	R	0.095
	s	0.064
	k	2.706
	Rmax=R+k*s	**0.269**
Method II (Wilkening) (75 % quantile)	R (0.75)	0.140
	Rber=2*R(0.75)	**0.280**

Summary of results:

Maximum residue values for a pre-harvest interval of: 14 days

Method I (all values)	0.27 mg/kg
Method II (75% quantile)	0.28 mg/kg

STMR (whole fruit): 0.05;0.05;0.05;0.05;0.05;0.07;**(0.08)**;0.08;0.08;0.08;0.16;0.17;0.25

STMR of 0.05 mg/kg was estimated in the dossier and also accepted by the rapporteur for the sum of tolylfluanid and DMST (expressed as tolylfluanid) in the edible part of the melons, i.e. pulp.

Table B.7.13-19 Revised MRL Calculations: Lettuce (Southern Europe + tolylfluanid in mixture with tebuconazole)

Table: Lettuce, head;

Active substance	tolylfluanid + DMST, SEU + tebuconazole	Crop group	Leaf and stem vegetables
Portion analysed	head	Commodity	Lettuce, head
Target value :	MRL	PHI :	7 d

No.	Crop	Days after appli-cation	Residue value (mg/kg) tolylfluanid	Residue value (mg/kg) tolylfluanid + DMST	Study-No. [1]/ Report-No.	No. of applic.	FL-Type	Product	Country
1	Lettuce, head	7	0.11	0.21	1409-98 / RA-2039/98	2	WP 50	FOLICUR EM WP 50	Italy
2	Lettuce, head	7	0.26	0.42	1410-98 / RA-2039/98	2	WP 50	FOLICUR EM WP 50	France
3	Lettuce, head	7	1.3	1.49	0033-99 / RA-2039/99	2	WP 50	FOLICUR EM WP 50	Italy
4	Lettuce, head	7	2.3	2.71	0034-99 / RA-2039/99	2	WP 50	FOLICUR EM WP 50	Portugal
5	Lettuce, head	7	2.9	3.52	0032-99 / RA-2039/99	2	WP 50	FOLICUR EM WP 50	France
6	Lettuce, head	7	4.6	5.33	0510-99 / RA-2039/99	2	WP 50	FOLICUR EM WP 50	Greece
7	Lettuce, head	7	8.5	10.44	0031-99 / RA-2039/99	2	WP 50	FOLICUR EM WP 50	Spain
8	Lettuce, head	6	9.7	11.64	0509-99 / RA-2039/99	2	WP 50	FOLICUR EM WP 50	Spain

[1] as given in the Tier 1 summaries

Results (Lettuce, head)

Method I (Weinmann/Nolting)	R	4.08
(all values)	s	4.446
	k	3.188
	Rmax=R+k*s	**18.25**
Method II (Wilkening)	R (0.75)	8.71
(75 % quantile)	**Rber=2*R(0.75)**	**17.42**

Summary of results:

Maximum residue values for a pre-harvest interval of: 7 days

Method I (all values)	18.25
Method II (75% quantile)	17.42

STMR: 0.21, 0.43, 1.49, 2.21, **(2.46)**, 2.71, 3.52, 10.44, 11.64

Table B.7.13-20 Revised MRL Calculations: Leeks (Northern Europe)

Table: Leek, northern Europe

Active substance :	tolylfluanid + DMST	Crop group :	Bulb vegetables
Portion analysed :	shoot	Commodity :	Leek
Target value :	MRL	PHI :	21 d

No.	Crop	Days after appli-cation	Residue value (mg/kg) tolylfluanid	Residue value (mg/kg) tolylfluanid + DMST	Study-No. [1]/ Report-No.	No. of applic.	FL-Type	Product	Country
1	Leek	22	0.17	0.25	0517-89 / 0517-89	5	WG 50	EUPAREN M WG 50	Netherlands
2	Leek	21	0.36	0.41	0132-00 / RA-2008/00	5	WG 50	EUPAREN M WG 50	Great Britain
3	Leek	27	0.34	0.45	0514-89 / 0514-89	5	WG 50	EUPAREN M WG 50	Netherlands
4	Leek	21	0.58	0.97	0441-97 / RA-2047/97	5	WG 50	EUPAREN M WG 50	Germany
5	Leek	21	0.92	1.07	0515-89 / 0515-89	5	WG 50	EUPAREN M WG 50	Netherlands
6	Leek	21	0.84	1.16	0241-97 / RA-2047/97	5	WG 50	EUPAREN M WG 50	Germany
7	Leek	21	0.94	1.52	0243-97 / RA-2047/97	5	WG 50	EUPAREN M WG 50	France
8	Leek	21	1.2	1.8	0442-97 / RA-2047/97	5	WG 50	EUPAREN M WG 50	Great Britain

[1] as given in the Tier 1 summaries

Results (Leek)

Method I (Weinmann/Nolting) (all values)	R	0.954
	s	0.553
	k	3.145
	Rmax=R+k*s	**2.692**
Method II (Wilkening) (75 % quantile)	R (0.75)	1.430
	Rber=2*R(0.75)	**2.860**

Summary of results:

Maximum residue values for a pre-harvest interval of: 21 days

Method I (all values)	2.69 mg/kg
Method II (75% quantile)	2.86 mg/kg

STMR: 0.25;0.41;0.45;0.97;**(1.02)**;1.07;1.16;1.52;1.8

Table B.7.13-21 Revised MRL Calculations: Hops (Northern Europe)

Table: Hops, northern Europe

Active substance :	tolylfluanid + DMST	Crop group :	Stimulant plants
Portion analysed :	cone, kiln-dried	Commodity :	Hop
Target value :	MRL	PHI :	13 d

No.	Crop	Days after appli-cation	Residue value (mg/kg) tolylfluanid	Residue value (mg/kg) tolylfluanid + DMST	Study-No. [1]/ Report-No.	No. of applic.	FL-Type	Product	Country
1	Hop	13	2.8	8.79	0167-96 / RA-2067/96	6	WG 50	EUPAREN M WG 50	Germany
2	Hop	14	7.8	13.47	0029-95 / RA-2102/95	6	WG 50	EUPAREN M WG 50	Germany
3	Hop	13	10	17.78	0570-96 / RA-2067/96	6	WG 50	EUPAREN M WG 50	Germany
4	Hop	13	5.4	19.33	0569-96 / RA-2067/96	6	WG 50	EUPAREN M WG 50	Germany
5	Hop	13	8.9	29.96	0568-96 / RA-2067/96	6	WG 50	EUPAREN M WG 50	Germany
6	Hop	14	9.1	31.78	0535-95 / RA-2102/95	6	WG 50	EUPAREN M WG 50	Germany
7	Hop	14	11	32.06	0613-95 / RA-2102/95	6	WG 50	EUPAREN M WG 50	Germany
8	Hop	14	27	70.74	0614-95 / RA-2102/95	6	WG 50	EUPAREN M WG 50	Germany

[1] as given in the Tier 1 summaries
value no. 8 is an outlier for t1

Results (Hop)

Method I (Weinmann/Nolting) (all values)	R	27.989
	s	19.350
	k	3.145
	Rmax=R+k*s	**88.838**
Method I (elimination of outliers)	R	21.881
	s	9.419
	k	3.355
	Rmax=R+k*s	**53.481**
Method II (Wilkening) (75 % quantile)	R (0.75)	31.990
	Rber=2*R(0.75)	**63.980**

Summary of results:

Maximum residue values for a pre-harvest interval of: 13 days

Method I (all values)	88.84 mg/kg
Method I (elimination of outliers)	53.48 mg/kg
Method II (75% quantile)	63.98 mg/kg

STMR: 8.79;13.47;17.78;19.33;**(24.65)**;29.96;31.78;32.06;70.74

B.7.16.1 Chronic exposure through diet

The calculations of a potential intake of tolylfluanid residues with food were conducted by using three models based on the European, the UK and the German diets. In a first step, the Theoretical Maximum Daily Intakes (TMDIs) were calculated on the basis of the revised MRLs (see Addensum 5, Point B.7.13) assuming that residue definition as a sum of tolylfluanid and DMST. As no residues are expected in animal products, these products were excluded from the dietary risk assessment. The results were then compared to the ADI value of 0.1 mg/kg bw/day proposed by the ECPO 10 Meeting.

In a second tier, a more refined risk assessment was made by calculating the International Estimated Daily Intakes (IEDIs) taking into account STMRs, residues in edible portions of the crops and processing effects. The STMR values represent the sum of tolylfluanid and DMST for all crops; for grapes two further metabolites were taken account. The STMR values were separately calculated for each data set and the highest one was selected for dietary risk assessment (see also the List of End Points 8.11.2004). The processing studies and processing factors are presented in the DAR, Point B.7.8.2.6.

A summary of TMDI and IEDI calculations of tolylfluanid residues (parent+DMST) are shown in Table B.7.16.1-1 These calculations indicate that it is unlikely that chronic intake of tolylfluadid residues would pose a risk to the consumer health. Detailed calculations are presented in the following pages.

The calculated TMDIs were 12-70 % of the ADI and the calculated IEDIs were 4-24 % of the ADI. It was concluded that it is unlikely that a chronic intake of residues of tolylfluanid and DMST from the use considered here to present a public health concern.

Table B.7.16-1a Summary of Theoretical Maximum Daily Intake (TMDI) calculations of tolylfluanid residues (tolylfluanid + DMST)

Guideline used	TMDI (mg/person/day)	TMDI (mg/kg bw/day)	% of ADI
WHO Guideline (1997, rev. 2003) European diet - 60 kg/bw	1.7049	0.0284	28.4
BBA Guideline Part IV 3 - 7 (1993) a) 4-6 year old female child - 13.5 kg/bw b) 36-50 year old woman - 60 kg bw	0.3958 0.7330	0.0293 0.0122	29.3 12.2
UK consumer exposure model (1999) a) adult - 70.1 kg bw b) school child - 43.6 kg bw c) toddler - 14.5 kg bw c) infant - 8.7 kg bw	1.4066 0.6557 1.0058 0.3173	0.0201 0.0150 0.0694 0.0365	20.1 15.0 69.4 36.5

Table B.7.16-1b Summary of International Estimated Daily Intake (IEDI) calculations of tolylfluanid residues (tolylfluanid and DMST for all supported crops, additionally 4-hydroxymethyl-DMST-glucoside and 2-hydroxyphenyl-DMST-glucoside for grapes expressed as tolylfluanid)

Guideline used	IEDI (mg/person/day)	IEDI (mg/kg bw/day)	% of ADI
WHO Guideline (1997, rev. 2003) European diet - 60 kg bw	0.7156	0.0119	11.9
BBA Guideline Part IV 3 - 7 (1993) a) 4-6 year old female child - 13.5 kg/bw b) 36-50 year old woman - 60 kg bw	 0.1211 0.3000	 0.0090 0.0050	 9.0 5.0
UK consumer exposure model (1999) a) adult - 70.1 kg bw b) school child - 43.6 kg bw c) toddler - 14.5 kg bw c) infant - 8.7 kg bw	 0.3137 0.1661 0.3474 0.0962	 0.0045 0.0038 0.0240 0.0111	 4.5 3.8 24.0 11.1

a) WHO Guidelines

When following the "Guidelines for predicting dietary intake of pesticide residues, revised" (WHO, 1997), the mean consumption figures relevant to the European diet were used (GEMS/FOOD Regional Diets; FAO/WHO, revised 2003). The average adult weight of 60 kg. Calculations are shown in Tables B.7.16-2 and B.7.16-3.

Table B.7.16-2 Calculation of the Theoretical Maximum Daily Intake (TMDI) of tolylfluanid (tolylfluanid + DMST) according to WHO Guideline (revised, 1997)

ADI: 0.1 mg/kg bw/day
Food consumption levels: European diet (FAO/WHO, rev. September 2003)
Body weight (bw): 60 kg

Commodity	MRL proposals (mg/kg)	Food consumption (g/person/day)	TMDI		% of ADI
			(mg/person/day)	(mg/kg bw/day)	
Pome fruit	3	51.3	0.153900	0.002565	2.6
Table grapes & Raisins	5	16.1	0.080500	0.001342	1.3
Wine*	5	97.8	0.48900	0.00815	8.2
Strawberries	3	5.3	0.015900	0.000265	0.3
Blackberries	5	0	-	-	-
Dewberries	5	0	-	-	-
Raspberries	5	0.5	0.002500	0.000042	0.0
Other small fruit and berries	3	23.5	0.070500	0.001175	1.2
Tomato	2	66.6	0.133200	0.002220	2.2
Eggplants	2	2.3	0.004600	0.000077	0.1
Peppers	2	10.4	0.020800	0.000347	0.4
Cucumbers, gherkins	2	9.0	0.018000	0.000300	0.3
Summer squash	2	3.5	0.007	0.000116	0.1
Melons (except watermelon)	0.3	18.3	0.005490	0.000092	0.1
Lettuce	20	22.5	0.45000	0.007500	7.5
Leeks	3	2.0	0.006000	0.000100	0.1
Hops	50	4.9[a)]	0.245000	0.004083	4.1
Water	0.0001	2000	0.000000	0.000000	0.0
Total			**1.7049**	**0.0284**	**28.4**

a) value taken from German food consumption data (BBA Guideline Part IV, 3 - 7; 1993)

* No MRL is proposed for wine.

Table B.7. 16-3 Calculation of the International Estimated Daily Intake (IEDI) of tolylfluanid (tolylfluanid + DMST) according to WHO Guideline (revised, 1997)

ADI: 0.1 mg/kg bw/day
Food consumption levels: European diet (FAO/WHO, rev. September 2003)
Body weight (bw): 60 kg

Commodity	STMR/ STMR-P (mg/kg)	Food consumption (g/person/day)	TMDI (mg/person/day)	TMDI (mg/kg bw/day)	% of ADI
Pome fruit	0.86	51.3	0.04412	0.00074	0.7
Table grapes	2.36	13.8	0.03257	0.00054	0.5
Raisins*	7.8	2.3	0.01791	0.00030	0.3
Wine**	3.07	97.8	0.30025	0.00500	5.0
Strawberries	1.1	5.3	0.00583	0.00010	0.1
Blackberries	1.96	0	-	-	-
Dewberries	1.96	0	-	-	-
Raspberries	1.96	0.5	0.00098	0.00002	0.0
Other small fruit and berries	0.79	23.5	0.01857	0.00031	0.3
Tomato	1.06	66.6	0.07060	0.00118	1.2
Tomato juice***	0.42	4	0.00170	0.00003	0.0
Tomato paste ****	2.33	4	0.00933	0.00016	0.2
Eggplants	1.06	2.3	0.00244	0.00004	0.0
Peppers	0.67	10.4	0.00697	0.00012	0.1
Cucumber, gherkin	0.37	9	0.00333	0.00006	0.1
Summer squash	0.37	3.5	0.00130	0.00130	0.0
Melons	0.05	18.3	0.00092	0.00002	0.0
Lettuce	3.31	22.5	0.07448	0.00124	1.2
Leeks	1.02	2	0.00204	0.00003	0.0
Hops	24.65	4.9	0.12079	0.00201	2.0
Water	0.00001	2000	0.00002	0.00000	0.0
Total			**0.7156**	**0.0119**	**11.9**

[a)] value taken from German food consumption data (BBA Guideline Part IV, 3 - 7; 1993)
* Mean transfer factor 3.3 (raisin)
* * Mean transfer factor 1.3 (wine)

b) BBA Guidelines

The German food consumption data were taken from BBA Guideline part IV, 3-7 (1993). The German data gave average consumption figures for a 4-6 year old female child with a body weight of 13.5 kg. The uptake of tolylfluanid residues with food commodities usually not consumed by a child, i.e. wine (represented by wine grapes) and beer (represented by hops) was estimated for a 36-50 year old woman with a body weight of 60 kg. Calculations are shown in the following Tables:

Table B.7.16-4. Calculation of the Theoretical Maximum Daily Intake (TMDI) of tolylfluanid residues (parent + DMST) according to BBA Guideline Part IV, 3 - 7 (1993)

ADI: 0.1 mg/kg bw/day
Food consumption levels: German diet
Body weight (bw): 13.5 kg / 4 - 6 year old female child

modity	MRL proposals (mg/kg)	Food consumption (g/person/day)	TMDI		% of ADI
			(mg/person/day)	(mg/kg bw/day)	
Pome fruit	3	48.6	0.14580	0.010800	10.8
Grapes	5	8.7	0.04350	0.003222	3.2
Strawberries	3	4.8	0.01440	0.001067	1.1
Cane fruit	5	0.8	0.00400	0.000296	0.3
Other small fruit and berries	3	3.2	0.00960	0.000711	0.7
Tomatoes and eggplants	2	15.8	0.03160	0.002341	2.3
Peppers	2	2.0	0.00400	0.000296	0.3
Cucumbers and courgettes	2	11.9	0.02380	0.001763	1.8
Melons	0.3	0.5	0.00015	0.000011	0.0
Lettuce and similar	20	4.6	0.09200	0.00681	6.8
Leeks	3	2.5	0.00750	0.000556	0.6
Other plant commodities	0.05*	388.6	0.01943	0.001439	1.4
Total			**0.3958**	**0.0293**	**29.3**

* represents the limit of quantification (LOQ)

Table B.7.16-5 Calculation of the International Estimated Daily Intake (IEDI) of tolylfluanid residues (parent + DMST) according to BBA Guideline Part IV, 3 - 7 (1993)

ADI: 0.1 mg/kg bw/day
Food consumption levels: German diet
Body weight (bw): 13.5 kg / 4 - 6 year old female child

Commodity	STMR/ STMR-P (mg/kg)	Food consumption (g/person/day)	TMDI (mg/person/day)	TMDI (mg/kg bw/day)	% of ADI
Pome fruit	0.86	13	0.01118	0.00083	0.8
Pome fruit, processed*	0.34	35.6	0.01210	0.00090	0.9
Grapes	2.36	6.1	0.01440	0.00107	1.1
Grapes, processed**	7.8	2.6	0.02028	0.00150	1.5
Strawberries	1.1	1.6	0.00176	0.00013	0.1
Strawberries, processed***	0.22	3.2	0.00070	0.00005	0.1
Cane fruit	1.96	0.8	0.00157	0.00012	0.1
Other small fruit and berries	0.79	0.8	0.00063	0.00005	0.0
Other small fruit and berries, processed****	0.474	2.4	0.00114	0.00008	0.1
Tomatoes and eggplants	1.06	8.5	0.00901	0.00067	0.7
Tomatoes and eggplants, processed*****	2.33	7.3	0.01701	0.00126	1.3
Peppers	0.67	2	0.00134	0.00010	0.1
Cucumbers and courgettes	0.37	11.9	0.00440	0.00033	0.3
Melons	0.05	0.5	0.00003	0.00000	0.0
Lettuce and similar	3.31	4.6	0.01523	0.00113	1.1
Leeks	1.02	2.5	0.00255	0.00019	0.2
Other plant commodities	0.02	388.6	0.00777	0.00058	0.6
Total			**0.1211**	**0.009**	**9.0**

* Mean transfer factor 0.4 (sauce)
** Mean transfer factor 3.3 (raisin)
***Mean transfer factor 0.2 (jam)
**** Mean transfer factor 0.6 (juice)
***** Mean transfer factor 2.2 (paste)

Table B.7.16-6. Calculation of the Theoretical Maximum Daily Intake (TMDI) of tolylfluanid residues (parent + DMST) according to BBA Guideline Part IV, 3 - 7 (1993)

ADI: 0.1 mg/kg bw/day
Food consumption levels: German diet
Body weight (bw): 60 kg / 36 -50 year old woman

Commodity	MRL proposals (mg/kg)	Food consumption (g/person/day)	TMDI (mg/person/day)	TMDI (mg/kg bw/day)	% of ADI
Wine grapes [a)]	5	97.6	0.4880	0.008133	8.1
Hops [b)]	50	4.9	0.2450	0.004083	4.1
Total			**0.7330**	**0.0122**	**12.2**

[a)] representing wine, [b)] representing beer

Table B.7.16-7 Calculation of the International Estimated Daily Intake (IEDI) of tolylfluanid residues (parent + DMST) according to BBA Guideline Part IV, 3 - 7 (1993)

ADI: 0.1 mg/kg bw/day
Food consumption levels: German diet
Body weight (bw): 60 kg / 36 -50 year old woman

Commodity	STMR-P proposals (mg/kg)	Food consumption (g/person/day)	TMDI (mg/person/day)	TMDI (mg/kg bw/day)	% of ADI
Wine grapes [a)] *	3.07	97.6	0.29944	0.004991	5.0
Hops [b)] *	0.12	4.9	0.00060	0.000010	0.0
Total			**0.3000**	**0.005**	**5.0**

[a)] representing wine, [b)] representing beer

* Mean transfer factor 1.3 (wine)

** Mean transfer factor 0.005 (beer)

a) PSD Guidelines

The UK model (The UK Pesticide Safety Directorate Consumer Exposure Model, Version 4, 1999) provided mean and high level food consumption data adults (16-64+ years), school children (10-11 and 14-15 years), toddlers (1 ½-4 ½ years) and infants (6-12 months). The average body weights were 70.1 kg, 43.6 kg, 14.5 and 8.7 kg, respectively. The total TMDI and the total NEDI were calculated using two highest 97.5th percentile intakes plus the mean population intakes from the remaining relevant foods.

Table B.7.16-8. Calculation of the Theoretical Maximum Daily Intake ulation of the Theoretical Maximum Daily Intake (TMDI) of tolylfluanid residues according to PSD Guideline (1999)

ADI: 0.1 mg/kg bw/day
Food consumption levels: UK diet (intake of lettuce and pome fruit 97.5th %ile, intake of all other food: mean)
Body weight (bw): 70.1 kg – adult

Commodity	MRL proposals (mg/kg)	Food consumption (kg/person/day)	TMDI		% of ADI
			(mg/person/day)	(mg/kg bw/day)	
Pome fruit	3	0.1703	0.51090	0.00729	7.3
Grapes, table	5	0.0016	0.00800	0.000114	0.1
Grapes, wine	5	0.0007	0.00350	0.000050	0.0
Strawberries	3	0.0025	0.00750	0.000107	0.1
Blackberries	5	L/C	-	-	-
Loganberries	5	L/C	-	-	-
Raspberries	5	0.0007	0.00350	0.000050	0.1
Currants, white	3	L/C	-	-	-
Currants, black	3	0.0006	0.00180	0.000026	0.0
Currants, red	3	L/C	-	-	-
Gooseberries	3	L/C	-	-	-
Tomatoes	2	0.0228	0.04560	0.000650	0.7
Peppers	2	0.0008	0.00160	0.000023	0.0
Eggplants	2	L/C	-	-	-
Cucumbers	2	0.004	0.00800	0.000114	0.1
Courgettes	2	0.0007	0.00140	0.000020	0.0
Melons	0.3	0.0022	0.00066	0.000009	0.0
Lettuce	20	0.0391	0.78200	0.01116	11.2
Leeks	3	0.0007	0.00210	0.000030	0.0
Hops	50	0.0006	0.03000	0.000428	0.4
Total			**1.4066**	**0.0201**	**20.1**

L/C = low % consuming

Table B.7. 16-9 Calculation of the International Estimated Daily Intake (IEDI) of tolylfluanid residues according to PSD Guideline (1999)

ADI: 0.1 mg/kg bw/day
Food consumption levels: UK diet (intake of lettuce and pome fruit: 97.5th %ile, intake of all other food: mean)
Body weight (bw): 70.1 kg – adult

Commodity	STMR/ STMR-P (mg/kg)	Food consumption (kg/person/day)	TMDI (mg/person/day)	TMDI (mg/kg bw/day)	% of ADI
Pome fruit	0.86	0.1703	0.146458	0.002089	2.1
Grapes table	2.36	0.002	0.00472	0.000067	0.1
Grapes wine*	3.07	0.0007	0.00215	0.00003	1.8
Strawberries	1.1	0.0025	0.00275	0.000039	0.0
Blackberries	1.96	L/C	-	-	-
Loganberries	1.96	L/C	-	-	-
Raspberries	1.96	0.0007	0.001372	0.000020	0.0
Currants, white	0.79	L/C	-	-	-
Currants, black	0.79	0.0006	0.000474	0.000007	0.0
Currants, red	0.79	L/C	-	-	-
Gooseberries	0.79	L/C	-	-	-
Tomatoes	1.06	0.0228	0.024168	0.000345	0.3
Peppers	0.67	0.0008	0.000536	0.000008	0.0
Eggplants	1.06	L/C	-	-	-
Cucumbers	0.37	0.004	0.00148	0.000021	0.0
Courgettes	0.37	0.0007	0.000259	0.000004	0.0
Melons	0.05	0.0022	0.000110	0.000002	0.0
Lettuce	3.31	0.0057	0.018867	0.000269	0.3
Leeks	1.02	0.0007	0.000714	0.000010	0.0
Hops**	0.12	0.0006	0.000072	0.000001	0.0
Total			**0.3137**	**0.0045**	**4.5**

L/C = Low % consuming
*Mean transfer factor 1.3 (wine)
**Mean transfer factor 0.005 (beer)

Table B.7.16-10 Calculation of the Theoretical Maximum Daily Intake (TMDI) of tolylfluanid residues according to PSD Guideline (1999)

ADI: 0.1 mg/kg bw/day
Food consumption levels: UK diet
(intake of pome fruit and lettuce 97.5th %ile, intake of all other food: mean)
Body weight (bw): 43.6 kg - school child

Commodity	MRL proposals (mg/kg)	Food consumption (kg/person/day)	TMDI		% of ADI
			(mg/person/day)	(mg/kg bw/day)	
Pome fruit	3	0.1357	0.40710	0.009337	9.3
Grapes, table	5	0.0003	0.00150	0.00003	0.0
Grapes, wine	5	L/C	-	-	-
Strawberries	3	0.0008	0.00240	0.000055	0.1
Blackberries	5	0.0001	0.00050	0.000011	0.0
Loganberries	5	L/C	-	-	-
Raspberries	5	0.0002	0.00100	0.000023	0.0
Currants, white	3	L/C	-	-	-
Currants, black	3	0.0006	0.00180	0.000041	0.0
Currants, red	3	L/C	-	-	-
Gooseberries	3	L/C	-	-	-
Tomatoes	2	0.0086	0.01720	0.000394	0.4
Peppers	2	0.0001	0.00020	0.000005	0.0
Eggplants	2	L/C	-	-	-
Cucumbers	2	0.001	0.00200	0.000046	0.0
Courgettes	2	N/C	-	-	-
Melons	0.3	L/C	-	-	-
Lettuce	20	0.0111	0.22200	0.005090	5.1
Leeks	3	L/C	-	-	-
Hops	50	L/C	-	-	-
Total			**0.6557**	**0.0150**	**15.0**

L/C = low % consuming

Table B.7.16-11 Calculation of the International Estimated Daily Intake (IEDI) of tolylfluanid residues according to PSD Guideline (1999)

ADI: 0.1 mg/kg bw/day
Food consumption levels: UK diet
(intake of pome fruit and lettuce 97.5th %ile, intake of all other food: mean)
Body weight (bw): 43.6 kg - school child

Commodity	STMR/ STMR-P (mg/kg)	Food consumption (kg/person/day)	IEDI (mg/person/day)	IEDI (mg/kg bw/day)	% of ADI
Pome fruit	0.86	0.1357	0.116702	0.002677	2.7
Grapes table	2.36	0.0003	0.000708	0.00002	0.0
Grapes wine*	3.07	L/C	-	-	-
Strawberries	1.1	0.0008	0.00088	0.000020	0.0
Blackberries	1.96	0.0001	0.000196	0.000004	0.0
Loganberries	1.96	L/C	-	-	-
Raspberries	1.96	0.0002	0.000392	0.000009	0.0
Currants, white	0.79	L/C	-	-	-
Currants, black	0.79	0.0006	0.000474	0.000011	0.0
Currants, red	0.79	L/C	-	-	-
Gooseberries	0.79	L/C	-	-	-
Tomatoes	1.06	0.0086	0.009116	0.000209	0.2
Peppers	0.67	0.0001	0.000067	0.000002	0.0
Eggplants	1.06	N/C	-	-	-
Cucumbers	0.37	0.001	0.00037	0.000008	0.0
Courgettes	0.37	N/C	-	-	-
Melons	0.05	L/C	-	-	-
Lettuce	3.31	0.0111	0.036741	0.00840	0.8
Leeks	1.02	L/C	-	-	-
Hops	0.12	L/C	-	-	-
Total			**0.1661**	**0.0038**	**3.8**

L/C = low % consuming, N/C = no consumers in survey
* Mean transfer factor 1.3

Table B.7.16-12 Calculation of the Theoretical Maximum Daily Intake (TMDI) of tolylfluanid residues according to PSD Guideline (1999)

ADI: 0.1 mg/kg bw/day
Food consumption levels: UK diet (intake of pome fruit and table grapes: 97.5th %ile, intake of all other food: mean)
Body weight (bw): 14.5 kg – toddler

Commodity	MRL proposals (mg/kg)	Food consumption (kg/person/day)	TMDI (mg/person/day)	TMDI (mg/kg bw/day)	% of ADI
Pome fruit	3	0.2232	0.669600	0.0461793	46.2
Grapes, table	5	0.0593	0.296500	0.020448	20.4
Grapes, wine	5	L/C	-	-	-
Strawberries	3	0.0022	0.006600	0.000455	0.5
Blackberries	5	L/C	-	-	-
Loganberries	5	L/C	-	-	-
Raspberries	5	0.0015	0.007500	0.000517	0.5
Currants, white	3	N/C	-	-	
Currants, black	3	0.0012	0.003600	0.000248	0.2
Currants, red	3	L/C	-	-	-
Gooseberries	3	L/C	-	-	-
Tomatoes	2	0.0061	0.012200	0.000841	0.8
Peppers	2	0.0004	0.000800	0.000055	0.1
Eggplants	2	L/C	-	-	-
Cucumbers	2	0.0015	0.003000	0.000207	0.2
Courgettes	2	L/C	-	-	-
Melons	0.3	L/C	-	-	-
Lettuce	20	0.0003	0.00600	0.000414	0.4
Leeks	3	L/C	-	-	-
Hops	50	L/C	-	-	-
Total			**1.0058**	**0.0694**	**69.4**

L/C = low % consuming, N/C = no consumers in survey

Table B.7.16-13 Calculation of the International Estimated Daily Intake (IEDI) of tolylfluanid residues according to PSD Guideline (1999)

ADI: 0.1 mg/kg bw/day
Food consumption levels: UK diet (intake of pome fruit and table grapes: 97.5th %ile, intake of all other food: mean)
Body weight (bw): 14.5 kg – toddler

Commodity	STMR/ STMR-P (mg/kg)	Food consumption (kg/person/day)	TMDI (mg/person/day)	TMDI (mg/kg bw/day)	% of ADI
Pome fruit	0.86	0.2232	0.191952	0.0132	13.2
Grapes table	2.36	0.0593	0.139948	0.0097	9.7
Grapes wine*	3.07	L/C	-	-	-
Strawberries	1.1	0.0022	0.00242	0.0002	0.2
Blackberries	1.96	L/C	-	-	-
Loganberries	1.96	L/C	-	-	-
Raspberries	1.96	0.0015	0.00294	0.0002	0.2
Currants, white	0.79	N/C	-	-	-
Currants, black	0.79	0.0012	0.000948	0.0001	0.1
Currants, red	0.79	L/C	-	-	-
Gooseberries	0.79	L/C	-	-	-
Tomatoes	1.06	0.0061	0.006466	0.00045	0.4
Peppers	0.67	0.0004	0.000268	0.00002	0.0
Eggplants	1.06	L/C			-
Cucumbers	0.37	0.0015	0.000555	0.00004	-
Courgettes	0.37	L/C	-	-	-
Melons	0.05	L/C	-	-	-
Lettuce	3.31	0.0003	0.000993	0.00007	0.1
Leeks	1.02	L/C	-	-	-
Hops	0.12	L/C	-	-	-
Total			**0.3474**	**0.0240**	**24.0**

L/C = low % consuming, N/C = no consumers in survey
* Mean transfer factor 1.3

Table B.7.16-14 Calculation of the Theoretical Maximum Daily Intake (TMDI) of tolylfluanid residues according to PSD Guideline (1999)

ADI: 0.1 mg/kg bw/day
Food consumption levels: UK diet
(intake of pome fruit and strawberries: 97.5th %ile, intake of all other food: mean)
Body weight (bw): 8.7 kg - infant

Commodity	MRL proposals (mg/kg)	Food consumption (kg/person/day)	TMDI		% of ADI
			(mg/person/day)	(mg/kg bw/day)	
Pome fruit	3	0.0874	0.262200	0.030138	30.1
Grapes, table	5	L/C	-	-	-
Grapes, wine	5	N/C	-	-	-
Strawberries	3	0.0167	0.050100	0.005759	5.8
Blackberries	5	L/C	-	-	-
Loganberries	5	N/C	-	-	-
Raspberries	5	L/C	-	-	-
Currants, white	3	N/C	-	-	-
Currants, black	3	0.0008	0.002400	0.000276	0.3
Currants, red	3	N/C	-	-	-
Gooseberries	3	N/C	-	-	-
Tomatoes	2	0.0013	0.002600	0.000299	0.3
Peppers	2	N/C	-	-	-
Eggplants	2	N/C	-	-	-
Cucumbers	2	L/C	-	-	-
Courgettes	2	L/C	-	-	-
Melons	0.3	L/C	-	-	-
Lettuce	20	L/C	-	-	-
Leeks	3	N/C	-	-	-
Hops	50	N/C	-	-	-
Total			**0.3173**	**0.0365**	**36.5**

L/C = low % consuming, N/C = no consumers in survey

Table B.7.16-15 Calculation of the International Estimated Daily Intake (IEDI) of tolylfluanid residues according to PSD Guideline (1999)

ADI: 0.1 mg/kg bw/day
Food consumption levels: UK diet
(intake of pome fruit and strawberries: 97.5th %ile, intake of all other food: mean)
Body weight (bw): 8.7 kg - infant

Commodity	STMR/ STMR-P proposals (mg/kg)	Food consumption (kg/person/day)	TMDI (mg/person/day)	TMDI (mg/kg bw/day)	% of ADI
Pome fruit	0.86	0.0874	0.075164	0.008640	8.6
Grapes table	2.36	L/C	-	-	-
Grapes wine*	3.07	N/C	-	-	-
Strawberries	1.1	0.0167	0.01837	0.002111	2.1
Blackberries	1.96	L/C	-	-	-
Loganberries	1.96	N/C	-	-	-
Raspberries	1.96	L/C	-	-	-
Currants, white	0.79	N/C	-	-	-
Currants, black	0.79	0.0008	0.000632	0.00007	0.2
Currants, red	0.79	N/C	-	-	-
Gooseberries	0.79	N/C	-	-	-
Tomatoes	1.06	0.0013	0.001378	0.00016	0.2
Peppers	0.67	N/C	-	-	-
Eggplants	1.06	N/C	-	-	-
Cucumbers	0.37	L/C	-	-	-
Courgettes	0.37	L/C	-	-	-
Melons	0.05	L/C	-	-	-
Lettuce	3.31	L/C	-	-	-
Leeks	1.02	N/C	-	-	-
Hops	0.12	N/C	-	-	-
Total			**0.0962**	**0.0111**	**11.1**

L/C = low % consuming. N/C = no consumers in survey
* Mean transfer factor 1.3 (wine)

B.7.16.2 Acute exposure through diet

The acute dietary risk assessment of tolylfluanid residues (tolylfluanid + DMST) were conducted by calculation of the International Estimated Short-Term Intake (IESTI) and the National Estimated Short-Term Intake (NESTI). The evaluation was based upon the ARfD-value of 0.25 mg/kg bw/day proposed by the ECPO 10 Meeting. The IESTI and NESTI calculations are discussed detailed in the following pages:

IESTI

The IESTI calculation is based on the deterministic model of the JMPR (revised, 2000). IESTI requires single day food consumption data at the 97.5th percentile, for recorded eaters only. for each sub-group together with a typical unit weight for each commodity and the highest residue (HR) level detected in residue trials conducted according to the critical GAP. Where possible, the IESTI is based on the residue level in the edible portion rather than the whole commodity.

International diets for the IESTI have been developed by the WHO on the basis of food consumption data and related information provided the Australian, Netherlands, French, Japanese, South African, the UK and the USA governments. The highest 97.5th percentile consumption taken from the data provided is used for the IESTI calculation. Other data are also required for IESTI calculations, including body weights of the general population and children provided by Australia, France, the Netherlands, South Africa, the United Kingdom and the USA. Data on unit weight and per cent edible portion have been provided by France, Japan (unit weight only), Sweden, the United Kingdom, and the USA.

Depending on the data on consumption, the IESTI for each commodity is calculated differently. Pesticide analyses are generally performed in composite samples, i.e., samples consisting more than one unit. Distribution of the pesticide within composite samples may not be evenly distribution. Variability factor,ν, describes the ratio of a high level residue in the individual commodity unit to the composite residue level. Due to a lack of empirical variability factors, default factors have been proposed. The variability factor depends on, e.g., the commodity characteristics and the nature of application of a plant protection product. In cases where unit weight of the commodity is less ≤ 25 g, consumption of meal-sized portion reflects the consumption of many units of the commodity (e.g. berries). No variability factor is needed as the residue levels in the composite samples reflect the residue level in the meal-sized portion of the commodity. Consequently, the following equation ("case 1") was used for IESTI calculations for tolylfluanid on berries:

IESTI = LP * (HR or HR-P)/bw

where:

LP Highest large portion provided (97.5th percentile of eaters), in kg food/day
HR Highest residue in composite sample of edible portion found in data from supervised residue trials from which the MRL or STMR was derivered, in mg/kg
HR-P Highest residue in a processed sample, in mg/kg, calculated by multiplying the HR in the processed commodity
bw Body weight in kg, provided by the country where from which the LP was reported

For some commodities such a single piece of fruit or vegetables, there might be a high variability of residue levels between the individual units within composite samples. Consequently, the following equation ("case 2a") and default variability factors were used for IESTI calculations for tolylfluanid on medium size commodities (unit weight s between 25-250 g. e.g. apple) and larger size commodities (unit weights > 250 g. e.g. melon).

$$IESTI = \frac{\{U * HR \text{ or } HR\text{-}P * \nu\} + (LP\text{-}U) * (HR \text{ or } HR\text{-}P)}{bw}$$

where:

U Unit weight of the edible portion, in kg, provided by the country where the trials, which gave the highest portion, was carried out
ν Variability factor
HR Highest residue in composite sample of edible portion found in data from supervised residue trials from which the MRL or STMR was derivered, in mg/kg
HR-P Highest residue in a processed sample, in mg/kg, calculated by multiplying the HR in the processed commodity
bw Body weight in kg, provided by the country where from which the LP was reported

In cases, where the unit weight of the whole portion is higher than that of the large portion the following equation were used (Case 2 b):

$$IESTI = \frac{LP*(HR \text{ or } HR\text{-}P)*}{bw} \nu$$

Where:

ν Variability factor
HR Highest residue in composite sample of edible portion found in data from supervised residue trials from which the MRL or STMR was derivered, in mg/kg
HR-P Highest residue in a processed sample, in mg/kg, calculated by multiplying the HR in the processed commodity
bw Body weight in kg, provided by the country where from which the LP was reported

In cases, where a processed commodity is bulked or blended, the STMR-P value represents the probable highest concentration of residues. Consequently, the following equation ("Case 3") was applied for IESTI calculations for tolylfluanid on wine:

$$IESTI = \frac{LP*STMR\text{-}P}{bw}$$

Where:

LP Highest large portion provided (97.5th percentile of eaters), in kg food/day
STMR-P Supervised trials median residue in processed commodity, in mg/kg
bw Body weight in kg, provided by the country where from which the LP was reported

A summary of the IESTI calculations for tolylfluanid (tolylfluanid + DMST) are given in Table B.7.16-16 and B.7.16-17.

The IESTI varied from 2 to 46 % of the ARfD for the general population and from 0 to 102 % of the ARfD for children. The short-term intake from grapes slightly exceeded the ARfD for children. However, the IESTI calculation was based on very conservative assumptions as high residue and high consumption figures were used. It is very likely that that the real intake also from grapes would be in acceptable levels.

Table B.7.16-16 International Estimated Short-term Intake (IESTI) calculation for tolylfluanid

IESTI – Tolylfluanid (Tolylfluanid + DMST)										
Guidelines used :JMPR (2000)										
General population										
Commodity	**HR or HR-P (mg/kg)**	**Large portion diet** **Country**	**Body weight (kg)**	**Large portion (kg)**	**Unit weight of edible portion (kg)/ Whole portion (kg)**	**Country**	**v**	**Case**	**IESTI (mg/kg bw/day)**	**% of the ARfD[1]**
Apple	2.45	USA	65	1.348	0.127/ 0.138	USA	7	2a	0.0795	31.8
Cucumber	0.96	Netherlands	63	0.3131	0.360/ 0.400	France	5	2b	0.0239	9.5
Currants, red, black and white	1.83	France	62.3	0.1533			1	1	0.0149	1.8
Eggplant	1.96	Australia	67	0.4871	0.444/ 0.548	USA	5	2b	0.0712	28.5
Grapes (excluding wine)	4.61	Australia	67	0.5152	0.118/ 0.125	France	7	2a	0.0840	33.6
Leek	1.8	France	62.3	0.3738	0.050/ 0.100	France	7	2a	0.0195	7.8
Lettuce, head	11.64	USA	65	0.2125	0.512/ 0.539	USA	3	2b	0.1342	45.7
Melon, except watermelon	0.08	USA	65	0.702	0.630/ 1.0	USA	5	2b	0.0039	1.6
Hops, dry	70.74	USA	65	0.006			1	1	0.0064	2.5
Raisins*	15.21	France	62.3	0.1351			1	1	0.0330	13.2
Raspberry, red, black	2.87	France	62.3	0.3239			1	1	0.0149	6.0
Pear	2.45	USA	65	0.6929	0.151/ 0.166	USA	7	2a	0.0603	24.1
Pepper, sweet	1.64	France	62.3	0.2075	0.160/ 0.172	UK	7	2a	0.0307	12.3
Strawberry	2.71	France	62.3	0.3457			1	1	0.0150	6.0
Summer squash	0.96	France	62.3	0.3426	0.270/ 0.300	France	5	2a	0.0022	8.8
Tomato	1.96	USA	65	0.3906	0.123/ 0.123	USA	7	2a	0.0340	13.6
Watermelon	0.08	USA	65	1.939	2.078/ 4.518	USA	5	2b	0.0119	4.8
Wine only**	3.07	Australia	67	1.1310				3	0.0518	20.7

[1] = 0.25 mg/kg

* mean transfer factor (sum of tolylfluanid +relevant metabolites) = 3.3 (raisin)

** STMR-P was used instead of HR-P (residue level of 2.36 mg/kg for tolylfluanid + relevant metabolites), mean transfer factor (sum of tolylfluanid + DMST) = 1.3 (wine)

Table B.7.16-17 International Estimated Short-term Intake (IESTI) calculation for tolylfluanid

IESTI – Tolylfluanid (Tolylfluanid + DMST)										
Guidelines used :JMPR (2000)										
Children										
Commodity	**HR or HR-P (mg/kg)**	**Large portion diet** **Country**	**Body weight (kg)**	**Large portion (kg)**	**Unit weight of edible portion (kg)/ Whole portion (kg)**	**Country**	**v**	**Case**	**IESTI (mg/kg bw/day)**	**% of the ARfD**
Apple	2.45	USA	15	0.6788	0.127/ 0.138	USA	7	2a	0.2353	94.1
Cucumber	0.96	Netherlands	17	0.1620	0.360/ 0.400	France	5	2b	0.0457	18.3
Currants, red, black and white	1.83	Australia	19	0.5843			1	1	0.0563	22.5
Eggplant	1.96	Japan	15.9	0.2193	-/ 0.080	Japan	7	2a	0.0862	34.5
Grapes (excluding wine)	4.61	Australia	19	0.3420	0.118/ 0.125	France	7	2a	0.2548	101.9
Leek	1.8	France	17.8	0.1214	0.050/ 0.100	France	7	2a	0.0426	17.0
Lettuce, head	11.64	Netherlands	17	0.0836	0.558/ 0.754	UK	3	2b	0.1718	68.7
Melon, except watermelon	0.08	Australia	19	0.4131	0.630/ 1.0	USA	5	2b	0.0087	3.5
Hops, dry	70.74	Japan	15.9	0.0005			1	1	0.0021	71.6
Pear	2.45	UK	14.5	0.2790	0.170/ 0.187	UK	7	2a	0.2195	87.8
Pepper, sweet	1.64	Australia	19	0.0600	0.160/ 0.172	UK	1	2b	0.0363	14.5
Raisins*	15.21	USA	15	0.0593			1	1	0.0601	24.0
Raspberry, red, black	2.87	France	17.8	0.0762			1	1	0.0123	4.9
Strawberry	2.71	Australia	19	0.1763			1	1	0.0251	10.1
Summer squash	0.96	Australia	19	0.2189	0.270/ 0.300	France	5	2b	0.0553	22.1
Tomato	1.96	USA	15	0.1590	0.123/ 0.123	USA	7	2a	0.1172	46.9
Watermelon	0.08	Australia	19	1.4727	2.078/ 4.518	USA	5	2b	0.0310	12.4
Wine only**	3.07	Australia	19	0.0040			1	3	0.0006	0.3

[1] = 0.25 mg/kg

* mean transfer factor (sum of tolylfluanid +relevant metabolites) = 3.3 (raisin)

** STMR-P was used instead of HR-P (residue level of 2.36 mg/kg for tolylfluanid + relevant metabolites), mean transfer factor (sum of tolylfluanid + DMST) = 1.3 (wine)

NESTI

A short-term dietary risk assessment of tolylfluanid residues was performed at national level by calculation the NESTI according to the PSD model (PSD's Data Requirement Handbook, 2001). The UK food consumption database provided information at 97.5th percentile on adults (16-64 years) and toddlers (1½-4½ years) over period of one whole day.

The following equation ("case 1") was used for NESTI calculations for tolylfluanid in cases where the commodity is well mixed during processing (e.g. juice) or where the consumption of normal portion size reflects the consumption of many units of the commodity (e.g. berries).

$$\text{NESTI} = \frac{(F * \text{HR or HR-P})}{\text{mean body weight}}$$

where:

F	Full portion consumption data for the commodity unit
HR-P	Highest residue level detected incorporating processing or edible portion factors

There might be a high variability of the residue levels between one individual units within composite samples and consequently. The following equation and default variability factors ("case 2") were used for NESTI calculations for tolylfluanid on medium size commodities (unit weights between 25-250 g, e.g. apple) and larger size commodities (unit weights > 250 g, e.g. melon):

$$\text{NESTI} = \frac{\{U * \text{HR or HR-P} * \nu\} + (F-U) * (\text{HR or HR-P})}{bw}$$

where:

F	Full portion consumption data for the commodity unit
U	Unit weight of the edible portion, in kg, provided by the country where the trials, which gave the highest portion, was carried out
ν	Variability factor
HR	Highest residue in composite sample of edible portion found in data from supervised residue trials from which the MRL or STMR was derivered, in mg/kg
HR-P	Highest residue in a processed sample, in mg/kg, calculated by multiplying the HR in the processed commodity
bw	Body weight in kg, provided by the country where from which the LP was reported

In cases, where the unit weight of the whole portion is higher than that of the large portion the following equation were used (Case 2 b):

$$\text{NESTI} = \frac{F*(\text{HR or HR-P})* \nu}{bw}$$

Where:

F	Full portion consumption data for the commodity unit
ν	Variability factor
HR	Highest residue in composite sample of edible portion found in data from supervised residue trials from which the MRL or STMR was derivered, in mg/kg
HR-P	Highest residue in a processed sample, in mg/kg, calculated by multiplying the HR in the processed commodity
bw	Body weight in kg, provided by the country where from which the LP was reported

A summary of the NESTI calculations for tolylfluanid (tolylfluanid + DMST) are given in Table B.7.16-18 and B.7.16-19.

The NESTI calculations resulted in 0-25 % of the ARfD for adults and 1-100 % of the ARfD for toddlers. It was concluded that a short term intake of residues of tolylfluanid and DMST would be in acceptable levels.

Table B.7.16-18 International Estimated Short-term Intake (IESTI) calculation for tolylfluanid

NESTI – (Tolylfluanid and DMST)								
Guidelines used :PSD (2001)								
Adults								
Commodity	**HR or HR-P (mg/kg)**	**F (kg)**	**Unit weight of edible portion (kg)**	**Body weight (kg)**	**v**	**Case**	**NESTI (mg/kg bw/day)**	**% of the ARfD[1]**
Apple (fruit)	2.45	0.308	0.112	70.1	7	2a	0.0343	13.7
Apple (juice)*	0.244	0.452		70.1	1	1	0.0016	0.6
Black currant (fruit)	1.83	0.072		70.1	1	1	0.0019	0.8
Black currant (juice)**	1.098	0.057		70.1	1	1	0.0009	0.4
Courgette	0.96	0.222	0.144	70.1	7	2a	0.0124	5.0
Cucumber	0.96	0.084	0.060	70.1	7	2a	0.0061	2.4
Grapes (bunches of table grapes)	4.61	0.19	0.500	70.1	5	2b	0.0625	25.0
Leek	1.8	0.248	0.140	70.1	7	2a	0.0279	11.2
Lettuce	11.64	0.093	0.558	70.1	3	2b	0.0463	18.5
Melon	0.08	0.513	0.322	70.1	5	2a	0.0020	0.8
Pear	1.99	0.274	0.150	70.1	7	2a	0.0410	16.4
Pepper	1.64	0.089	0.160	70.1	7	2b	0.0146	5.8
Strawberry	2.71	0.203		70.1	1	1	0.0078	3.1
Tomato	1.96	0.157	0.085	70.1	7	2a	0.0186	7.5

[1] = 0.25 mg/kg
* mean transfer factor (sum of tolylfluanid + DMST) = 0.1(juice)
** mean transfer factor (sum of tolylfluanid + DMST) = 0.6 (juice)

Table B.7.16-19 National Estimated Short-term Intake (NESTI) calculations for tolylfluanid

NESTI – (Tolylfluanid and DMST)								
Guidelines used :PSD (2001)								
Toddlers								
Commodity	**HR or HR-P (mg/kg)**	**F (kg)**	**Unit weight of edible portion (kg)**	**Body weight (kg)**	**v**	**Case**	**NESTI (mg/kg bw/day)**	**% of the ARfD[1]**
Apple (fruit)	2.45	0.199	0.112	14.5	7	2a	0.14717	58.9
Apple (juice)*	0.245	0.559		14.5	1	1	0.00945	3.8
Black currant (fruit)	1.83	0.053		14.5		1	0.00669	2.7
Black currant (juice)**	1.098	0.049		14.5	1	1	0.00371	1.5
Courgette	0.96	0.060	0.114	14.5	7	2b	0.02781	11.1
Cucumber	0.96	0.072	0.060	14.5	7	2a	0.02860	11.4
Grapes (bunches of table grapes)	4.61	0.158	0.500	14.5	5	2b	0.25117	100.5
Leek	1.8	0.025	0.140	14.5	7	2b	0.0217	8.7
Lettuce	11.64	0.025	0.558	14.5	5	2b	0.06021	24.1
Melon	0.08	0.303	0.322	14.5	5	2b	0.00836	3.3
Pear	2.45	0.279	0.150	14.5	7	2a	0.19921	79.7
Pepper	1.64	0.050	0.160	14.5	7	2b	0.03959	15.8
Strawberry	2.71	0.111		14.5	1	1	0.02075	8.3
Tomato	1.96	0.093	0.085	14.5	7	2a	0.08151	32.6

* mean transfer factor (sum of tolylfluanid + DMST) = 0.1 (juice)
** mean transfer factor (sum of tolylfluanid + DMST) = 0.6 (juice)

B.7.18 References relied on

Annex point/ reference number	**Author(s)**	**Year**	**Title** **Source** (where different from company) **Company name. Report No. Date**. **GLP status** (where relevant). published or not	**Data protect. claimed**	**Owner**
Annex IIA 6.7; Annex IIIA 8.6	Weile. M.	2004	Statement on MRL calculations based on the critical residue data selected by the rapporteur raking into consideration the sum of tolylfluanid + DMST. Bayer CropScience AG. Date: 07.09.2004 Non Published	No	BAY
Annex IIA 6.7; Annex IIIA 8.6	Weile. M	2004	Statement on intake calculation for chronic dietary exposure to the sum of tolylfluanid and DMST based on revised MRL calculation. Bayer CropScience AG. Date: 07.09.2004 Non Published	No	BAY

B.8 Environmental fate and behaviour

At the expert meeting in June 2004, it was decided that the Predicted Environmental Concentrations in soil (PEC_{soil}) and surface water (PEC_{sw}) for tolylfluanid and the main metabolite DMST should be recalculated using the worst case DT_{50} values, Thus, the Notifier has conducted new PEC calculations, which are presented below,

B.8.3 Predicted environmental concentrations in soil (Annex III A, 9,1,3)

Report: Schad, T, and Klein, S, (2004), Predicted environmental concentrations of tolylfluanid and its metabolite tolylfluanid-dimethylaminosulfotoluidide (DMST) in soil – use in apples, grapes, strawberries, BayerCropScience AG, unpublished report No, MEF-04/379, Date: 2004-09-02,

Test method

Half-life values

The DT_{50} values from laboratory study 1 presented in Chapters B.8.1.1.1 and B.8.1.2.1 of the DAR were used to describe the degradation of tolylfluanid and DMST in soil, The half-life values obtained at experimental temperature of 22 °C were normalized to a reference temperature of 20 °C using following equation:

$$DT_{50}(T_2) = DT_{50}(T_1) * Q_{10}^{((T1-T2)/10)}$$

with $Q_{10} = 2.2$,
T_1: Soil temperature during the study, $T_1 = 22$ °C
T_2: Reference temperature, $T_2 = 20$ °C

The resulting maximum DT_{50} values used in PEC_{soil} calculations were 2,6 days for tolylfluanid and 6,7 days for DMST, However, in PEC_{soil} calculations of DMST the geometric mean value of the parent of 1,5 days was used to characterize the generation of DMST from tolylfluanid, It was assumed that the formation fraction of the metabolite DMST out of the parent substance tolylfluanid was 1 (100 % formation),

Use patterns

The use patterns of tolylfluanid used for calculation of PEC_{soil} values are presented in Table B.8.3-1, According to the intended safe uses of tolylfluanid the use in apples, grapes and strawberries was assessed, with different use patterns for Northern and Southern Europe, For each crop and region a worst case application sequence was used, taking into account the shortest application interval and the maximum number of applications, Crop interception values were taken from the last FOCUS groundwater report (2002),

Table B.8.3-1 Use patterns of tolylfluanid used for calculation of PEC_{soil},

Crop	Region	Assumed application period	Intended application rate (kg as/ha)	Shortest application interval (days)	Crop interception (%)	Amount of as reaching the soil (kg as/ha)
Apples	Northern Europe	April-June	7 x 1,125	7	50, 50, 70, 80, 80, 80, 80	2 x 0,563, 1 x 0,338, 4 x 0,225
	Southern Europe	June-July	3 x 1,5	7	80, 80, 80	3 x 0,300
Grapes	Northern Europe	April-July	0,6, 0,8, 1,2, 1,4, 1,6, 3 x 1,8	10	50, 50, 70, 85, 85, 85, 85, 85	0,3, 0,4, 0,36, 0,24, 0,21, 3 x 0,27
	Southern Europe	June-July	3 x 2,0	8	85, 85, 85	3 x 0,3
Strawberries	Northern Europe	May	3 x 2,5	8	60, 60, 60	3 x 1,0
	Southern Europe	April-May	3 x 1,25	7	60, 60, 60	3 x 0,5

Calculations

The predicted environmental concentrations of tolylfluanid and DMST in soil were modelled using MICROSOFT EXCEL 2000, PEC_{soil} values were calculated as concentrations in the 0 - 5 cm soil layer assuming a soil bulk density of 1,5 kg/L,

The actual PEC_{soil} values of tolylfluanid were calculated on a daily basis taking the decline of concentrations due degradation as well as the increase of concentrations due to additional applications into account, The actual PEC_s values of DMST were calculated corresponding to the degraded amount of the parent substance taking a transformation fraction of 100 % into account,

The maximum actual PEC_{soil} value of each compound occurring at any time during or after the application period was defined and reported as the global maximum PEC_{soil} (day 0), Because of the fast degradation of both compounds and the increasing crop interception for application in apples and grapes and due to increasing foliage this global maximum PEC_{soil} was not necessarily reached after last application, The time dependent PEC_{soil} values were defined as actual values at 1 day, 2 days, 4 days, 7 days, 28 days, 50 days and 100 days after the global maximum,

The time weighted average values (TWA_{soil} or TWA PEC_{soil}) represent the maximum concentrations of the moving average PEC_{soil} values for the respective time interval, Calculations were based on following equation:

$$TWA_{SOIL} = \frac{1}{\Delta t} \; MAX\left[\int_{t}^{t+\Delta t} PEC_{SOIL}(t) \; dt\right]$$

This approach ensures that for each TWA PEC_{soil} time interval Δt the period with the highest average concentration will be detected and reported (either of the parent substance or of the metabolite), The time weighted average values were calculated for time periods Δt of 1 day, 2 days, 4 days, 7 days, 21 days, 28 days, 50 days and 100 days for each day following the first application, A daily time step was used to move the time window for which averages were calculated,

Results

Maximum PEC_{soil} values

The global maximum PEC_{soil} values of tolylfluanid and DMST following application to apples, grapes and strawberries according to the intended use patterns in Northern and Southern Europe have been summarized in Table B.8.3-2, Additionally, Table B.8.3-2 gives the time periods after the first application after which the maximum concentrations of tolylfluanid and DMST are expected to occur in soil, Time periods, expressed as days after the first application, are listed for each use pattern and region separately, As an example (of the occurrence of the maximum concentrations) the graphical output of the actual tolylfluanid and DMST concentrations in soil certain days after the first application to apples are given in Figures B.8.3-1 to B.8.3-4,

Table B.8.3-2 Maximum PEC_{soil} values and their occurrence,

Crop	Region	Tolylfluanid		DMST	
		Max, PEC_{soil} (µg/kg)	Occurrence of max, PEC_{soil}, DAA*	Max, PEC_{soil} (µg/kg)	Occurrence of max, PEC_{soil}, DAA*
Apples	Northern Europe	866,8	7	522,7	10
	Southern Europe	471,5	14	336,3	17
Grapes	Northern Europe	561,1	10	341,6	23
	Southern Europe	453,0	16	315,0	19
Strawberries	Northern Europe	1510,1	16	1050,1	19
	Southern Europe	785,8	14	560,5	17

*DAA = days after the first application

Short-term and long-term PEC_{soil} values

The PEC_{soil} values of tolylfluanid are presented in Tables B.8.3-3 (actual values) and B.8.3-4 (time weighted values) and the PEC_{soil} values of DMST are presented in Tables B.8.3-5 (actual values) and B.8.3-6 (time weighted values), Actual PEC_{soil} values refer to time after the maximum PEC_{soil} whereas the term time for timely weighted average values refer to the width of time window used for averaging,

Table B.8.3-3 Actual PEC_{soil} values of tolylfluanid in Northern Europe (NE) and Southern Europe (SE),

Crop	Region	Actual concentration in soil on certain days after the maximum concentration (µg/kg)								
		0 d	1 d	2 d	4 d	7 d	21 d	28 d	50 d	100 d
Apples	NE	866,8	664,0	508,6	298,4	584,8	360,4	355,8	6,5	<0,05
	SE	471,5	361,1	276,6	162,3	72,9	1,7	0,3	<0,05	<0,05
Grapes	NE	561,1	429,8	329,2	277,2	86,8	242,1	37,5	386,7	<0,05
	SE	453,0	347,0	265,8	156,0	70,1	1,7	0,3	<0,05	<0,05
Strawberries	NE	1510,1	1156,7	886,0	519,8	233,6	5,6	0,9	<0,05	<0,05
	SE	785,8	601,9	461,0	270,5	121,6	2,9	0,5	<0,05	<0,05

Table B.8.3-4 TWA PEC_{soil} values of tolylfluanid in Northern Europe (NE) and Southern Europe (SE),

Crop	Region	TWA concentration in soil /time period (µg/kg)							
		1 d	2 d	4 d	7 d	21 d	28 d	50 d	100 d
Apples	NE	765,4	679,8	545,5	464,5	379,3	335,4	261,4	133,4
	SE	416,3	369,7	296,7	267,5	222,2	175,5	100,5	50,8
Grapes	NE	495,5	440,1	353,1	264,2	220,6	201,3	174,2	130,9
	SE	400,0	355,3	285,1	213,3	215,3	174,7	100,5	50,8
Strawberries	NE	1333,4	1184,3	950,3	711,0	717,7	582,5	335,1	169,2
	SE	693,8	616,2	494,5	445,8	370,4	292,6	167,6	84,6

Table B.8.3-5 Actual PEC_{soil} values of DMST in Northern Europe (NE) and Southern Europe (SE),

Crop	Region	Actual concentration in soil on certain days after the maximum concentration (µg/kg)								
		0 d	1 d	2 d	4 d	7 d	21 d	28 d	50 d	100 d
Apples	NE	522,7	515,9	493,2	428,1	509,3	352,2	321,7	78,9	0,4
	SE	336,3	327,0	309,8	266,4	202,0	48,3	23,4	2,4	<0,05
Grapes	NE	341,6	335,8	320,2	277,2	211,0	240,8	218,0	266,3	1,9
	SE	315,0	307,5	292,0	251,7	191,1	45,7	22,1	2,3	<0,05
Strawberries	NE	1050,1	1024,9	973,4	838,9	636,9	152,3	73,8	7,6	<0,05
	SE	560,5	545,0	516,4	444,0	336,6	80,4	39,0	4,0	<0,05

Table B.8.3-6 TWA PEC_{soil} values of DMST in Northern Europe (NE) and Southern Europe (SE),

Crop	Region	TWA concentration in soil/time period (µg/kg)							
		1 d	2 d	4 d	7 d	21 d	28 d	50 d	100 d
Apples	NE	519,3	513,3	499,1	493,0	438,1	410,3	352,3	195,8
	SE	333,7	331,5	321,0	300,5	247,5	221,7	145,5	74,6
Grapes	NE	338,7	335,8	325,5	306,0	275,3	261,7	240,3	190,6
	SE	311,6	310,2	299,8	281,7	236,3	216,0	145,1	74,6
Strawberries	NE	1038,6	1034,1	999,3	939,1	787,7	720,0	483,6	248,6
	SE	556,2	552,4	535,0	500,9	412,5	369,5	242,4	124,3

Figure B.8.3-1 Actual PEC_{soil} of tolylfluanid after application to apples in Northern Europe,

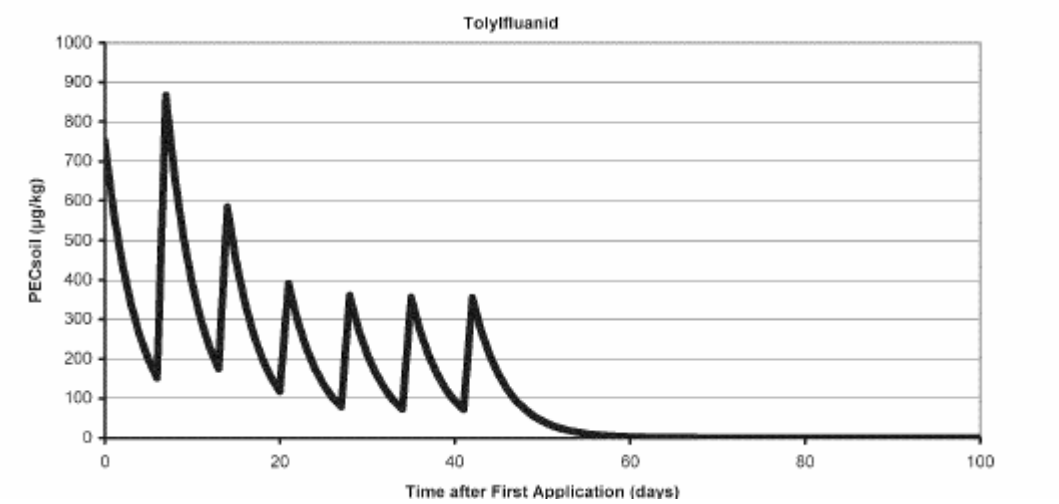


Figure B.8.1-2 Actual PEC_{soil} of DMST after application of tolylfluanid to apples in Northern Europe,

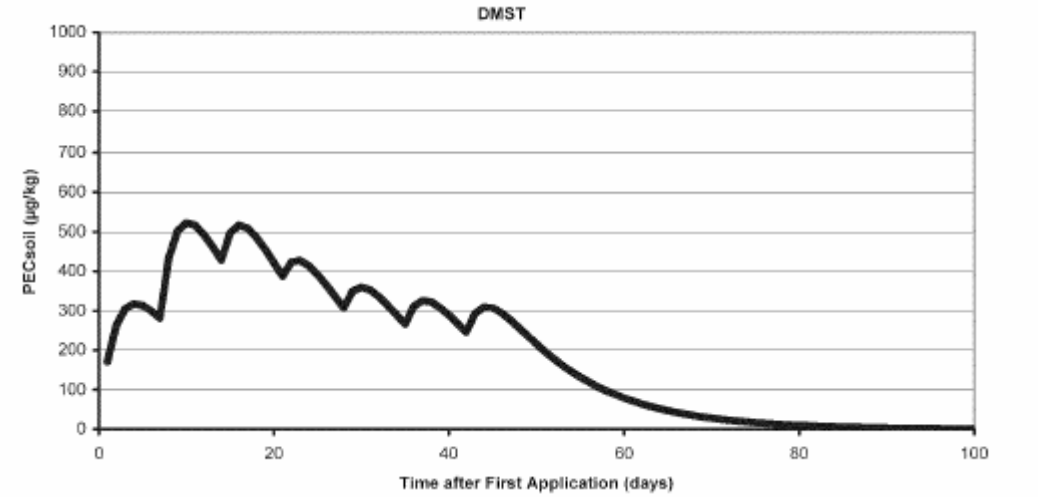


Figure B.8.1-3 Actual PEC_{soil} of tolylfluanid after application to apples in Southern Europe,

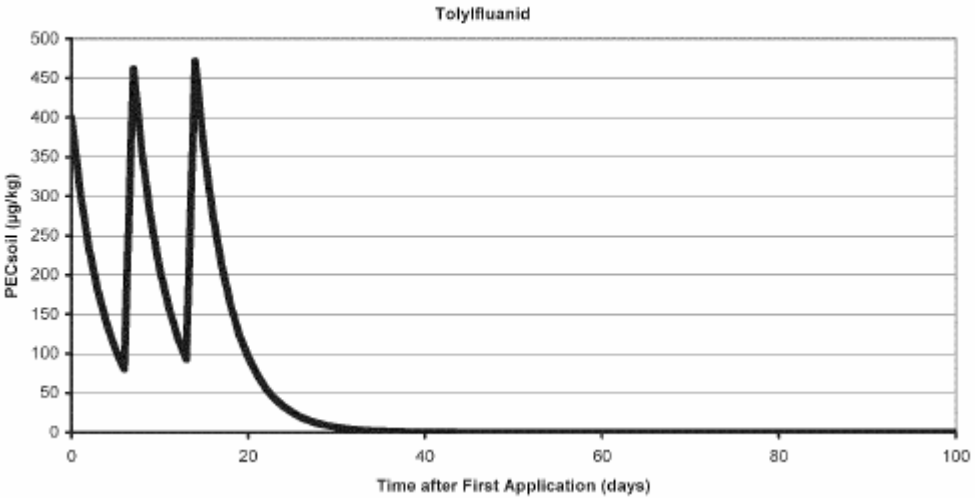
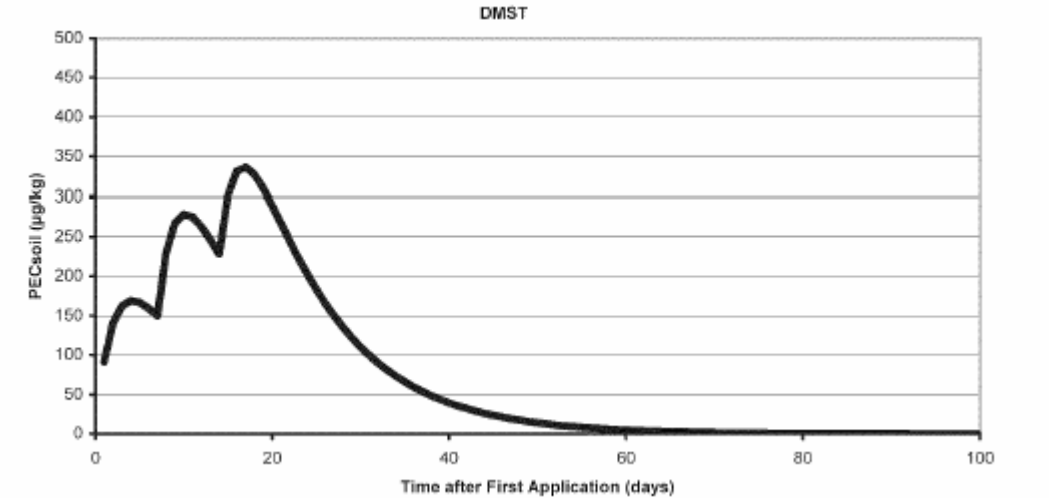


Figure B.8.3-4 Actual PEC_{soil} of DMST after application of tolylfluanid to apples in Southern Europe,



Comments
The use patterns of tolylfluanid with several applications and different application rates and intervals are rather complicated and therefore it is not possible to conduct the PEC_{soil} calculations according to the standard assumptions, The RMS has found the current situation difficult because official and sufficient guidance concerning the PEC calculations for products with complicated use patterns has not been available

The Notifier has recalculated the PEC_{soil} values of tolylfluanid and DMST using worst-case DT_{50} values according to the requirements of the expert meeting, However, in the PEC_{soil} calculations of DMST the geometric mean value of tolylfluanid has been used to characterize the generation of DMST from tolylfluanid, The Notifier has justified that the geometric mean value of the parent was used in order to address worst-case conditions for the PEC_{soil} calculation of metabolite DMST, The RMS agrees with this justification and finds the calculation acceptable although the RMS or the expert meeting has not required using the mean value in calculations,

The RMS considers the data requirement fulfilled,

B.8.6 Predicted environmental concentrations in surface water and ground water (PEC_{sw}, PEC_{gw}) (Annex IIIA 9,2,1, 9,2,3)

B.8.6.1 Predicted environmental concentrations in surface water (PEC_{sw})

Report: Reinken, G, and Klein, S, (2004) Predicted environmental concentrations of tolylfluanid and its main metabolite tolylfluanid-dimethylaminosulfotoluidide (DMST) in surface water and sediment - use in apples, grapes and strawberries in Europe, BayerCropScience AG, unpublished report No, MEF-04/403, Date: 2004-09-28,

Test method
Half-life values
The DT_{50} values from laboratory studies 1 and 3 presented in Chapter B.8.4.3.2 of the DAR were used to describe the degradation of tolylfluanid and DMST in surface water, The worst-case half-life value of 0,25 days obtained in study 3 (20 ^{o}C) was used in PEC_{sw} calculations of tolylfluanid, The worst case DT_{50} value of DMST (75,8 days) was obtained in study 1, The experimental temperature of study 1 was, however, 22 ^{o}C, Thus the half-life value was normalized to a reference temperature of 20 ^{o}C using following equation:

$$k_{ref}\ (T_{ref}) = k_{lab}\ (T_{lab}) * Q_{10}^{((Tref-Tlab)/10)}$$

with

Q_{10} 2.2
k_{ref} degradation rate at reference conditions [1/d]
k_{lab} degradation rate during the study [1/d]
T_{ref} reference temperature [°C] (T_{ref} = 20°C)
T_{lab}: temperature during the study [°C] ($T_{lab,DMST}$ = 22 °C)

The resulting DT_{50} value of DMST used in PEC_{sw} calculations was 88,7 days,

Occurrence of DMST
To estimate the initial concentrations of DMST in surface water the maximum occurrence of DMST in water phase of four sediment systems (the DAR, B.8.4.3.2, studies 1 and 3) was taken into account, In study 1 DMST occurred at a maximum rate of 75,7 % of applied radioactivity in the water phase, This fraction was taken into account for the calculation of the maximum (pseudo-) application rate of DMST,

Scenario data
The generic worst-case scenario for aquatic exposure assessments used was a shallow, static water body that receives spray drift from an adjacent field, The water body was 0,3 m deep, For the PEC calculations it was assumed that the substance is perfectly mixed over the whole depth of the water layer,

The use patterns for calculation of PEC_{sw} values are presented in Table B.8.6-1, For each crop and region a worst-case application sequence was assumed, taking the shortest application interval, the maximum number of applications and the maximum application rate into account,

Single and multiple applications were assessed for both compounds and each crop using the overall 90th percentile spray drift rates according to Rautmann (2000) as proposed by FOCUS (2001), A detailed summary of the maximum drift rates used in the calculations is given in Table B.8.6-1, Drift mitigation by the introduction of different buffer strips was considered using the corresponding spray drift rates for buffer strips of 5 m to 20 m,

Table B.8.6-1, Use patterns of tolylfluanid used for calculation of PEC_{sw},

Crop	Region	Assumed application period	Intended application rate (kg as/ha)	Shortest application interval (days)	Max, spray drift for single applications (%)*	Max, spray drift for multiple applications (%)*
Apples	Northern Europe	April-June	7 x 1,125	7	29,20 (pre-blossom) 15,73 (post-blossom)	22,69 (pre-blossom) 9,01 (post-blossom)
	Southern Europe	June-July	3 x 1,5	7	15,73	11,01
Grapes	Northern Europe	April-July	0,6, 0,8, 1,2, 1,4, 1,6, 3 x 1,8	10	8,02	6,26
	Southern Europe	June-July	3 x 2,0	8	8,02	6,90
Strawberries	Northern Europe	May	3 x 2,5	8	2,77	2,01
	Southern Europe	April-May	3 x 1,25	7	2,77	2,01

* = no extra buffer

Calculations, initial and maximum PEC_{sw}
The initial PEC_{sw} depends on the application rate a, the spray drift rate s and the depth of water body d_w, according to equation:

$$PEC_{SW\ INI} = \frac{a\ s}{d_W}$$

For one application per season the initial PEC in the water phase is equivalent to the maximum PEC, i,e, $PEC_{swMAX} = PEC_{swINI}$,

For multiple applications with constant application rate the PEC_{swMAX} was calculated as:

$$PEC_{SW\,MAX} = \frac{a\,s}{d_w}\,\frac{1-e^{-n\,k_{SW}\,\Delta t}}{1-e^{-k_{SW}\,\Delta t}}$$

where k_{sw} is the first order rate constant for dissipation in the water phase, n is the number of applications and Δt is the application interval,

The above-described formulas also apply to metabolites, except that the application rate must be corrected for the ratio of the molecular weights of metabolites, In addition, the application rates are corrected for the maximum amount of the metabolite observed in water,

Calculations, actual PEC_{sw} and TWA PEC_{sw} for multiple applications with constant application rates
With the first order rate constant k_{sw} ($days^{-1}$), **the actual PEC_{sw}** can be calculated as function of time t after the occurrence of the maximum concentration as:

$$PEC_{SW}(t) = PEC_{SW\,MAX}\;e^{-k_{SW}\cdot t}$$

The rate constant k is related to the half-life (DT50) value by:

$$k = \frac{\ln(2)}{DT50}$$

The time-weighted average (TWA or TWA PEC_{sw}) concentrations at time t after the maximum PEC are calculated as:

$$TWA_{SW}(t) = PEC_{MAX}\,\frac{1-e^{-k_{SW}\,t}}{k_{sw}\,t}$$

Calculations, actual PEC_{sw} and TWA PEC_{sw} for multiple applications with different application rates
In cases where application rates or drift rates were not constant (application to apples and grapes in Northern Europe) **actual PEC_{sw}** values of tolylfluanid and the metabolite DMST were calculated on a daily basis taking the decline of concentrations due to degradation as well as the increase of concentrations due to additional applications into account,

The maximum actual PEC_{sw} value of each compound was defined as global maximum PEC_{sw} (day 0), The time dependent PEC_{sw} values were defined as actual values at 1 day, 2 days, 4 days, 7 days, 14 days, 21, days, 28 days, 42 days and 100 days after the global maximum,

The time weighted average values were calculated for time periods Δt of 1 day, 2 days, 4 days, 7 days, 14 days, 21 days, 28 days, 42 days and 100 days for each day following the first application, A daily time step was used to move the time window for which averages were calculated, This approach ensures that for each time interval Δt the period with the highest average concentration, either of the parent substance or of the metabolite will be detected,

Results
Maximum PEC_{sw} values
Tolyfluanid realistically degrades completely between applications and thus the maximum PEC_{sw} values for the parent were obtained by the calculations for single applications, The maximum PEC_{sw} values for DMST were obtained by calculations for multiple applications due to moderate dissipation rate of DMST, The global maximum PEC_{sw} values of tolylfluanid and DMST are summarized in Table B.8.6-2, These maximum PEC_{sw} values are given for different no-spray-zones up to 20 m,

Table B.8.6-2 The maximum PEC_{sw} values of tolylfluanid and DMST

Crop	Width of buffer strip (m)	PEC_{sw} (µg/L)			
		Tolylfluanid		DMST	
		Northern Europe	Southern Europe	Northern Europe	Southern Europe
Apples	0	109,55	78,65	130,39	73,11
	5	74,62	42,05	77,65	40,11
	10	44,31	18,00	38,62	17,73
	15	20,82	9,05	18,82	9,23
	20	10,39	5,45	9,70	5,31
Grapes	0	48,12	53,47	87,27	60,63
	5	21,72	24,13	38,76	26,98
	10	7,38	8,20	12,97	8,96
	15	3,90	4,33	6,83	4,75
	20	2,52	2,80	4,32	2,99
Strawberries	0	23,08	11,54	22,08	11,12
	5	4,75	2,38	4,50	2,27
	10	2,42	1,21	2,20	1,11
	15	1,67	0,83	1,54	0,77
	20	1,25	0,63	1,10	0,55

Short-term and long-term PEC_{sw} values

The PEC_{sw} values of tolylfluanid are presented in Tables B.8.6-3 (actual values) and B.8.6-4 (time weighted values) and the PEC_{sw} values of DMST are presented in Tables B.8.6-5 (actual values) and B.8.6-6 (time weighted values), The values are listed with no extra buffer zone, Actual PEC_{sw} values refer to time after the maximum PEC_{sw} whereas the term time for timely weighted average values refer to the width of time window used for averaging,

Table B.8.6-3 Actual PEC_{sw} values of tolylfluanid in Northern Europe (NE) and Southern Europe (SE), no extra buffer,

Crop	Region	Actual concentration on certain days after the maximum concentration (µg/L)									
		0 d	1 d	2 d	4 d	7 d	14 d	21 d	28 d	42 d	100 d
Apples	NE	109,55	33,02	10,11	1,06	59,01*	58,99*	58,99*	58,99*	<0,01	<0,01
	SE	78,65	4,92	0,31	<0,01	<0,01	<0,01	<0,01	<0,01	<0,01	<0,01
Grapes	NE	48,12	3,01	0,19	<0,01	<0,01	<0,01	<0,01	<0,01	<0,01	<0,01
	SE	53,47	3,34	0,21	<0,01	<0,01	<0,01	<0,01	<0,01	<0,01	<0,01
Strawberries	NE	23,08	1,44	0,09	<0,01	<0,01	<0,01	<0,01	<0,01	<0,01	<0,01
	SE	11,54	0,72	0,05	<0,01	<0,01	<0,01	<0,01	<0,01	<0,01	<0,01

* = concentrations caused by applications at days 7, 14, 21 and 28 after the maximum peak

Table B.8.6-4 TWA PEC_{sw} values of tolylfluanid in Northern Europe (NE) and Southern Europe (SE), no extra buffer,

Crop	Region	TWA concentration in surface water/time period (µg/L)								
		1 d	2 d	4 d	7 d	14 d	21 d	28 d	42 d	100 d
Apples	NE	71,29	50,90	31,40	27,05	19,95	17,05	15,46	12,48	5,31
	SE	26,59	14,13	7,09	4,05	2,03	1,35	1,01	0,68	0,28
Grapes	NE	25,56	17,11	10,27	6,42	3,42	2,33	1,77	1,19	0,51
	SE	18,08	9,60	4,82	2,75	1,38	0,92	0,69	0,46	0,19
Strawberries	NE	7,81	4,15	2,08	1,19	0,59	0,40	0,30	0,20	0,08
	SE	3,90	2,07	1,04	0,59	0,30	0,20	0,15	0,10	0,04

Table B.8.6-5 Actual PEC_{sw} of DMST in Northern Europe (NE and Southern Europe (SE), no extra buffer,

Crop	Region	Actual concentration on certain days after the maximum concentration (µg/L)									
		0 d	1 d	2 d	4 d	7 d	14 d	21 d	28 d	42 d	100 d
Apples	NE	130,39	129,38	128,37	126,38	123,45	116,88	110,66	104,77	93,91	59,69
	SE	73,11	72,54	71,97	70,86	69,22	65,53	62,04	58,74	52,65	33,46
Grapes	NE	87,27	86,59	85,92	84,59	82,63	78,23	74,06	70,12	62,85	39,95
	SE	60,63	60,16	59,69	58,77	57,41	54,35	51,46	48,72	43,67	27,75
Strawberries	NE	22,08	21,91	21,74	21,40	20,90	19,79	18,74	17,74	15,90	10,11
	SE	11,12	11,04	10,95	10,78	10,53	9,97	9,44	8,94	8,01	5,09

Table B.8.6-6 TWA PEC_{sw} values of DMST in Northern Europe (NE) and Southern Europe (SE), no extra buffer,

Crop	Region	TWA concentration in surface water/time period (µg/L)								
		1 d	2 d	4 d	7 d	14 d	21 d	28 d	42 d	100 d
Apples	NE	129,88	129,38	128,38	126,89	123,52	120,27	117,13	111,18	90,53
	SE	72,82	72,54	71,98	71,14	69,25	67,42	65,66	62,32	50,73
Grapes	NE	86,93	86,59	85,92	84,93	82,67	80,50	78,39	74,41	60,59
	SE	60,40	60,16	59,69	59,00	57,43	55,92	54,46	51,69	42,07
Strawberries	NE	21,99	21,91	21,74	21,49	20,91	20,36	19,83	18,82	15,32
	SE	11,08	11,04	10,95	10,82	10,54	10,26	9,99	9,48	7,72

Comments
The calculations were carried out in a reasonable way, However, the Notifier stated by mistake in his report that drift rates used for the application in apples in Southern Europe were pre-blossom drift rates, Nevertheless, in compliance with the assumed application period: June-July post-blossom drift rates were used for calculation, Since mistake was only done in the report but not in calculation, it does not affect the validity of the PEC calculations, The RMS considers the calculations acceptable and the data requirement fulfilled,

B.8.10 References relied on

Annex point/ reference number	**Author(s)**	**Year**	**Title** **Source** (where different from company) **Company name, Report No,, Date**, **GLP status** (where relevant), published or not	**Data protect, claimed**	**Owner**
III A, 9,1,3	Schad, T,; Klein, S,	2004	Predicted environmental concentrations of tolylfluanid and its metabolite tolylfluanid-dimethylaminosulfotoluidide (DMST) in soil BayerCropScience AG, Report-No,: MEF-04/379 Date:02,09,2004 Non GLP, Non Published	Yes	BAY
IIIA, 9,2,3	Reinken, G,; Klein, S,	2004	Predicted environmental concentrations of tolylfluanid and its main metabolite tolylluanid-dimethylaminosulfotoluidide (DMST) in surface water and sediment BayerCropScience AG, Report-No,: MEF-04/403 Date:28,09,2004 Non GLP, Non Published	Yes	BAY

B.9 Ecotoxicology

INTRODUCTION

This addendum addresses the open points identified for tolylfluanid at the expert meeting EPCO 8 22,-23,6,2004 (c,f, Evaluation table, Tolylfluanid, doc, 16497/EPCO/BVL/04 rev, 0-3 (21,09,04)),

The notifier has provided a revised risk assessment for birds, mammals, aquatic organisms and earthworms, As requested by regulatory authorities during the EPCO 7, new predicted environmental concentrations (PECs) in soil (Schad, T,, Klein, S,, 2004) and surface water (Reinken, G,, Klein, S,, 2004) have been calculated, In this present addendum to the DAR – EU-Monograph from July 2003, the new calculated predicted environmental concentrations (PECs) of tolylfluanid and its major metabolite tolylfluanid-dimethylaminosulfotoluidide (DMST) were used where necessary,

The aquatic risk assessment was mainly updated for the major metabolite DMST, Since all calculations in previous documents were already based on the actual maximum predicted environmental concentrations, no update of TER calculations for the aquatic risk assessment or secondary poisoning in surface water are necessary for tolylfluanid, Only the final TER-values for toxicity of tolylfluanid to fish based on the result of the outdoor microcosm study are updated because of the change of uncertaintity factor,

Since the refinement of PT in the risk assessment for birds was questioned at the expert meeting in June 2004, the notifier provided a detailed refined risk assessment in August 2004 supporting the previous assumption of a worst case generic PT of 0,6, This data, however, was not in the data package RMS received to write Addendum 1, it was submitted after the expert meeting (EPCO 8) and according to the EFSA cannot be taken into account for the risk refinement, Therefore it is not included in this addendum and the risks are calculated using PT of I,

The chronic risk assessment for mammals in the Annex II/III Dossier as submitted by the notifier was based on the NOEL of 100 mg/kg bw/day from the teratogenicity study since according to the notifier this study reflects the long-term exposure of mammals better than the reproduction study, This endpoint was also used for the new risk assessment (Addendum 1) according to the final version of the Guidance Document, The expert meeting in June (EPCO 8) concluded to base a further refined risk assessment on the rat reproduction study with a NOAEL of 9 mg/kg/bw/day, However, the expert meeting in July 2004 (EPCO 9) concluded to base a risk assessment on the new rat reproduction study with a NOAEL of 12 mg/kg/bw/day,

The numbering of the titles refers to the numbers of the titles in the DAR,

B.9.1.4 Summary and Risk assessment for birds

The Bayer Crop Science (BCS) Annex II/III Dossier was not based on the valid version of the Guidance Document for Birds and Mammals, but on the current draft version of this Guidance Document, which was available at that time, The refined risk assessment for birds submitted in November 2003 as requested from the notifier in accordance to the final version of the Guidance Document for Birds and Mammals was based on a generic bird species (as recommended in the GD) and on a PT value of 0,6 (strawberries only), Since the refinement of PT was questioned at the expert meeting in June 2004, BCS provided a detailed refined risk assessment in August 2004 supporting the previous assumption of a worst case generic PT of 0,6: two bird species had been identified as relevant for strawberries, grey partridge (resulting to $TER_a > 18$ with a refinement of PT of 0,43 based on the extensive litterature data), and as a second species, skylarks: no refined PT was necessary (PT 1,0) since the PT was incorporated into the PD figures (0,21 - 0,63) considering the diet proportions of this species (resulting to $TER_a > 41$), This data, however, was not in the data package RMS received to write Addendum 1, it was submitted after the expert meeting (EPCO 8) and according to the EFSA cannot be taken into account for the risk refinement, For convenience the first tier risk assessment (just for herbivores) is repeated below and the second tier long-term risks recalculated using PT of 1,

The use pattern of tolylfluanid (only for strawberries) on which the revised risk assessments are based is shown in Table B.9.1.4-1,

Table B.9.1.4-1 Crops, application rates and intervals for tolylfluanid WG 50 formulation,

Crop	Northern Europe (NE)/ Southern Europe (SE)	Max, application rate kg ai/ha	Max, no, of applications	Application interval [d]
Strawberries	NE	2,5	3	8 - 12
Strawberries	SE	1,25	3	7 - 10

The toxicity endpoints for birds used in the original dossier are re-presented in Table B.9.1,4-2,

Table B.9.1.4-2 Toxicological endpoints for birds (tolylfluanid),

Organisms	Duration	Test-substance	Origin	Ecotoxicological endpoint
Bobwhite quail	Acute, oral	ai	Annex II, 8,1,1 /01	LD_{50} > **2,000** mg ai/kg bw
Bobwhite quail	Reproduction 21 w, dietary	ai	Annex II, 8,1,3 /01	NOEC **791** mg ai/kg diet

value with **bold**: value used in risk assessment

B.9.1.4.1 Exposure of birds to tolylfluanid WG 50

Table B.9.1.4-3 Assumptions regarding the assessment of risks to birds (based on recommendations detailed in the Birds and Mammals Guidance Document (SANCO/4145/2000 final Sept 2002)),

Generic species	Body weight (bw)	Feed	Food intake (FIR) [g fresh weight per day]	FIR/bw
[1]Medium herbivorous bird (e,g,: partridge or pigeon)	300 g	Leafy crops	228	0,76
[2]Small insectivorous bird (e,g,: wren)	10 g	Small insects	10,4	1,04
[3]Bird with mixed diet feeding exclusively on fruits (e,g, blackbird)	100 g	fruits	118,12	1,18

[1] and [2] according to the Birds and Mammals Guidance Document (SANCO/4145/2000 final Sept 2002)
[3] according to Nagy (1987)

With regard to predicted residues on food items following foliar spray applications, initial Tier 1 estimates are based on the worst-case values presented in tables 4, 6 and 7 of the SANCO guidance document, As recommended in the guidance, depending on the time scale of the exposure, either 90th percentile or arithmetic mean residue concentrations are used for acute or chronic exposures as appropriate,

B.9.1.4.2 Acute Risk Assessment - Tier 1

The initial worst-case calculations for tolylfluanid are presented in Table B.9.1,4-4 and are based on the default values presented in tables 3 and 4 of the Birds and Mammals Guidance Document,

Table B.9.1.4-4 TER calculations based on <u>acute</u> toxicity (calculations based on recommendations detailed in the Birds and Mammals Guidance Document (SANCO/4145/2000 final Sept 2002)),

Strawberries (Northern Europe): 2,5 kg ai/ha; 3 applications / 8 d interval	
Toxicological endpoint: Bobwhite quail, acute	**LD_{50} > 2,000 mg ai/kg bw**
Generic bird species[1]	medium herbivore
RUD (90%)	87
Calculated maximum initial residues in feed [mg/kg feed]	217,5
FIR/bw	0,76
MAF (multiple application factor)	1,7
ETE [mg/kg bw/day]	281,0
TER_a [2]	**>7,1**

[1] see Table B.9.1.4-3
[2] the risk is considered acceptable, if the TER-value is >10

Conclusions
A refined assessment for herbivorous avian species is not considered particularly relevant for strawberries as the crop will not provide an attractive food source for herbivorous birds; in addition weed and grass cover in the treated area will be minimised as a result of mulching, Also, it should be noted that the acute TER value has been calculated based on a LD_{50} value of >2000 mg ai/kg bw, a dose at which no mortality or treatment-related effects were recorded, This together with the unrealistic scenario that bird would eat strawberry leaves results in an over estimation of the potential risk, The RMS considers the data requirement fulfilled,

B.9.1.4.6 Long-term Risk Assessment - Tier 1

The relevant calculations for long-term avian exposure are summarised in Table B.9.1,4-5; these initial Tier 1 calculations are based on the default values presented in Tables 5 and 7 of the Birds and Mammals Guidance Document,

Table B.9.1.4-5 TER calculations based on long-term toxicity (147 days) (calculations based on recommendations detailed in the Birds and Mammals Guidance Document (SANCO/4145/2000 final Sept 2002)),

Toxicological endpoint: Bobwhite quail, reproduction **NOEC 791 mg ai/kg wet diet corresponding to a daily dietary dose of 78,1 mg ai/kg bw/day**[+]	
Generic bird species[1]	medium herbivore
Strawberries (Northern Europe): 2,5 kg ai/ha; 3 applications / 8 d interval	
RUD (50%)	40
Calculated maximum initial residues in feed [mg/kg wet weight feed]	100
FIR/bw	0,76
MAF (multiple application factor)	2,0
f_{twa}	0,53
ETE [mg/kg bw/day]	80,56
TER_{lt} [2]	**1,0**
Refined Risk Assessment required	**Yes**
Strawberries (Southern Europe): 1,25 kg ai/ha; 3 applications / 7 d interval	
RUD (50%)	40
Calculated maximum initial residues in feed [mg/kg wet weight feed]	50
FIR/bw	0,76
MAF (multiple application factor)	2,0
f_{twa}	0,53
ETE [mg/kg bw/day]	40,3
TER_{lt} [2]	**1,9**
Refined Risk Assessment required	**Yes**

[1] see Table B.9.1,4-3
[2] the risk is considered acceptable, if the TER-value is > 5

Conclusions
According to the TER values calculated above, a long-term risk for herbivorous birds exists, Tier 2 risk assessment is needed,

B.9.1.4.7 Long-term Risk Assessment - Tier 2

For this assessment the same approach as in the Addendum 1 is used (a refined RUD of 25,0 mg/kg is used for residues on leaves and the MAF and Twa are refined using the equations given in Sections 5,3 of the guidance document and based on the mean measured DT_{50} value on grass of 2,47 days (Barfknecht, 2003)), The only difference from the approach presented in the Addendum 1 is that the PT is changed from 0,6 to 1,

Since the relevant toxicity value for a long-term exposure is based on a 147-days study and the measured half-life of tolylfluanid in plant material is very short (grass, mean 2,47 days; see Barfknecht, 2003), a more realistic exposure is calculated using the 7-day twa exposure (according to current guidelines, in the case of repeated applications the averaging time should not be longer than the spray interval; thus for tolylfluanid a 7-day twa is appropriate),

Table B.9.1.4-6 TER calculation based on long-term toxicity (147 days) and more realistic exposure of tolylfluanid after the last application,

Toxicological endpoint: Bobwhite quail, reproduction **NOEC 791 mg ai/kg wet diet corresponding to a daily dietary dose of 78,1 mg ai/kg bw/day**		
Generic bird species[1]	frugivore	herbivore
Food type	**strawberry fruits**	**leaves**
Strawberries (Northern Europe): 2,5 kg ai/ha; 3 applications / 8 d interval		
Calculated maximum initial residues in feed [mg/kg feed]	7,90 (based on residue trials data)	62,5 (based on mean RUD of 25,0)
FIR/bw	1,18	0,76
MAF (multiple application factor)	na	1,12
f_{twa} [2]	0,44	0,44
AV (avoidance factor)	na	1
PT (proportion of food obtained in treated area)	na	1
PD (proportion of food type in diet i,e, 100 %)	na	1
ETE [mg/kg bw/day]	4,1	23,4
TER_{lt} [3]	**19,0**	**3,3**
Refined Risk Assessment required	**No**	**Yes**

Table to be continued

Table B.9.1.4-6 continues

Strawberries (Southern Europe): 1,25 kg ai/ha; 3 applications / 7 d interval		
Calculated maximum initial residues in feed [mg/kg feed]	7,90 (based on residue trials data)	31,3 (based on mean RUD of 25,0)
FIR/bw	1,18	0,76
MAF (multiple application factor)	na	1,16
f_{twa} [2]	0,44	0,44
AV (avoidance factor)	na	1
PT (proportion of food obtained in treated area i,e, 60%)	na	1
PD (proportion of food type in diet i,e, 100 %)	na	1
ETE [mg/kg bw/day]	4,1	12,1
TER_{lt} [3]	**19,0**	**6,5**
Refined Risk Assessment required	**No**	**No**

[1] see Table B.9.1,4-3
[2] time weighed average residues (based on an averaging time of 7 days, the minimum spray interval and a mean DT50 value of 2,47 days, as determined on grass (Barfknecht 2003))
[3] the risk is considered acceptable, if the TER-value is > 5

Conclusions
According to the TER values calculated above, a long-term risk for herbivorous birds still exists for Northern Europe strawberry scenario, The notifier has therefore provided a detailed refined risk assessment in August 2004 supporting the previous assumption of a worst case generic PT of 0,6: two bird species had been identified as relevant for strawberries, grey partridge (with a refinement of PT of 0,43 based on the extensive litterature data), and as a second species, skylarks: no refined PT was necessary (PT 1,0) since the PT was incorporated into the PD figures (0,21 - 0,63) considering the diet proportions of this species, This data, however, is not taken into account for the risk refinement (see introduction), As already stated, it is highly unlikely that birds will feed on the strawberry foliage and therefore RMS considers the risk overestimated in the calculations above and considers the data requirement fullfilled,

B.9.1.7 Effects on secondary poisoning

B.9.1.7.1 Risk for earthworm eating birds

For a worst case risk assessment from secondary poisoning of earthworm eating birds an estimated BCF for earthworms is calculated according to Jager (1998) with the following equation: $BCF = (0,84 + 0,01 \times K_{OW}) / (f_{OC} \times K_{OC})$, The BCF is based on earthworm fresh weight and soil dry weight, K_{OW} represents the octanol-water partition coefficient: for tolylfluanid this value is 8,000 (log P_{OW} = 3,90), "f_{OC}" represents the organic carbon content of the soil, A value of 0,02 is used in the calculations, K_{OC} is the organic carbon adsorption coefficient: for tolylfluanid this value is 2,220 mL/g (Sommer, 2000),

The estimated residues in earthworms are calculated as follows: $PEC_{worm} = PEC_{soil}(TWA) \times BCF$, The daily dietary dose is calculated by multiplying the PEC_{worm} with 1,1 (food intake factor for earthworm eating birds), The daily dietary dose for birds is compared to the bird long term NOEC and the risk is considered to be acceptable, if the TER_{lt} value is > 5, In this case, for the PEC_{worm} calculations, not the $PEC_{soil}(TWA)$ but even the maximum initial residues of tolylfluanid after the last application are used, Even with these unrealistic worst case assumptions, the TER values are clearly above the Annex VI - trigger of 5, indicating no risk from secondary poisoning for earthworm eating birds,

Table B.9.1.7-2 Risk from secondary poisoning for earthworm eating birds calculated with the maximum exposure of earthworms under worst case assumptions,

Toxicological endpoint: Bobwhite quail, reproduction **NOEC (daily dietary dose): 78,1 mg ai/kg bw/day** *)	
Apples / Pears (Northern Europe): 1,125 kg ai/ha; 7 applications / 7 d interval	
PEC_{soil}[1] [mg ai/kg d,wt,s,]	0,867
Estimated BCF[2]	1,821
PEC_{worm}[3] [mg ai/kg]	1,579
Intake factor[4]	1,11
Maximum daily residue intake[5] [mg ai/kg bw]	1,753
TER_{lt}[7]	**44,6**
Refined Risk Assessment required [6]	**No**
Apples / Pears (Southern Europe): 1,5 kg ai/ha; 3 applications / 7 d interval	
PEC_{soil}[1] [mg ai/kg d,wt,s,]	0,472
Estimated BCF[2]	1,821
PEC_{worm}[3] [mg ai/kg]	0,860
Intake factor[4]	1,11
Maximum daily residue intake[5] [mg ai/kg bw]	0,955
TER_{lt}[7]	**81,8**
Refined Risk Assessment required [6]	**No**
Grapes (Northern Europe): 1,8 kg ai/ha; 8 applications / 10 d interval	
PEC_{soil}[1] [mg ai/kg d,wt,s,]	0,561
Estimated BCF[2]	1,821
PEC_{worm}[3] [mg ai/kg]	1,022
Intake factor[4]	1,11
Maximum daily residue intake[5] [mg ai/kg bw]	1,134
TER_{lt}[7]	**68,9**
Refined Risk Assessment required [6]	**No**
Grapes (Southern Europe): 2,0 kg ai/ha; 3 applications / 8 d interval	
PEC_{soil}[1] [mg ai/kg d,wt,s,]	0,453
Estimated BCF[2]	1,821
PEC_{worm}[3] [mg ai/kg]	0,825
Intake factor[4]	1,11
Maximum daily residue intake[5] [mg ai/kg bw]	0,916
TER_{lt}[7]	**85,3**
Refined Risk Assessment required [6]	**No**
Strawberries (Northern Europe): 2,5 kg ai/ha; 3 applications / 8 d interval	
PEC_{soil}[1] [mg ai/kg d,wt,s,]	1,510
Estimated BCF[2]	1,821
PEC_{worm}[3] [mg ai/kg]	2,75
Intake factor[4]	1,11
Maximum daily residue intake[5] [mg ai/kg bw]	3,05
TER_{lt}[7]	**25,6**
Refined Risk Assessment required [6]	**No**
Strawberries (Southern Europe): 1,25 kg ai/ha; 3 applications / 7 d interval	
PEC_{soil}[1] [mg ai/kg d,wt,s,]	0,786
Estimated BCF[2]	1,821
PEC_{worm}[3] [mg ai/kg]	1,431
Intake factor[4]	1,11
Maximum daily residue intake[5] [mg ai/kg bw]	1,59
TER_{lt}[7]	**49,1**
Refined Risk Assessment required [6]	**No**

*) see Section B.9.1,4c: Long-term toxicity

[1] maximum PEC_{soil} after the last application
[2] BCF calculated as described above
[3] 'PEC_{soil}' × 'BCF', see above
[4] Intake factor according to Table B.9.1,7-1
[5] TER for a long term time scale: NOEC (daily dietary dose) / maximum daily residue intake
[6] the risk is considered acceptable, if the TER-value is >5

B.9.1.7.2 Risk for fish eating birds

In the EPCO 8 meeting RMS was asked to add which distance between application area and water body was taken into account in connection with the assessment of secondary poisoning of birds, The buffer zones are addedd after PECs in the table below,

Table B.9.1.7-3 Risk from secondary poisoning for fish eating birds calculated with the <u>maximum exposure</u> of fish under worst case assumptions,

Toxicological endpoint: Bobwhite quail, reproduction **NOEC (daily dietary dose): 78,1 mg ai/kg bw/day** *)	
Apples / Pears (Northern Europe): 1,125 kg ai/ha; 7 applications / 7 d interval	
PEC_{water}[1] [mg ai/L] (buffer zone of 10 m)	0,0443
BCF[2]	74
PEC_{fish}[3] [mg ai/kg]	3,27
Intake factor[4]	0,21
Maximum daily residue intake[5] [mg ai/kg bw]	0,69
TER_{lt}[6]	**114**
Refined Risk Assessment required [7]	**No**
Apples / Pears (Northern Europe): 1,125 kg ai/ha; 7 applications / 7 d interval	
PEC_{water}[1] [mg ai/L] (buffer zone of 5 m)	0,0746
BCF[2]	74
PEC_{fish}[3] [mg ai/kg]	5,53
Intake factor[4]	0,21
Maximum daily residue intake[5] [mg ai/kg bw]	1,16
TER_{lt}[6]	**67**
Refined Risk Assessment required [7]	**No**
Apples / Pears (Southern Europe): 1,5 kg ai/ha; 3 applications / 7 d interval	
PEC_{water}[1] [mg ai/L] (buffer zone of 5 m)	0,0421
BCF[2]	74
PEC_{fish}[3] [mg ai/kg]	3,12
Intake factor[4]	0,21
Maximum daily residue intake[5] [mg ai/kg bw]	0,65
TER_{lt}[6]	**119**
Refined Risk Assessment required [7]	**No**

Table to be continued

Table B.9.1.7-3 continued

Toxicological endpoint: Bobwhite quail, reproduction **NOEC (daily dietary dose): 78,1 mg ai/kg bw/day** *)	
Grapes (Northern Europe): 1,8 kg ai/ha; 8 applications / 10 d interval	
PEC_{water}[1] [mg ai/L] (buffer zone of 5 m)	0,0217
BCF[2]	74
PEC_{fish}[3] [mg ai/kg]	1,60
Intake factor[4]	0,21
Maximum daily residue intake[5] [mg ai/kg bw]	0,34
TER_{lt}[6]	**233**
Refined Risk Assessment required [7]	**No**
Grapes (Southern Europe): 2,0 kg ai/ha; 3 applications / 8 d interval	
PEC_{water}[1] [mg ai/L] (buffer zone of 5 m)	0,0241
BCF[2]	74
PEC_{fish}[3] [mg ai/kg]	1,78
Intake factor[4]	0,21
Maximum daily residue intake[5] [mg ai/kg bw]	0,37
TER_{lt}[6]	**209**
Refined Risk Assessment required [7]	**No**
Strawberries (Northern Europe): 2,5 kg ai/ha; 3 applications / 8 d interval	
PEC_{water}[1] [mg ai/L] (buffer zone of 5 m)	0,00475
BCF[2]	74
PEC_{fish}[3] [mg ai/kg]	0,353
Intake factor[4]	0,21
Maximum daily residue intake[5] [mg ai/kg bw]	0,074
TER_{lt}[6]	**1054**
Refined Risk Assessment required [7]	**No**
Strawberries (Southern Europe): 1,25 kg ai/ha; 3 applications / 7 d interval	
PEC_{water}[1] [mg ai/L] (buffer zone of 5 m)	0,00238
BCF[2]	74
PEC_{fish}[3] [mg ai/kg]	0,176
Intake factor[4]	0,21
Maximum daily residue intake[5] [mg ai/kg bw]	0,037
TER_{lt}[6]	**2112**
Refined Risk Assessment required [7]	**No**

*) see Long-term toxicity evaluation
[1] maximum PEC_{water}
[2] BCF (whole fish, see above)
[3] 'PEC_{water}' × 'BCF', see above
[4] Intake factor according to Table B.9.1.7-1
[5] 'PEC_{fish}' × 'intake factor'
[6] TER for a long term time scale: NOEC (daily dietary dose) / maximum daily residue intake
[7] the risk is considered acceptable, if the TER-value is >5

B.9.2 Effects on aquatic organisms

B.9.2.1 Risk assessment

The relevant endpoint of an aquatic community - outdoor microcosm study was discussed in an expert meeting (EPCO 8) and the endpoint RMS presented in the DAR (99 µg/L) was confirmed, The meeting did not decide about the precise uncertainty factor but agreed that it should be 3-5, The uncertainty factor is not so critical, because to assess the final risk to fish (which was the most sensitive species) the outdoor microcosm study with rainbow trout was more relevant leading to an NOEC of 60 µg/l, Additionally acute tests on several fish species were submitted and rainbow trout is the most sensitive species, Furthermore the acute/chronic ratio is low, Taking this information together it was warranted to lower the uncertainty factor to 5 (3 was proposed in the DAR), A lower value would only be warranted if indirect effects within the community would be covered by a study, The outcome of the change of uncertainty factor is seen in the table B.9.2.10-24,

Table B.9.2.10-24 Final TER-values for toxicity of tolylfluanid to fish based on the result of the multiple application outdoor microcosm study and the maximum PEC_{sw},

Toxicological Endpoint: Rainbow trout, chronic, 35 d, multiple application NOEC 60,0 µg ai/L						
	TER based on maximum PEC_{sw} of tolylfluanid[1]					
Width of Buffer Strip [m]	1	5	10	15	20	30
Apples / Pears (Northern Europe): 1,125 kg ai/ha; 7 applications / 7 d interval	---	0,80	1,35	2,88	5,77	15,4
Apples / Pears (Southern Europe): 1,5 kg ai/ha; 3 applications / 7 d interval	---	1,43	3,33	6,63	11,0	22,2
Grapes (Northern Europe): 1,8 kg ai/ha; 8 applications / 10 d interval	---	2,76	8,13	15,4	23,8	46,2
Grapes (Southern Europe): 2,0 kg ai/ha; 3 applications / 8 d interval	---	2,49	7,32	13,9	21,4	40,0
Strawberries (Northern Europe): 2,5 kg ai/ha; 3 applications / 8 d interval	2,60	12,6	24,8	35,9	48,0	72,3
Strawberries (Southern Europe): 1,25 kg ai/ha; 3 applications / 7 d interval	5,20	25,2	49,6	72,3	95,2	143
Refined Risk Assessment[2]	**No**					

[1] actual maximum PEC_{sw}, see Table B,8.6-2 in this Addendum

[2] **the risk is considered acceptable, if the TER-value is > 5**

TER > 5 is met with corresponding buffer zone

Conclusion

The only outcome from the change of the uncertainty factor was that Apples/Pears in Southern Europe need 15 m buffer zone (instead of 10 presented in the DAR),

PECs and TERs of DMST

Since the PECs for DMST were slightly changed due to the new open points in EPCO 7 (fate), the new TER calculations were necessary (presented in the tables below),

Table 9,2,10 Actual PEC_{sw} of DMST in surface water according to the new EXAMS calculations (Reinken, G,, Klein, S, 2004),

	Maximum PEC_{sw} of DMST (µg/L)			
Width of Buffer Strip [m]	5	10	15	20
Apples / Pears (Northern Europe): 1,125 kg ai/ha; 7 applications / 7 d interval	77,7	38,6	18,8	9,7
Apples / Pears (Southern Europe): 1,5 kg ai/ha; 3 applications / 7 d interval	40,1	17,7	9,2	5,3
Grapes (Northern Europe): 1,8 kg ai/ha; 8 applications / 10 d interval	38,8	13,0	6,8	4,2
Grapes (Southern Europe): 2,0 kg ai/ha; 3 applications / 8 d interval	27,0	9,0	4,8	3,0
Strawberries (Northern Europe): 2,5 kg ai/ha; 3 applications / 8 d interval	4,5	2,2	1,5	1,1
Strawberries (Southern Europe): 1,25 kg ai/ha; 3 applications / 7 d interval	2,3	1,1	0,77	0,63
Width of Buffer Strip[1] [m]	10/5	15/10	20/15	30/20
Apples / Pears (Northern Europe): 1,125 kg ai/ha; 7 applications / 7 d interval	38,6	18,8	9,7	

[1] buffer strip [m] for pre-blossom applications / post-blossom applications

Table B.9.2.10-9 TER_a-values for <u>acute</u> toxicity of DMST to fish based on LC_{50} of the acute study and <u>maximum</u> PEC_{sw},

Toxicological Endpoint: Rainbow trout, acute, 96 h	LC_{50} 35000 µg/L
	TER_a based on maximum PEC_{sw} of DMST[1]
Width of Buffer Strip [m]	5
Apples / Pears (Northern Europe): 1,125 kg ai/ha; 7 applications / 7 d interval	450
Apples / Pears (Southern Europe): 1,5 kg ai/ha; 3 applications / 7 d interval	873
Grapes (Northern Europe): 1,8 kg ai/ha; 8 applications / 10 d interval	902
Grapes (Southern Europe): 2,0 kg ai/ha; 3 applications / 8 d interval	1296
Strawberries (Northern Europe): 2,5 kg ai/ha; 3 applications / 8 d interval	7778
Strawberries (Southern Europe): 1,25 kg ai/ha; 3 applications / 7 d interval	15217
Refined Risk Assessment required[2]	**No**

[1] after the last application; in case of apples in Northern Europe maximum value during the application period

[2] **the risk is considered acceptable, if the TER-value is > 100**

TER > 100 is met with corresponding buffer zone

Table B.9.2.10-12 TER_a-values for <u>acute</u> toxicity of DMST to aquatic invertebrates based on the EC_{50} of the acute study and <u>maximum</u> PEC_{sw},

Toxicological Endpoint: *Daphnia magna,* acute, 48 h	EC_{50} 31000 µg/L
	TER_a based on maximum PEC_{sw} of DMST[1]
Width of Buffer Strip [m]	5
Apples / Pears (Northern Europe): 1,125 kg ai/ha; 7 applications / 7 d interval	399
Apples / Pears (Southern Europe): 1,5 kg ai/ha; 3 applications / 7 d interval	773
Grapes (Northern Europe): 1,8 kg ai/ha; 8 applications / 10 d interval	799
Grapes (Southern Europe): 2,0 kg ai/ha; 3 applications / 8 d interval	1148
Strawberries (Northern Europe): 2,5 kg ai/ha; 3 applications / 8 d interval	6889
Strawberries (Southern Europe): 1,25 kg ai/ha; 3 applications / 7 d interval	13478
Refined Risk Assessment required[2]	**No**

[1] after the last application; in case of apples in Northern Europe maximum value during the application period
[2] **the risk is considered acceptable, if the TER-value is > 100**
TER > 100 is met with corresponding buffer zone

Table B.9.2.10-14 TER_{lt}-values for toxicity of DMST to green algae based on the result of the E_rC_{50} of a toxicity study to algae and <u>maximum</u> PEC_{sw},

Toxicological Endpoint: *Pseudokirchneriella subcapitata*, 72 h, static system, DMST	E_rC_{50} 71200 µg p,m,/L
	TER_{lt} based on maximum PEC_{sw} of DMST[1]
Width of Buffer Strip [m]	5
Apples / Pears (Northern Europe): 1,125 kg ai/ha; 7 applications / 7 d interval	916
Apples / Pears (Southern Europe): 1,5 kg ai/ha; 3 applications / 7 d interval	1776
Grapes (Northern Europe): 1,8 kg ai/ha; 8 applications / 10 d interval	1835
Grapes (Southern Europe): 2,0 kg ai/ha; 3 applications / 8 d interval	2637
Strawberries (Northern Europe): 2,5 kg ai/ha; 3 applications / 8 d interval	15822
Strawberries (Southern Europe): 1,25 kg ai/ha; 3 applications / 7 d interval	30967
Refined Risk Assessment required[2]	**No**

[1] after the last application; in case of apples in Northern Europe maximum value during the application period
[2] **the risk is considered acceptable, if the TER-value is > 10**
TER > 10 is met with corresponding buffer zone

Table B.9.2.10-19 TER_{lt}-values for chronic toxicity of DMST to fish based on the NOEC of the early life stage flow-through study and maximum PEC_{sw},

Toxicological Endpoint: Rainbow trout, early life stage test, 32 d, flow-through system	NOEC ≥ 10000 µg/L
	TER_{lt} based on maximum PEC_{sw} of DMST[1]
Width of Buffer Strip [m]	5
Apples / Pears (Northern Europe): 1,125 kg ai/ha; 7 applications / 7 d interval	≥ 129
Apples / Pears (Southern Europe): 1,5 kg ai/ha; 3 applications / 7 d interval	≥ 249
Grapes (Northern Europe): 1,8 kg ai/ha; 8 applications / 10 d interval	≥ 258
Grapes (Southern Europe): 2,0 kg ai/ha; 3 applications / 8 d interval	≥ 353
Strawberries (Northern Europe): 2,5 kg ai/ha; 3 applications / 8 d interval	≥ 2222
Strawberries (Southern Europe): 1,25 kg ai/ha; 3 applications / 7 d interval	≥ 4348
Refined Risk Assessment required[2]	**No**

[1] after the last application; in case of apples in Northern Europe maximum value during the application period
[2] **the risk is considered acceptable, if the TER-value is > 10**
TER > 10 is met with corresponding buffer zone

Table B.9.2.10-20 TER_{lt}-values for chronic toxicity of DMST to aquatic invertebrates based on the result of the 21 d NOEC of a static renewal study and maximum PEC_{sw},

Toxicological Endpoint: *Daphnia magna,* chronic 21 days, static renewal system	NOEC 5600 µg/L
	TER_{lt} based on maximum PEC_{sw} of DMST[1]
Width of Buffer Strip [m]	5
Apples / Pears (Northern Europe): 1,125 kg ai/ha; 7 applications / 7 d interval	72
Apples / Pears (Southern Europe): 1,5 kg ai/ha; 3 applications / 7 d interval	140
Grapes (Northern Europe): 1,8 kg ai/ha; 8 applications / 10 d interval	144
Grapes (Southern Europe): 2,0 kg ai/ha; 3 applications / 8 d interval	207
Strawberries (Northern Europe): 2,5 kg ai/ha; 3 applications / 8 d interval	1244
Strawberries (Southern Europe): 1,25 kg ai/ha; 3 applications / 7 d interval	2435
Refined Risk Assessment required[2]	**No**

[1] after the last application; in case of apples in Northern Europe maximum value during the application period
[2] **the risk is considered acceptable, if the TER-value is > 10**
TER > 10 is met with corresponding buffer zone

Conclusions
Overall the differences to the DAR are minor ones only and they do not have any impact on the final risk assessment,

B.9.3 Effects on terrestrial vertebrates other than birds

The decision of the EPCO 8 meeting was that the long-term risk assessment for mammals should be based on a NOAEL of 9 mg/kg (reproduction) instead of the 20-day NOEC (100 mg/kg bw/day) from the teratogenity study, However, after the EPCO 8 meeting in the EPCO 9 meeting the toxicity experts proposed a NOAEL of 200 ppm (12 mg/kg bw/day) on the basis of the new 2-generation reproduction study (Young & Fickbohm 2004, see Addendum 4 and Discussion table, Tolylfluanid, doc, 16763/EPCO/BVL/04 (17,08,04)), Hence an endpoint of 12 mg/kg bw/day has been used to calculate the long-term TER values,

B.9.3.1 Exposure of mammals to tolylfluanid WG 50

For convenience, Table B.9.3-2 is repeated here, For other details of assumptions regarding the exposure of mammals see Addendum 1,

Table B.9.3-2 Assumptions regarding the assessment of risks to mammals (based on recommendations detailed in the Birds and Mammals Guidance Document (SANCO/4145/2000 final, Sept 2002)),

Generic species[1]	Body weight (bw)	Feed	Food intake (FIR) [g fresh weight per day]	FIR/bw
small herbivorous mammal (e,g,: vole)	25 g	Grasses	34,8	1,39
medium herbivorous mammal (e,g,: hare)	3000 g	Leafy crops	832	0,28

[1] according to recommendations detailed in the Birds and Mammals Guidance Document (SANCO/4145/2000 final, Sept 2002)

B.9.3.4 Long-term Risk Assessment - Tier 1

The long-term exposure assessment aims at a time frame of a few weeks, therefore residue estimates are based on arithmetic means, In addition, multiple application factors are incorporated into the assessment and time-weighted average (twa) residues are used as these better reflect long-term exposure, As usual in a first tier assessment, mammals are assumed to feed on treated food items only, The relevant calculations for long-term mammalian exposure to formulations containing tolylfluanid are summarised in Table B.9.3-4, These initial Tier 1 calculations are based on the default values for all parameters presented in Tables 5 and 7 of the Birds and Mammals Guidance Document,

Table B.9.3-4 TER calculations based on reproduction toxicity (calculations based on recommendations detailed in the Birds and Mammals Guidance Document (SANCO/4145/2000 final Sept 2002)),

Toxicological endpoint: Rat, two-generation reproduction **NOAEL (reproduction) 12 mg ai/kg bw/day**		
Generic mammal species[1]	small herbivore	medium herbivore
RUD (50 %)	[2]46	40
Apples / Pears (Northern Europe): 1,125 kg ai/ha; 7 applications / 7 d interval		
Calculated maximum initial residues in feed [mg/kg feed]	51,8	-
FIR/bw	1,39	-
MAF (multiple application factor)	2,5	-
f_{twa}	0,53	-
ETE [mg/kg bw/day]	95,4	-
TER_{lt} [3]	**0,13**	**-**
Refined Risk Assessment required	**Yes**	**na**
Apples / Pears (Southern Europe): 1,5 kg ai/ha; 3 applications / 7 d interval		
Calculated maximum initial residues in feed [mg/kg feed]	69	-
FIR/bw	1,39	-
MAF (multiple application factor)	2,0	-
f_{twa}	0,53	-
ETE [mg/kg bw/day]	101,7	-
TER_{lt} [3]	**0,12**	**-**
Refined Risk Assessment required	**Yes**	**na**
Grapes (Northern Europe): 1,8 kg ai/ha; 8 applications / 10 d interval		
Calculated maximum initial residues in feed [mg/kg feed]	82,8	-
FIR/bw	1,39	-
MAF (multiple application factor)	2,0	-
f_{twa}	0,53	-
ETE [mg/kg bw/day]	122,0	-
TER_{lt} [3]	**0,10**	**-**
Refined Risk Assessment required	**Yes**	**na**
Grapes (Southern Europe): 2,0 kg ai/ha; 3 applications / 8 d interval		
Calculated maximum initial residues in feed [mg/kg feed]	92	-
FIR/bw	1,39	-
MAF (multiple application factor)	2,0	-
f_{twa}	0,53	-
ETE [mg/kg bw/day]	135,6	-
TER_{lt} [3]	**0,09**	**-**
Refined Risk Assessment required	**Yes**	**na**

Table B.9.3-4 continued

Toxicological endpoint: Rat, two-generation reproduction **NOAEL (reproduction) 12 mg ai/kg bw/day**		
Generic mammal species[1]	small herbivore	medium herbivore
RUD (50 %)	[2]46	40
Strawberries (Northern Europe): 2,5 kg ai/ha; 3 applications / 8 d interval		
Calculated maximum initial residues in feed [mg/kg feed]	-	100
FIR/bw	-	0,28
MAF (multiple application factor)	-	2,0
f_{twa}	-	0,53
ETE [mg/kg bw/day]	-	29,7
TER_{lt} [3]	-	**0,40**
Refined Risk Assessment required	**na**	**Yes**
Strawberries (Southern Europe): 1,25 kg ai/ha; 3 applications / 7 d interval		
Calculated maximum initial residues in feed [mg/kg feed]	-	50
FIR/bw	-	0,28
MAF (multiple application factor)	-	2,0
f_{twa}	-	0,53
ETE [mg/kg bw/day]	-	14,8
TER_{lt} [3]	-	**0,81**
Refined Risk Assessment required	**na**	**Yes**

[1] see Table B.9.3-2
[2] an interception factor of 0,4 is included in the RUD value
[3] the risk is considered acceptable, if the TER-value is >5

Conclusions
The worst-case Tier 1 TER_{lt} values for mammals presented in Table B.9.3-4 are all below the Annex VI -trigger of 5, A Tier 2 refinement with more realistic exposure scenarios is therefore required,

B.9.3.5 Long-term Risk Assessment - Tier 2

According to the Tier 1 TER-values calculated in Table 9,3-4 above, a refined risk assessment for long-term exposure to mammals is required for all scenarios,

The long-term TER values have been refined in-line with current guidance using measured residues on short grass (Barfknecht, 2003), refinement of the twa and MAF values and reconsideration of the appropriate interception factors in orchards and vineyards based on the timing of applications, The details of these refinements (which are the same as in Addendum 1) are presented below :

Refinement of Mammalian Exposure in Orchards and Vineyards

In the refined risk assessment for orchards and vineyards, the dietary intake of small herbivores feeding predominately on grass is considered, In order to refine this exposure, residues data have been generated in field trials in which Tolylfluanid WG 50 was applied on three grass plots (10 x 1,5 m) at an application rate of 1,125

kg product/ha (corresponding to 562,5 g ai/ha), The three grass plots were treated at different times to catch different climatic conditions (Barfknecht, 2003), From each plot a 100 g sample of grass was harvested on days 0, 1, 2, 4, 7, 10 and 14 after treatment and analysed for residues of tolylfluanid and its metabolite DMST, From these data, the mean measured DT_{50} value for tolylfluanid on grass was determined as 2,47 days and the initial residue concentration was calculated as 19,62 mg ai/kg wet grass, based on an application rate of 562,5 g ai/ha, For the purposes of the risk assessment, the residue concentration is normalised to 34,88 mg ai/kg wet grass for an application rate of 1 kg/ha (this is the value used to calculate the refined TER_{lt} values presented in Table 9,3-5),

Since the toxicity value used in this assessment is based on a two-generation reproduction study and the measured half-life of tolylfluanid in plant material is very short (grass, mean value of 2,47 days), a more realistic longer term exposure is calculated using the 7 day -twa residues rather than the initial residue concentrations (according to the guidance in the case of repeated applications, the averaging time should not be longer than the spray interval; the shortest interval for tolylfluanid being 7 days), For tolylfluanid the twa values have been refined based on the calculation presented below, using a 7-day averaging time and the mean measured DT_{50} in grass (2,47 days):

$F_{twa} = (1-e^{-kt})/kt$
k: ln2/DT50 (velocity constant)
t: averaging time

Similarly the MAF has been recalculated using the following equation and assuming first-order kinetics:

$MAF = (1-e^{-nki})/(1-e^{-ki})$
k: ln2/DT50 (velocity constant)
n: Number of applications
i: Interval between applications (days)

For fungicides such as tolylfluanid applied in tall-growing crops such as orchards and vineyards it is assumed that a fraction of 60% of the applied spray reaches the ground, This is a default value which is applied to crop stages without leaves (FOCUS 2000), Following application in later crop stages, the interception is higher and accordingly the deposition is lower; for refinement the values given in FOCUS (2000) have been used, For early applications in orchards at a rate of 1,125 kg/ha, 50 % crop interception is assumed, Whereas in orchards and vineyards for late applications (once the foliage has developed) at rates of 1,5 to 2,0 kg/ha, 70 % crop interception is assumed, In accordance with the guidelines these interception values are included in the calculation of the TER values presented in Table 9,3-5,

Refinement of Mammalian Exposure in Strawberry Crops

In the refined risk assessment for strawberry crops, the dietary intake of medium herbivores (e,g, hares) feeding on leafy vegetation is considered, In general hares have a large home range (dependent on season) and feeding habitats are influenced by food choice and safety from predators (Wolfe & Hayden 1996), Their diet consists mainly of grasses (in winter), herbs (in summer) and arable crops e,g, cereals at early growth stages (Gurney et al, 1998), It can therefore be concluded that leafy foliage (e,g, strawberry leaves) are unlikely to be a preferred food source, Additionally, in strawberries a short grass scenario is not relevant as weed and grass cover within the treated area will be minimised by mulching, Although, mammals feeding in strawberry crops are unlikely to consume treated leaves, a risk assessment is presented in Table 9,3-5 to cover this unlikely scenario, In the long-term risk evaluation, averaging of residues is expected to occur over a period of days and so it is appropriate to use the 50^{th} percentile for residues in food items, Therefore a refined RUD of 25,0 mg/kg (Luttik, 2000) is used for residues on leaves and the f_{twa} and MAF have been refined using the same DT_{50} value and spray interval as for the orchard and vineyard exposures (see above), The refined TER values are presented in Table 9,3-5,

Mammalian exposure to tolylfluanid residues in strawberries is possible through feeding on the ripening fruits, since the diet of e,g, the fat dormouse (*Glis glis*), includes strawberries (Storch 1978), Fruit residue calculations are based on the highest measured initial residues in strawberry fruit on day 0 after the last application in field trials (7,9 mg/kg fresh weight fruit (three applications of 2,5 kg ai/ha), see Annex II, chapter 6: report No, 8253-87), Due to the direct application in strawberries, a crop interception factor is not applicable in this case, A MAF is also not applicable on the fruit as the measured residue already accounts for multiple applications, The twa for fruit residue concentrations has been refined based on a 7-day averaging time and the measured DT_{50} value on grass,

Table B.9.3-5 TER calculations based on reproduction toxicity and more realistic exposure of tolylfluanid after the last application,

Toxicological endpoint: Rat, two-generation reproduction **NOAEL (reproduction) 12 mg ai/kg bw/day**	
Generic mammal species[1]	small herbivore
Measured initial residues in feed (normalised for an application rate of 1 kg/ha) [mg/kg feed]	**grass** 34,88
Apples / Pears (Northern Europe): 1,125 kg ai/ha; 7 applications / 7 d interval	
Spray Interception Factor (FOCUS, 2000)	50% (early application)
Calculated maximum initial residues in feed [mg/kg feed]	19,62
MAF (multiple application factor)	1,16
f_{twa}	0,44
FIR/bw	1,39
ETE [mg/kg bw/day]	13,92
TER_{lt} [2]	**0,86**
Refined Risk Assessment required	**Yes**
1.1.3 Apples / Pears (Southern Europe): 1,5 kg ai/ha; 3 applications / 7 d interval	
Spray Interception Factor (FOCUS, 2000)	70% (late application)
Calculated maximum initial residues in feed [mg/kg feed]	15,69
MAF (multiple application factor)	1,16
f_{twa}	0,44
FIR/bw	1,39
ETE [mg/kg bw/day]	11,13
TER_{lt} [2]	**1,08**
Refined Risk Assessment required	**Yes**

[1] see Table B.9.3-2
[2] the risk is considered acceptable, if the TER-value is >5

Table to be continued

Table B.9.3-5 continued

Toxicological endpoint: Rat, two-generation reproduction **NOAEL (reproduction) 12 mg ai/kg bw/day**		
Generic mammal species[1]	small herbivore	
Measured initial residues in feed (normalised for an application rate of 1 kg/ha) [mg/kg feed]	**grass** 34,88	
Grapes (Northern Europe): 1,8 kg ai/ha; 8 applications / 10 d interval		
Spray Interception Factor (FOCUS, 2000)	70% (late application)	
Calculated maximum initial residues in feed [mg/kg feed]	18,83	
MAF (multiple application factor)	1,06	
f_{twa}	0,44	
FIR/bw	1,39	
ETE [mg/kg bw/day]	12,21	
TER_{lt} [2]	**0,98**	
Refined Risk Assessment required	**Yes**	
Grapes (Southern Europe): 2,0 kg ai/ha; 3 applications / 8 d interval		
Spray Interception Factor (FOCUS, 2000)	70% (late application)	
Calculated maximum initial residues in feed [mg/kg feed]	20,92	
MAF (multiple application factor)	1,12	
f_{twa}	0,44	
FIR/bw	1,39	
ETE [mg/kg bw/day]	14,33	
TER_{lt} [2]	**0,84**	
Refined Risk Assessment required	**Yes**	
Toxicological endpoint: Rat, two-generation reproduction **NOAEL (reproduction) 12 mg ai/kg bw/day**		
Generic mammal species[1]	medium herbivore	
Food type	**strawberry fruits**	**leaves**
Strawberries (Northern Europe): 2,5 kg ai/ha; 3 applications / 8 d interval		
Calculated maximum initial residues in feed [mg/kg feed]	7,90 (residue trials data)	62,5 (based on a theoretical RUD of 25 mg/kg)
MAF (multiple application factor)	na	1,12
f_{twa}	0,44	0,44
FIR/bw	0,28	0,28
ETE [mg/kg bw/day]	0,97	8,62
TER_{lt} [2]	**12,4**	**1,39**
Refined Risk Assessment required	**No**	**Yes**

[1] see Table B.9.3-2

[2] the risk is considered acceptable, if the TER-value is >5

Table B.9.3-5 continued

Strawberries (Southern Europe): 1,25 kg ai/ha; 3 applications / 7 d interval		
Calculated maximum initial residues in feed [mg/kg feed]	7,90 (residue trials data)	31,3 (based on a theoretical RUD of 25 mg/kg)
MAF (multiple application factor)	na	1,12
f_{twa}	0,44	0,44
FIR/bw	0,28	0,28
ETE [mg/kg bw/day]	0,97	4,31
TER_{lt} [3]	**12,4**	**2,78**
Refined Risk Assessment required	**No**	**Yes**

[1] see Table B.9.3-2
[3] the risk is considered acceptable, if the TER-value is >5

Conclusions
Based on this Tier 2 evaluation and considering the more realistic exposure scenarios presented in Table B.9.3-5, all but one (strawberry fruits) tier 2 TER_{lt} values are still under the Annex VI - trigger of 5, indicating unacceptable long-term risk to mammals, The notifier argues that the mentioned NOAEL is not based on compound-related clinical signs, but on effects attributable to avoidance of feed with high tolylfluanid levels (reduced food consumption and body weight), According to the notifier, instead of the NOAEL of 12 mg/kg bw/day, a NOAEL of 237 mg/kg bw/day should be used since this endpoint is only relevant for the chronic risk assessment for mammals, as demonstrated in the newly submitted risk assessment (August 2004), However, no spesific avoidance test has been provided,

Open point is still open,

B.9.3.6 Mammals – effects of secondary poisoning

In accordance with the change of the end point of the long-term risk assessment for mammals also bioaccumulation potential to mammals from secondary poisoning has been re-assessed, However, there is no impact on the outcome of the original assessment i,e, no risk from secondary poisoning via earthworms or fish,

Table B.9.3-6 Assumptions for the assessment of risks from secondary poisoning to mammals,

Generic mammal species	Body weight (bw)	Feed	Food intake [g wet weight per day]	Food intake factor
earthworm-eating mammal	10 g	earth-worms	14	1,4
fish-eating mammal	3000 g	fish	390	0,13

B.9.3.6.1 Risk assessment for earthworm eating mammals

For a worst case risk assessment from secondary poisoning of earthworm eating mammals an estimated BCF for earthworms is calculated according to Jager (1998) with the following equation: $BCF = (0{,}84 + 0{,}01 \times K_{OW}) / (f_{OC} \times K_{OC})$, The BCF is based on earthworm fresh weight and soil dry weight, K_{OW} represents the octanol-water partition coefficient: for tolylfluanid this value is 8000 (log P_{OW} = 3,90), "f_{OC}" represents the organic

carbon content of the soil, A value of 0,02 is used in the calculations, K_{OC} is the organic carbon adsorption coefficient: for tolylfluanid this value is 2220 mL/g (Sommer, 2000),

The estimated residues in earthworms are calculated as follows: $PEC_{worm} = PEC_{soil}(TWA) \times BCF$, The daily dietary dose is calculated by multiplying the PEC_{worm} with 1,4 (food intake factor for earthworm eating mammals, see Table B.9.3-6), The daily dietary dose for mammals is compared to the relevant mammal long term NOAEL (i,e, 12 mg/kg bw/day, see B.9.3.4) and the risk is considered to be acceptable, if the TER_{lt} value is > 5, In this case, for the PEC_{worm} calculations, the PEC_{soil}(TWA, 3 weeks) values are taken from the fate section of this Addendum, Table B,8.3.-4,

Table B.9.3-7 Risk from secondary poisoning for earthworm eating mammals calculated with the maximum exposure of residues in earthworms under worst case assumptions,

Toxicological endpoint: Rat, two-generation reproduction **NOAEL (reproduction) 12 mg ai/kg bw/day** *)	
Apples / Pears (Northern Europe): 1,125 kg ai/ha; 7 applications / 7 d interval	
PEC_{soil}[1] [mg ai/kg d,wt,s,]	0,379
Estimated BCF[2]	1,821
PEC_{worm}[3] [mg ai/kg]	0,690
Intake factor[4]	1,4
Maximum daily residue intake[5] [mg ai/kg bw]	0,966
TER_{lt}[7]	**12,4**
Refined Risk Assessment required [6]	**No**
Apples / Pears (Southern Europe): 1,5 kg ai/ha; 3 applications / 7 d interval	
PEC_{soil}[1] [mg ai/kg d,wt,s,]	0,222
Estimated BCF[2]	1,821
PEC_{worm}[3] [mg ai/kg]	0,404
Intake factor[4]	1,4
Maximum daily residue intake[5] [mg ai/kg bw]	0,566
TER_{lt}[7]	**21,2**
Refined Risk Assessment required [6]	**No**
Grapes (Northern Europe): 1,8 kg ai/ha; 8 applications / 10 d interval	
PEC_{soil}[1] [mg ai/kg d,wt,s,]	0,221
Estimated BCF[2]	1,821
PEC_{worm}[3] [mg ai/kg]	0,402
Intake factor[4]	1,4
Maximum daily residue intake[5] [mg ai/kg bw]	0,563
TER_{lt}[7]	**21,3**
Refined Risk Assessment required [6]	**No**
Grapes (Southern Europe): 2,0 kg ai/ha; 3 applications / 8 d interval	
PEC_{soil}[1] [mg ai/kg d,wt,s,]	0,215
Estimated BCF[2]	1,821
PEC_{worm}[3] [mg ai/kg]	0,392
Intake factor[4]	1,4
Maximum daily residue intake[5] [mg ai/kg bw]	0,548
TER_{lt}[7]	**21,9**
Refined Risk Assessment required [6]	**No**
Strawberries (Northern Europe): 2,5 kg ai/ha; 3 applications / 8 d interval	
PEC_{soil}[1] [mg ai/kg d,wt,s,]	0,718
Estimated BCF[2]	1,821
PEC_{worm}[3] [mg ai/kg]	1,31
Intake factor[4]	1,4
Maximum daily residue intake[5] [mg ai/kg bw]	1,83
TER_{lt}[7]	**6,56**
Refined Risk Assessment required [6]	**No**

Table to be continued

Table B.9.3-7 continued

Toxicological endpoint: Rat, two-generation reproduction **NOAEL (reproduction) 12 mg ai/kg bw/day** *)	
Strawberries (Southern Europe): 1,25 kg ai/ha; 3 applications / 7 d interval	
PEC_{soil} [1] [mg ai/kg d,wt,s,]	0,370
Estimated BCF[2]	1,821
PEC_{worm} [3] [mg ai/kg]	0,674
Intake factor[4]	1,4
Maximum daily residue intake[5] [mg ai/kg bw]	0,943
TER_{lt} [7]	**12,7**
Refined Risk Assessment required [6]	**No**

*) see chapter B.9.3.4: Long-term toxicity
[1] PEC_{soil} (twa, 3 weeks), see Table B,8.3-4
[2] BCF calculated as described above
[3] 'PEC_{soil}' × 'BCF', see above
[4] Intake factor according to Table B.9.3-6
[5] TER for a long term time scale: NOEC (daily dietary dose) / maximum daily residue intake
[6] the risk is considered acceptable, if the TER-value is >5

Conclusions
The TER values are clearly above the Annex VI - trigger of 5, indicating no unacceptable risk from secondary poisoning for earthworm eating mammals,

B.9.3.6.2 Risk assessment for fish eating mammals

Tolylfluanid is unstable in water (dissipation time in the water phase of a water-sediment study: DT_{50} 2,7 hours; Scholz (1997), Therefore, an exposure of fish to tolylfluanid is given only for a very short time, Since the depuration measured in the fish-BCF study is very fast (whole fish clearance time: $t_{½}$ 0,38 days), a bioaccumulation of tolylfluanid cannot be expected, Despite these facts, a risk assessment for secondary poisoning via fish is performed in the following,

For a worst case risk assessment from secondary poisoning of fish eating mammals, the steady state BCF of 74 for the whole fish, based on TRR of a flow-through study with bluegill sunfish is used, The estimated residues in fish (PEC_{fish}) are usually calculated as follows: PEC_{water}(TWA) × BCF, Nevertheless, not the PEC_{water}(TWA), but the maximum initial concentrations of tolylfluanid are used in this case for the PEC_{fish} calculations, The daily dietary dose for mammals is calculated by multiplying the PEC_{fish} with 0,13 (food intake factor for fish eating mammals), The daily dietary dose for mammals is compared to the relevant mammal long term NOEC (i,e, 100 mg/kg bw/day) and the risk is considered to be acceptable, if the TER_{lt} value is > 5,

Table B.9.3-8 Risk from secondary poisoning for fish eating mammals calculated with the maximum exposure of residues in fish under worst case assumptions,

Toxicological endpoint: Rat, two-generation **NOAEL (reproduction) 12 mg ai/kg bw/day** *)	
Apples / Pears (Northern Europe): 1,125 kg ai/ha; 7 applications / 7 d interval	
PEC_{water} [1] [mg ai/L] (buffer zone of 10 m)	0,0442
BCF[2]	74
PEC_{fish} [3] [mg ai/kg] (	3,27
Intake factor[4]	0,13
Maximum daily residue intake[5] [mg ai/kg bw]	0,43
TER_{lt} [6]	**27,9**
Refined Risk Assessment required [7]	**No**
Apples / Pears (Northern Europe): 1,125 kg ai/ha; 7 applications / 7 d interval	
PEC_{water} [1] [mg ai/L] (buffer zone of 5 m)	0,0747
BCF[2]	74
PEC_{fish} [3] [mg ai/kg]	5,53
Intake factor[4]	0,13
Maximum daily residue intake[5] [mg ai/kg bw]	0,72
TER_{lt} [6]	**16,7**
Refined Risk Assessment required [7]	**No**
Apples / Pears (Southern Europe): 1,5 kg ai/ha; 3 applications / 7 d interval	
PEC_{water} [1] [mg ai/L] (buffer zone of 5 m)	0,0421
BCF[2]	74
PEC_{fish} [3] [mg ai/kg]	3,12
Intake factor[4]	0,13
Maximum daily residue intake[5] [mg ai/kg bw]	0,41
TER_{lt} [6]	**29,3**
Refined Risk Assessment required [7]	**No**
Grapes (Northern Europe): 1,8 kg ai/ha; 8 applications / 10 d interval	
PEC_{water} [1] [mg ai/L] (buffer zone of 5 m)	0,0216
BCF[2]	74
PEC_{fish} [3] [mg ai/kg]	1,60
Intake factor[4]	0,13
Maximum daily residue intake[5] [mg ai/kg bw]	0,21
TER_{lt} [6]	**57,1**
Refined Risk Assessment required [7]	**No**

*) see chapter B.9.3.4: Long-term toxicity
[1] maximum PEC_{water}
[2] BCF (whole fish, see above)
[3] 'PEC_{water}' × 'BCF', see above
[4] Intake factor according to Table B.9.3-6
[5] 'PEC_{fish}' × 'intake factor'
[6] TER for a long term time scale: NOEC (daily dietary dose) / maximum daily residue intake
[7] the risk is considered acceptable, if the TER-value is >5

Table to be continued

Table B.9.3-8 continued

Toxicological endpoint: Rat, two-generation reproduction **NOAEL (reproduction) 12 mg ai/kg bw/day** *)	
Grapes (Southern Europe): 2,0 kg ai/ha; 3 applications / 8 d interval	
PEC_{water}[1] [mg ai/L] (buffer zone of 5 m)	0,0241
BCF[2]	74
PEC_{fish}[3] [mg ai/kg]	1,78
Intake factor[4]	0,13
Maximum daily residue intake[5] [mg ai/kg bw]	0,23
TER_{lt}[6]	**52,2**
Refined Risk Assessment required [7]	**No**
Strawberries (Northern Europe): 2,5 kg ai/ha; 3 applications / 8 d interval	
PEC_{water}[1] [mg ai/L] (buffer zone of 5 m)	0,00477
BCF[2]	74
PEC_{fish}[3] [mg ai/kg]	0,353
Intake factor[4]	0,13
Maximum daily residue intake[5] [mg ai/kg bw]	0,046
TER_{lt}[6]	**260,9**
Refined Risk Assessment required [7]	**No**
Strawberries (Southern Europe): 1,25 kg ai/ha; 3 applications / 7 d interval	
PEC_{water}[1] [mg ai/L] (buffer zone of 5 m)	0,00238
BCF[2]	74
PEC_{fish}[3] [mg ai/kg]	0,176
Intake factor[4]	0,13
Maximum daily residue intake[5] [mg ai/kg bw]	0,023
TER_{lt}[6]	**521,7**
Refined Risk Assessment required [7]	**No**

*) and [1-7] Explanations see above,

Conclusions
Even with these worst-case assumptions, the TER values are clearly above the Annex VI - trigger of 5, indicating no unacceptable risk from secondary poisoning for fish eating mammals,

B.9.6.3 Risk assessment to earthworms

Recalculated TER-values for tolylfluanid are available in the tables below as the EFSA noted that no correction factor for the LogPow exceeding 2 was taken into account in the risk assessment presented in the Addendum 5 dated 8.11.2004.

Table B.9.6.3-3. TER calculation based on acute toxicity and calculated maximum concentrations of tolylfluanid in soil after the last application.

Toxicological endpoint: earthworm acute, 14 d	**LC_{50}> 961/2 mg ai/kg d.wt.s.[1] = 480.5 mg ai/kg d.wt.s.[1]**
Apples / Pears (Northern Europe): 1.125 kg ai/ha; 7 applications / 7 d interval	
Calculated maximum concentrations in soil[2] after the last application. PEC_{soil} [mg/kg]	0.867
TER_a [3]	**> 554**
Refined Risk Assessment required[4]	**No**
Apples / Pears (Southern Europe): 1.5 kg ai/ha; 3 applications / 7 d interval	
Calculated maximum concentrations in soil[2] after the last application. PEC_{soil} [mg/kg]	0.472
TER_a [3]	**> 1018**
Refined Risk Assessment required[4]	**No**
Toxicological endpoint: earthworm acute, 14 d	**LC_{50} > 961 mg ai/kg d.wt.s.[1]**
Grapes (Northern Europe): 1.8 kg ai/ha; 8 applications / 10 d interval	
Calculated maximum concentrations in soil[2] after the last application. PEC_{soil} [mg/kg]	0.561
TER_a [3]	**> 857**
Refined Risk Assessment required[4]	**No**
Grapes (Southern Europe): 2.0 kg ai/ha; 3 applications / 8 d interval	
Calculated maximum concentrations in soil[2] after the last application. PEC_{soil} [mg/kg]	0.453
TER_a [3]	**> 1061**
Refined Risk Assessment required[4]	**No**
Strawberries (Northern Europe): 2.5 kg ai/ha; 3 applications / 8 d interval	
Calculated maximum concentrations in soil[2] after the last application. PEC_{soil} [mg/kg]	1.510
TER_a [3]	**> 318**
Refined Risk Assessment required[4]	**No**
Strawberries (Southern Europe): 1.25 kg ai/ha; 3 applications / 7 d interval	
Calculated maximum concentrations in soil[2] after the last application. PEC_{soil} [mg/kg]	0.786
TER_a [3]	**> 611**
Refined Risk Assessment required[4]	**No**

[1] d.wt.s.: dry weight soil
[2] maximum PEC_{soil} of tolylfluanid after the last application
[3] Toxicity Exposure Ratio based on LC_{50} and PEC_{soil}
[4] the risk is considered acceptable, if the TER-value is >10

Table B.9.6.3-4 TER calculation based on acute toxicity and calculated maximum concentrations of DMST in soil after the last application,

Toxicological endpoint: earthworm acute, 14 d	**LC_{50} > 100 mg/kg d,wt,s,[1]**
Apples / Pears (Northern Europe): 1,125 kg ai/ha; 7 applications / 7 d interval	
Calculated maximum concentrations in soil[2] after the last application, PEC_{soil} [mg/kg]	0,523
TER_a [3]	**> 191**
Refined Risk Assessment required[4]	**No**
Apples / Pears (Southern Europe): 1,5 kg ai/ha; 3 applications / 7 d interval	
Calculated maximum concentrations in soil[2] after the last application, PEC_{soil} [mg/kg]	0,336
TER_a [3]	**> 298**
Refined Risk Assessment required[4]	**No**
Grapes (Northern Europe): 1,8 kg ai/ha; 8 applications / 10 d interval	
Calculated maximum concentrations in soil[2] after the last application, PEC_{soil} [mg/kg]	0,342
TER_a [3]	**> 292**
Refined Risk Assessment required[4]	**No**
Grapes (Southern Europe): 2,0 kg ai/ha; 3 applications / 8 d interval	
Calculated maximum concentrations in soil[2] after the last application, PEC_{soil} [mg/kg]	0,315
TER_a [3]	**> 317**
Refined Risk Assessment required[4]	**No**
Strawberries (Northern Europe): 2,5 kg ai/ha; 3 applications / 8 d interval	
Calculated maximum concentrations in soil[2] after the last application, PEC_{soil} [mg/kg]	1,050
TER_a [3]	**> 95**
Refined Risk Assessment required[4]	**No**
Strawberries (Southern Europe): 1,25 kg ai/ha; 3 applications / 7 d interval	
Calculated maximum concentrations in soil[2] after the last application, PEC_{soil} [mg/kg]	0,561
TER_a [3]	**> 178**
Refined Risk Assessment required[4]	**No**

[1] d,wt,s,: dry weight soil
[2] maximum PEC_{soil} of DMST after the last application
[3] Toxicity Exposure Ratio based on NOEC(14d) (instead of the LC_{50} (14d)) and maximum PEC_{soil}
[4] the risk is considered acceptable, if the TER-value is >10

Table B.9.6.3-5 TER calculation based on chronic toxicity and calculated maximum concentrations of tolylfluanid in soil after the last application.

Toxicological endpoint: earthworm reproduction, 56 d **NOEC** **corresponding to**	**24/2 kg ai/ha = 12 kg ai/ha 16 mg ai/kg soil**[1]
Apples / Pears (Northern Europe): 1.125 kg ai/ha; 7 applications / 7 d interval	
Actual concentrations in soil[2] after the last application. PEC_{soil} [mg/kg]	0.867
TER_{lt}[3]	**18**
Refined Risk Assessment required[4]	**No**
Apples / Pears (Southern Europe): 1.5 kg ai/ha; 3 applications / 7 d interval	
Actual concentrations in soil[2] after the last application. PEC_{soil} [mg/kg]	0.472
TER_{lt}[3]	**34**
Refined Risk Assessment required[4]	**No**
Grapes (Northern Europe): 1.8 kg ai/ha; 8 applications / 10 d interval	
Actual concentrations in soil[2] after the last application. PEC_{soil} [mg/kg]	0.561
TER_{lt}[3]	**29**
Refined Risk Assessment required[4]	**No**
Grapes (Southern Europe): 2.0 kg ai/ha; 3 applications / 8 d interval	
Actual concentrations in soil[2] after the last application. PEC_{soil} [mg/kg]	0.453
TER_{lt}[3]	**35**
Refined Risk Assessment required[4]	**No**
Strawberries (Northern Europe): 2.5 kg ai/ha; 3 applications / 8 d interval	
Actual concentrations in soil[2] after the last application. PEC_{soil} [mg/kg]	1.510
TER_{lt}[3]	**11**
Refined Risk Assessment required[4]	**No**
Strawberries (Southern Europe): 1.25 kg ai/ha; 3 applications / 7 d interval	
Actual concentrations in soil[2] after the last application. PEC_{soil} [mg/kg]	0.786
TER_{lt}[3]	**20**
Refined Risk Assessment required[4]	**No**

[1] application rate × factor 1.33
[2] actual PEC_{soil} of tolylfluanid after the last application
[3] Toxicity Exposure Ratio based on NOEC and PEC_{soil}
[4] the risk is considered acceptable, if the TER-value is >5

Conclusions

The TER-values did not breach the Annex VI trigger value even if the correction factor of 2 has been taken into account indicating a low acute risk to earthworms for the representative uses evaluated.

Table B.9.6.3-6 TER calculation based on chronic toxicity and calculated maximum concentrations of DMST in soil after the last application,

Toxicological endpoint: earthworm reproduction, 56 d	**NOEC 100 mg/kg d,wt,s,**[1]
Apples / Pears (Northern Europe): 1,125 kg ai/ha; 7 applications / 7 d interval	
Calculated maximum concentrations in soil[2] after the last application, PEC_{soil} [mg/kg]	0,523
TER_{lt} [3]	**191**
Refined Risk Assessment required[4]	**No**
Apples / Pears (Southern Europe): 1,5 kg ai/ha; 3 applications / 7 d interval	
Calculated maximum concentrations in soil[2] after the last application, PEC_{soil} [mg/kg]	0,336
TER_{lt} [3]	**298**
Refined Risk Assessment required[4]	**No**
Grapes (Northern Europe): 1,8 kg ai/ha; 8 applications / 10 d interval	
Calculated maximum concentrations in soil[2] after the last application, PEC_{soil} [mg/kg]	0,342
TER_{lt} [3]	**292**
Refined Risk Assessment required[4]	**No**
Grapes (Southern Europe): 2,0 kg ai/ha; 3 applications / 8 d interval	
Calculated maximum concentrations in soil[2] after the last application, PEC_{soil} [mg/kg]	0,315
TER_{lt} [3]	**317**
Refined Risk Assessment required[4]	**No**
Strawberries (Northern Europe): 2,5 kg ai/ha; 3 applications / 8 d interval	
Calculated maximum concentrations in soil[2] after the last application, PEC_{soil} [mg/kg]	1,050
TER_{lt} [3]	**95**
Refined Risk Assessment required[4]	**No**
Strawberries (Southern Europe): 1,25 kg ai/ha; 3 applications / 7 d interval	
Calculated maximum concentrations in soil[2] after the last application, PEC_{soil} [mg/kg]	0,561
TER_{lt} [3]	**178**
Refined Risk Assessment required[4]	**No**

[1] d,wt,s,: dry weight soil
[2] maximum PEC_{soil} of DMST after last the application
[3] Toxicity Exposure Ratio based on NOEC(56d) and maximum PEC_{soil}
[4] the risk is considered acceptable, if the TER-value is >5

Conclusions
Overall, the differences between the former calculated and presented TERs and the new ones are marginal, They do have any influence on the final ecotoxicological risk assessment for earthworm for tolylfluanid and its major metabolite DMST,

B.9.7 Effects on other soil non-target macro-organisms (Annex IIA 8.6; Annex IIIA 10.5.)

Risk assessment

To address potential concerns regarding other soil non-target macro-organisms, a study with DMST and *Folsomia candida* was performed because of the instability of tolylfluanid. The NOEC determined for DMST for the reproduction of *Folsomia candida* was 250 mg/kg d.wt.s. The exposure calculation (PEC_{soil}) is similar to used in the Addendum 5 in the risk assessment to earthworms (Table B.9.6.3-6.). The TER´s calculated for Collembola are presented in Table B.9.7-2. They do not indicate any unacceptable risk for soil non-target macro-organisms.

Table B.9.7-2 TER calculation on Collembola based on chronic toxicity and calculated maximum concentrations of DMST in soil after the last application.

Toxicological endpoint: Folsomia reproduction , 28 d	**NOEC 250 mg/kg d.wt.s.**[1]
Apples / Pears (Northern Europe): 1.125 kg ai/ha; 7 applications / 7 d interval	
Calculated maximum concentrations in soil[2] after the last application. PEC_{soil} [mg/kg]	0.523
TER_{lt}[3]	**478**
Refined Risk Assessment required[4]	**No**
Apples / Pears (Southern Europe): 1.5 kg ai/ha; 3 applications / 7 d interval	
Calculated maximum concentrations in soil[2] after the last application. PEC_{soil} [mg/kg]	0.336
TER_{lt}[3]	**744**
Refined Risk Assessment required[4]	**No**
Grapes (Northern Europe): 1.8 kg ai/ha; 8 applications / 10 d interval	
Calculated maximum concentrations in soil[2] after the last application. PEC_{soil} [mg/kg]	0.342
TER_{lt}[3]	**731**
Refined Risk Assessment required[4]	**No**
Grapes (Southern Europe): 2.0 kg ai/ha; 3 applications / 8 d interval	
Calculated maximum concentrations in soil[2] after the last application. PEC_{soil} [mg/kg]	0.315
TER_{lt}[3]	**794**
Refined Risk Assessment required[4]	**No**
Strawberries (Northern Europe): 2.5 kg ai/ha; 3 applications / 8 d interval	
Calculated maximum concentrations in soil[2] after the last application. PEC_{soil} [mg/kg]	1.050
TER_{lt}[3]	**238**
Refined Risk Assessment required[4]	**No**
Strawberries (Southern Europe): 1.25 kg ai/ha; 3 applications / 7 d interval	
Calculated maximum concentrations in soil[2] after the last application. PEC_{soil} [mg/kg]	0.561
TER_{lt}[3]	**446**
Refined Risk Assessment required[4]	**No**

[1] d.wt.s.: dry weight soil
[2] maximum PEC_{soil} of DMST after the last application
[3] Toxicity Exposure Ratio based on NOEC(28d) and maximum PEC_{soil}
[4] the risk is considered acceptable, if the TER-value is >5

B.9.11 References relied on

Author (s)	Section reference number	Year	Title **Source** (where different from company) **Company name, Report No,, Date, GLP status** (where relevant)**, published or not**	Data protect, claimed	Owner
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Corrections to Addendum 5, Volume 3, B.7 Residue data

February 2005

- **Table B.7.16-1a Summary of Theoretical Maximum Daily Intake (TMDI) calculations of tolylfluanid residues (tolylfluanid + DMST)**

Guideline used	TMDI (mg/person/day)	TMDI (mg/kg bw/day)	% of ADI
UK consumer exposure model (1999) a) adult - 70.1 kg bw	~~1.4066~~ 1.7530	~~0.0201~~ 0.0250	~~20.1~~ 25.0

- **Table B.7.16-1b**

Summary of International Estimated Daily Intake (IEDI) calculations of tolylfluanid residues (tolylfluanid and DMST for all supported crops, additionally 4-hydroxymethyl-DMST-glucoside and 2-hydroxyphenyl-DMST-glucoside for grapes expressed as tolylfluanid)

Guideline used	IEDI (mg/person/day)	IEDI (mg/kg bw/day)	% of ADI
UK consumer exposure model (1999) a) adult - 70.1 kg bw	~~0.3137~~ 0.6621	~~0.0045~~ 0.0094	~~4.5~~ 9.4

- **Table B.7.16-8, p. 149**

Calculation of the Theoretical Maximum Daily Intake ulation of the Theoretical Maximum Daily Intake (TMDI) of tolylfluanid residues according to PSD Guideline (1999)

ADI: 0.1 mg/kg bw/day
Food consumption levels: UK diet (intake of lettuce and ~~pome fruit~~ wine grapes 97.5th %ile, intake of all other food: mean)
Body weight (bw): 70.1 kg – adult

Pome fruit	3	~~0.1703~~	~~0.51090~~	~~0.00729~~	~~7.3~~
Pome fruit (corrected)		0.0321	0.09630	0.00137	1.4
Grapes, wine	5	0.0007	0.00350	0.000050	0.0
Grapes, wine (corrected)		0.1529	0.782	0.01116	11.2
Total			~~**1.4066**~~	~~**0.0201**~~	~~**20.1**~~
Total (corrected)			1.7530	0.0250	25.0

- **Table B.7. 16-9, p. 150**

Calculation of the International Estimated Daily Intake (IEDI) of tolylfluanid residues according to PSD Guideline (1999)

ADI: 0.1 mg/kg bw/day
Food consumption levels: UK diet (intake of lettuce and ~~pome fruit~~ grape wine: 97.5th %ile, intake of all other food: mean)
Body weight (bw): 70.1 kg – adult

Commodity	STMR/ STMR-P (mg/kg)	Food consumption (kg/person/day)	TMDI (mg/person/day)	TMDI (mg/kg bw/day)	% of ADI
Pome fruit	0.86	~~0.1703~~	~~0.146458~~	~~0.002089~~	~~2.1~~
		0.0321	0.0276	0.00039	0.4
Grapes wine*	3.07	0.0007	~~0.00215~~	~~0.00003~~	~~1.8~~
		0.1529	0.4694	0.00670	6.7
Total			**~~0.3137~~**	**~~0.0045~~**	**~~4.5~~**
Total			**0.6621**	**0.0094**	**9.4**

L/C = Low % consuming
*Mean transfer factor 1.3 (wine)
**Mean transfer factor 0.005 (beer)