EUROPEAN COMMISSION
HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL

Directorate C - Scientific Opinions
C2 - Management of scientific committees ; scientific co-operation and networks

SCIENTIFIC COMMITTEE ON PLANTS **SCP/FENTHION-BIS/002 Final**

OPINION OF THE SCIENTIFIC COMMITTEE ON PLANTS ON ADDITIONAL QUESTIONS FROM THE COMMISSION CONCERNING THE EVALUATION OF FENTHION IN THE CONTEXT OF COUNCIL DIRECTIVE 91/414/EEC

(Opinion adopted by the Scientific Committee on Plants, 17 December 2002)

A. TITLE

OPINION OF THE SCIENTIFIC COMMITTEE ON PLANTS ON ADDITIONAL QUESTIONS FROM THE COMMISSION CONCERNING THE EVALUATION OF FENTHION IN THE CONTEXT OF COUNCIL DIRECTIVE 91/414/EEC
(Opinion adopted by the Scientific Committee on Plants on 17 December 2002)

B. TERMS OF REFERENCE

The Scientific Committee on Plants (SCP) is requested to respond to the following questions in the context of the Commission's work on the implementation of Council Directive 91/414/EEC concerning the placing of plant protection products on the market.

1. Can the Committee comment on the relevance of the new data and arguments related to the risk assessment to birds presented by the Rapporteur Member State regarding the intended uses (bait use in citrus and olive orchards, 75 g a.s./ha)

2. Considering the intended uses (bait uses in citrus and olive groves) does the Committee consider that the additional toxicological information alters its previous assessment?

C. OPINION OF THE COMMITTEE

Opinion on question 1:

Despite a change of application method and the provision of new studies, the Committee concludes that risks to birds from the proposed uses of fenthion are very uncertain. Therefore, the concerns raised in the Committee's previous opinion remain unresolved.

The Committee considered the assessment by the rapporteur Member State (RMS), correspondence between the RMS, Sweden and Denmark, and new field and laboratory studies provided by the notifier. The Committee identified a number of serious limitations in the field studies and took account of these in its evaluation.

The Committee would expect the proposed use of fenthion in olive orchards as bait applications between mid-July and the end of August to present less risk than the full cover application, which has been shown to cause substantial avian mortality. The available data are compatible with this. However, due to the fact that there was only one available field study for bait applications of fenthion to olives, and due to a number of other limitations in this study, the magnitude of the reduction in residues, exposure and effects compared to the full cover application is very uncertain.

Based on the available data, there is substantial uncertainty regarding the levels and frequency of avian mortality that would be caused by bait applications of fenthion to olives. Also, it is uncertain whether breeding birds would be present

during these applications and, if so, whether reproductive effects would be expected.

The data provided for olives cannot be used to assess risk in citrus because residues and exposure would be different.

The Committee notes that some of the birds exposed to the use of fenthion in olive and citrus orchards may be migrants from more northerly parts of Europe.

In order to improve the risk assessment for birds in olives or citrus, the Committee would recommend monitoring residues and mortality in a larger number of field sites. The Committee has identified a number of factors to consider in the design of such studies. Depending on the potential for exposure of breeding birds, further studies of reproductive toxicity might be desirable to complete the risk assessment.

Opinion on question 2:

The additional toxicological information does not alter the Committee's previous opinion regarding the mutagenic properties of fenthion. Available new data indicate that fenthion is unlikely to pose a risk of delayed neurotoxicity in humans.

A. TITLE

REPORT OF THE SCIENTIFIC COMMITTEE ON PLANTS ON ADDITIONAL QUESTIONS FROM THE COMMISSION CONCERNING THE EVALUATION OF FENTHION IN THE CONTEXT OF COUNCIL DIRECTIVE 91/414/EEC

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C. BACKGROUND

Fenthion is an existing active substance (a.s.) in the context of Directive 91/414/EEC[1]. A draft evaluation report (monograph) has been prepared by the rapporteur Member State (RMS, Greece) on the basis of a dossier presented by the notifier (Bayer A.G.).

In its original opinion (1998[2]), the SCP identified several issues of concern regarding the risk to bees and non-target arthropods, the risk to aquatic organisms and the risk to birds.

Additional data were subsequently submitted to the RMS and evaluated (see addendum to the Monograph dated 16 Feb 2001 and Sept. 2001 for non-target organisms).

The RMS carried out a risk assessment for aquatic organisms (p 55 to 58 of addendum to DAR April 2001) and concluded that "the bait application of fenthion to olives and citrus at a rate of 75 g a.s./ha is safe for the aquatic environment". The risk assessment did not raise specific comment from MS and unless it wishes to do so, the Committee is not specifically requested to comment on the risk assessment for aquatic organisms.

As regards the risk to birds, the SCP concluded in its original opinion that:

- a semi-field study to determine acute risk under field conditions was missing,
- no data on reproductive effects at sublethal doses were available,

[1] OJ N° L 230, 19. 8.1991, P. 1.
[2] http://europa.eu.int/comm/food/fs/sc/scp/out22_en.html

- the issue of secondary poisoning had not been addressed.

Three new studies to address the SCP's concerns have been submitted and assessed by the RMS (in the addendum dated 16 February 2001, pages 51 to 54).

Denmark (in letter dated 12 June 2001) and Sweden (in letter dated 31 May 2001) commented on the risk assessment for birds and raised several issues to which the RMS responded (2 documents one undated, one letter dated 29 June).

The Committee is now asked to comment on the risk assessment of the RMS concerning birds and on the issues raised by Sweden (including the response from the RMS to Swedish comments).

Regarding toxicology, the Committee concluded in its original assessment that, "*health concerns of fenthion relate to its acute toxicity. Therefore long-term effects do not play a crucial role in the overall risk assessment. Delayed neurotoxicity deserves further investigation which may modify the current risk assessment*". The Committee identified some shortcomings in the mutagenicity data package as well, but was not concerned about the mutagenicity profile of fenthion (carcinogenicity study and 2 generation reproductive study were all negative).

Additional data were submitted and evaluated by the RMS. The Committee is now requested to consider whether the additional information alters its previous opinion.

In order to prepare its opinion the Scientific Committee on Plants had access the documents listed below.

<u>Source documents made available to the Committee</u>:

1. Fenthion: Terms of Reference, submitted by DG Health and Consumer Protection, 25 January 2002 (SCP/FENTHION-BIS/001).

2. Fenthion-bis: Evaluation table, Doc. 5631/VI/97 rev. 7 (02.04.2001), submitted by DG Health and Consumer Protection, 25 January 2002 (SCP/FENTHION-BIS/003).

3. Fenthion: Danish comments on the risk assessment to birds (12 June 2001), submitted by DG Health and Consumer Protection, 25 January 2002 (SCP/FENTHION-BIS/004).

4. Fenthion: Swedish comments on the risk assessment to birds (31 May 2001), submitted by DG Health and Consumer Protection, 25 January 2002 (SCP/FENTHION-BIS/005).

5. Fenthion: Response from RMS to Danish and Swedish comments (birds risk assessment), submitted by DG Health and Consumer Protection, 25 January 2002 (SCP/FENTHION-BIS/006).

6. Fenthion: Additional response from RMS to Swedish comments of 20 April 2001 (birds risk assessment) (30 May 2001), submitted by DG Health and Consumer Protection, 25 January 2002 (SCP/FENTHION-BIS/007).

7. Fenthion: Additional response from RMS to Swedish comments of 31 May 2001 (birds risk assessment) (29 June 2001), submitted by DG Health and Consumer Protection, 25 January 2002 (SCP/FENTHION-BIS/008).

8. Fenthion: Belgium comments (I) on the genotoxic potential, submitted by DG Health and Consumer Protection, 25 January 2002 (SCP/FENTHION-BIS/009).

9. Fenthion: Belgium comments (II) on the genotoxic potential, submitted by DG Health and Consumer Protection, 25 January 2002 (SCP/FENTHION-BIS/010).

10. Fenthion: Belgium comments (III) on the mutagenicity profile (27 September 2001), submitted by DG Health and Consumer Protection, 25 January 2002 (SCP/FENTHION-BIS/011).

11. Fenthion: France comments (I) on the genotoxic potential (26 June 2001), submitted by DG Health and Consumer Protection, 25 January 2002 (SCP/FENTHION-BIS/012).

12. Fenthion: France comments (II) on the genotoxic potential (14 May 2001), submitted by DG Health and Consumer Protection, 25 January 2002 (SCP/FENTHION-BIS/013).

13. Fenthion: Swedish comments on the mammalian toxicological aspects (18 April 2001), submitted by DG Health and Consumer Protection, 25 January 2002 (SCP/FENTHION-BIS/014).

14. Fenthion: U.K. comments on the mutagenic potential (18 April 2001), submitted by DG Health and Consumer Protection, 25 January 2002 (SCP/FENTHION-BIS/015).

15. Fenthion: RMS response to French comments of 14 May 2001 (genotoxicity) (11 June 2001), submitted by DG Health and Consumer Protection, 25 January 2002 (SCP/FENTHION-BIS/016).

16. Fenthion: RMS responses to U.K comments of 18 April 2001 (genotoxicity) and to Swedish comments of 18 April 2001 (mammalian tox. aspects), submitted by DG Health and Consumer Protection, 25 January 2002 (SCP/FENTHION/017).

17. Fenthion: draft review report, 7754/VI/97 and 2 appendices- revision 7, submitted by DG Health and Consumer Protection.

18. Addenda to the Draft Assessment Report, submitted by DG Health and Consumer Protection:
    - Addendum of 16 February 2001
    - Addendum of March 2001
    - Addendum on ARfD
    - Addendum of April 2001 (residues)
    - Addendum of April 2001 (ecotoxicology)
    - Addendum on UDS evaluation
    - Addendum of September 2001

19. Andrews, P. and Popp, A. (2000) Study for the delayed neurotoxicity following acute oral administration to hens, Report. no. 29668/MO-00-004721, submitted by Bayer AG, 29 May 2002, 82 pp.

20. Barfknecht, R. (2000) Fenthion techn. ai: Effects of a subacute, 7-day dietary exposure on japanese quail including effects on reproduction and behaviour (modified reproduction study), Report. no. BAR/REP004 MO-00-015528, submitted by Bayer AG, 29 April 2002, 112 pp.

21. Barfknecht, R. (2000) Fenthion EC 500: Field monitoring of birds after a bait spray spot application in greek olive-yards, Report. no. BAR/FS004 MO-00-015525, submitted by Bayer AG, 29 April 2002, 25 pp.

22. Barfknecht, R. and Wolf, C. (1998) Effects of fenthion on the bird community in a sweet cherry cultivation, Report. no. BAR/FS001 MO-01-007729, submitted by Bayer AG, 29 April 2002, 58 pp.

23. Barfknecht, R. (2000) Fenthion EC 500: Field monitoring of birds in greek olive-yards after a full cover application during the breeding season, Report.no. BAR/FS002 MO-00-010436, submitted by Bayer AG, 29 April 2002, 52 pp.

24. Herbold, B. (1997) Dominant lethal test on the male mouse, Report. no. 26620/MO-01-014429, submitted by Bayer AG, 29 May 2002, 37 pp.

25. Herbold, B. (2001) Micronucleus-test on the male mouse, Report. no. 30631/MO-01-000750, submitted by Bayer AG, 28 May 2002, 43 pp.

26. Herbold, B. (2002) Chromosome aberration assay in bone marrow cells of the mouse with E 1752, Report. no. R8121/MO-02-003927, submitted by Bayer AG, 29 May 2002, 28 pp.

27. Marzin, (2001) Summary of the genotoxicity of fenthion, Report. no. -, submitted by Bayer AG, 28 May 2002, 4 pp.

28. Rosenberg, K. and Leicht, W. (2001) Fenthion: Studies submitted after the completion of the monograph, Report. no. -, submitted by Bayer AG, 29 May 2002, 12 pp.

D. SCIENTIFIC BACKGROUND ON WHICH THE OPINION IS BASED

I. Question 1

Can the Committee comment on the relevance of the new data and arguments related to the risk assessment to birds presented by the Rapporteur Member State regarding the intended uses (bait use in citrus and olive orchards, 75 g a.s./ha)

<u>Opinion:</u>

Despite a change of application method and the provision of new studies, the Committee concludes that risks to birds from the proposed uses of fenthion are very

uncertain. Therefore, the concerns raised in the Committee's previous opinion remain unresolved.

The Committee considered the assessment by the rapporteur Member State (RMS), correspondence between the RMS, Sweden and Denmark, and new field and laboratory studies provided by the notifier. The Committee identified a number of serious limitations in the field studies and took account of these in its evaluation.

The Committee would expect the proposed use of fenthion in olive orchards as bait applications between mid-July and the end of August to present less risk than the full cover application, which has been shown to cause substantial avian mortality. The available data are compatible with this. However, due to the fact that there was only one available field study for bait applications of fenthion to olives, and due to a number of other limitations in this study, the magnitude of the reduction in residues, exposure and effects compared to the full cover application is very uncertain.

Based on the available data, there is substantial uncertainty regarding the levels and frequency of avian mortality that would be caused by bait applications of fenthion to olives. Also, it is uncertain whether breeding birds would be present during these applications and, if so, whether reproductive effects would be expected.

The data provided for olives cannot be used to assess risk in citrus because residues and exposure would be different.

The Committee notes that some of the birds exposed to the use of fenthion in olive and citrus orchards may be migrants from more northerly parts of Europe.

In order to improve the risk assessment for birds in olives or citrus, the Committee would recommend monitoring residues and mortality in a larger number of field sites. The Committee has identified a number of factors to consider in the design of such studies. Depending on the potential for exposure of breeding birds, further studies of reproductive toxicity might be desirable to complete the risk assessment.

Scientific background on which the opinion is based

I.1 Description of intended uses

The Committee was asked to consider applications of fenthion to olives and citrus. In the Evaluation Table[3] provided to the Committee, the uses currently proposed for these crops are described as follows:

- "In citrus 10% of the canopy of each tree is treated by a single shot of a spray pistol….thus only 10% of the total area is treated."
- "In olives 20% of the canopy of every second tree is treated by a very short spray of a spray pistol….(thus) in the case of olives only 10% of the total area is treated."

[3] SANCO Doc. 5631/VI/91/rev. 7 (02.04.2001), page 34.

The Committee interprets these statements to mean that applications are made from the ground. The Committee's assessment therefore relates specifically to ground applications done in the manner quoted above. The Committee notes that treating 10% of the total area by other methods (especially aerial applications) would present significantly higher risks.

I.2 Description and discussion of new data

I.2.1. Field studies

The notifier provided two field studies on olives. No study was provided for use in citrus. In addition, they provided a third study of fenthion in cherries, which was not of direct relevance to the proposed use of fenthion as bait in olive orchards, but contained important information of general relevance to the estimation of residues in insects.

1) Effects of fenthion on the bird community in a sweet cherry cultivation (1998) Report no. BAR/FS 001, pp. 58,
2) Fenthion EC 500: field monitoring of birds in Greek olive-yards after a full cover application during the breeding season (Report no. BAR/FS 002, pp. 52), and
3) Fenthion EC 500: field monitoring of birds after a bait spray spot application in Greek olive yards (Report no. BAR/FS 004, pp 250).

Study 1 (cherries) took place in the second half of June 1998 in Germany. Fenthion was sprayed on every cherry tree up to the point of run-off, resulting in application rates of 0.47 and 0.62 kg fenthion per hectare. Insects were sampled for residue analysis by beating trees over plastic sheets in the shape of funnels ('pounding funnels'). The results shown in Table 1 (see page 10, below) indicate lower residues on insects collected by pitfall trapping compared with 'pounding funnels'. Furthermore, insects captured in pounding funnels – which are likely to be more representative of those taken by small insectivorous birds - contained consistently higher residues than insects from pitfall traps. This is consistent with the Committee's comments concerning the estimation of residues on insects, expressed in its Opinion on the draft guidance document on risk assessment for birds and mammals (2002[4]).

Study 2 (olives, full cover application) was carried out in 1999 on 2 test plots in Greece each approximately 1 hectare in size. The distance between rows was 5.7 to 6.4 meters and distance between trees 4.7 to 6.1 meters, and there were no untreated control plots. Full cover applications were carried out in the second week of May. Each olive tree was individually sprayed from all directions from a low distance, trees were sprayed up to the point of run-off with a concentration of fenthion of 0.1% resulting in an application concentration of 995 to 1116 g a.s. per hectare. Carcass searching was carried out on both sites before spraying and daily on days 0-5 (one site from 0-7 days). The efficiency of carcass searching was estimated by placing dummy carcasses in the test plot, but details of the method are not reported. In each area, a bird census was carried out (early morning, duration 30 min) 8 to 9 times before application and 5 to 6 times after application. Leaf dwelling insects were collected, using pounding funnels once before treatment and on days 1, 3, 5 and 10, in order to quantify the exposure for insect eating birds. In addition leaves were collected.

[4] http://europa.eu.int/comm/food/fs/sc/scp/out125_ppp_en.pdf

A total of 19 bird carcasses were found after treatment (6 Great Tits, 11 Chaffinches, 1 Goldfinch and 1 unidentified songbird; many were fledglings), 1 on day 0, 3 on day 1, 5 on day 2, 3 on day 3, 6 on day 4 and 1 several days old on day 7 (7 on site 1 and 12 on site 2). Seven carcasses were fresh and intact and could be analysed for the activity of AchE in their brain tissue. The activity was 60 to 90% lower, which indicates life-threatening intoxication (Ludke et al. 1975). The efficiency of the carcass searching team was 92 to 100%.
17 birds[5] showing behavioural effects were observed; the first effects were seen 14 minutes after application and the last effects were detected 3 days after application. The species most frequently found to be affected were Great Tits and Chaffinches, but also one Sardinian Warbler, one Greenfinch and one Goldfinch showed symptoms. 8 of these birds were found sitting on the ground, showing signs of paralysis.

The abundance and activity of birds in the orchards was high (5 to 7 breeding species). The treatment had no negative effects on the number of species or the number of territories inside the orchards. On the contrary, the numbers seemed to increase, but it is not known whether the numbers were higher or lower than normal for the time of year, because a control is lacking.

Results concerning residues on insects are summarised in Table 1. Leaves collected at sites 1 and 2 before application contained mean residue values of 5.6 and 2.0 mg a.s./kg leaves, immediately after application values of 31.6 and 38.8 mg a.s./kg leaves were measured, the maximum values amounted to 36.6 on day 4 and 41.2 on day 5, respectively at site 1 and site 2. On day 10 values of 22 mg/a.s./kg leaves were measured at site 1 and 27.8 mg a.s./kg leaves were measured at site 2.

Study 3 (olives, bait application) was carried out in 2000 in Greece, on the same test plots that were used in study 2 in the previous year. Approximately every third olive tree[6] was treated (site 1 on the 7th of July and site 2 on the 14th of July) with approximately 0.3 L solution "sprayed in the centre of each tree". The Committee notes that the application method in this study does not correspond precisely to the currently proposed use for olives, which prescribes application to "20% of the canopy of every second tree" (see section 1.1 above). The volumes actually applied were 0.325 L solution per tree on site 1 and 0.354 L per tree on site 2. Due to differing densities of trees the actual application rates were estimated to be 85.9 g a.s./ha on site 1 and 62.1 g a.s./ha on site 2 (compared to 75 g a.s./ha stated in the question to the Committee).

Searches were made for carcasses at both sites before spraying and daily on days 0-5. The efficiency of carcass searching was estimated using dummy carcasses. Observation of exposed birds (numbers and behavioural aspects) started on day 0 at the time of application and ended two hours after application. On days 1, 3 and 5 observations were made for 2.5 hours in the morning starting at 6 o'clock. Leaf dwelling insects were collected at each site, once before treatment and on days 1, 3 and 5 using pounding funnels. Leaves were collected prior to application and on days 0, 2 and 5.

[5] The study does not give a decisive answer whether the birds seen behaviourally affected were the same individuals as were subsequently found dead.

[6] Eight-eight of 257 trees were treated (one tree in every 2.9) at site 1, and 59 of 167 trees (one in every 2.8) at site 2.

No carcasses were found and the efficiency of searching was estimated to be 83 to 85%. No effects of fenthion were observed on the behaviour of the birds during the trial. The abundance of birds was lower than in the previous year's study.

Results concerning residues on insects are summarised in Table 1. Leaves collected before application in sites 1 and 2 contained mean residue values of 2.16-5.43 and 0.02-0.14 mg a.s./kg leaves, respectively. The maximum values measured after treatment amounted to 111.6 mg a.s./kg leaves in site 1 and 68.5 mg a.s./kg leaves in site 2. The maximum concentrations measured on untreated leaves were 15.16 mg a.s./kg in site 1 and 0.59 mg a.s./kg in site 2.

Table 1. Summary of data on residues in/on insects (mg/kg insect, wet weight) in Studies 1 to 3, caught in pounding funnels or in pit-falls.

Number of study	Before treatment	After 1 day	After 3 days	After 5 days	After 10 days	Collecting Method
Study 1 site 1	0.01	8.71	15.16	6.56		Pounding funnels
Study 1 site 2	0.2	9.71	10.63	6.01		Pounding funnels
Study 1 site 3	0.11	12.23	5.13	6.27		Pounding funnels
Study 1 site 1	0.0	6.01	1.31	0.14		Pit-falls
Study 1 site 2	0.0	4.45	0.24	0.91		Pit-falls
Study 1 site 3	0.02	0.05	0.14	0.05		Pit-falls
Study 2 site 1	0.16	14.95	11.97	10.01	3.72	Pounding funnels
Study 2 site 2	0.07	11.67	8.6	5.4	3.9	Pounding funnels
Study 3 site 1	1.59	4.12	3.76	1.63		Pounding funnels
Study 3 site 2	0.19	0.48	0.92	0.55		Pounding funnels

Note that the residue levels found on insects collected by pounding funnels after 1 day at site 1 of study 3 are greater than would be estimated according to the method of Kenaga (1973) and EPPO (1994).

I.2.2. Laboratory study

In the first conclusion in its opinion of 1998, the Committee suggested that a reproductive study including sublethal concentrations be conducted. Instead, a laboratory study with a shorter exposure period was submitted:

> Barfknecht, R. (2000) Fenthion techn. ai: Effects of a subacute, 7-day dietary exposure on japanese quail including effects on reproduction and behaviour (modified reproduction study), BAR/REP004 MO-00-015528, 112 pp.

In this study Japanese quails were exposed to technical fenthion in the diet for 7 days at 0, 10, 33 and 100 mg fenthion/kg food, and effects on reproduction and behaviour were monitored (modified reproduction study). Dose-related effects were observed on parental birds. These effects were only slight at the lowest test concentration, diarrhoea but no effect on reproductive performance and no reduced food intake. The birds in the other two treatment groups (33 and 100 mg a.s./kg) were partly heavily affected: severe body weight reduction, reduced food intake, uncoordinated movement, premature deaths. At the 33 mg a.s./kg exposure level the food intake was reduced by 7 % on day 1, 35% on day 2 and approximately 60% on days 3 to 7, and 3 birds died on day 7 of the exposure period. At the 100 mg a.s./kg exposure level the food intake was reduced by 52% on day 1 and approximately by 90% on days 2 to 7; 2 birds died on day 4 of the exposure period and 1 on day 5. At the same levels there were also changes in reproductive parameters: reduced egg laying rate and egg weight, increased cracking rate, reduced hatching rate and reduced hatchling weight. In the second and subsequent weeks following exposure the reproductive success of the treated birds showed no differences compared to the control. The NOEC was 10 mg a.s./kg food.

I.3 Uncertainties affecting risk assessment for bait applications

1) No field studies are available for use of fenthion in citrus.

Risks from the use of fenthion in citrus are very uncertain, because exposure and risk in citrus orchards may differ from olive orchards and no field studies are available from citrus.

2) The application method in the field studies for olives differed from the proposed use.

The proposed use for olives involves bait application to 20% of the canopy of every second tree, whereas in the most relevant field study approximately 0.3L of solution was sprayed ‘in the centre’ of approximately every third tree. The field study is therefore not strictly representative of the proposed use, and the relevance of this to the results is uncertain.

3) The number of sites in the field study of bait applications to olives is low.

Because only two sites were used in the field study of bait applications in olives, the results are subject to very high levels of sampling uncertainty. The potential for variation between sites is illustrated by the large difference between residue levels measured at the two sites in study 3 (Table 1). This difference, together with the high sampling uncertainty, means that an upper confidence limit for average residue levels would be very high (see Appendix 1).

No adverse effects were detected at the two study sites, but due to the small sample it is not possible to estimate with any certainty what proportion of sites would show effects in normal use. First, residues at other sites may be higher, as already mentioned. Second, other factors affecting exposure (for example, the species and numbers of birds present, the extent to which they use the treated areas and the effect of varying tree density on application rate per hectare) will also be different at other sites. Therefore, the range of effects to be expected from the proposed use is very uncertain. The Committee considers this point more quantitatively in Appendix 1.

4) There is insufficient information to judge whether the study sites for olives should be considered as worst-case.

The applicant stated that “Both study sites were chosen on behalf of their high bird diversities and abundance”. This implies that the diversity and abundance of birds around the study site were above average for this type of olive orchard. However, this may not be a good indicator of the proportion of their diet that birds were deriving from these orchards. For example, it is possible that the high bird densities were caused by the attractive habitats that were stated to be adjacent to the orchard, in which case it is also plausible that the birds obtained most of their food in those habitats and not in the orchards. Furthermore, the presence of study personnel in the orchards for substantial periods of intensive study (as is indicated by the study report) may have disturbed the birds and caused them to spend less time in the orchard than normal.

5) There is insufficient information on residue sampling methods.
Details are lacking of where within the sites the residue samples were collected, and how they were combined for analysis. This is needed to show the extent of variation within and between sites. For the bait application, it would be desirable to report residues separately for insects collected from treated and untreated trees.

6) Uncertainty due to significant residues in pre-treatment samples.
The interpretation of the study of bait application in olives is greatly complicated by the presence of significant residues on insects (1.59 mg/kg) and leaves (max 5.43 mg/kg) at site 1 prior to the bait application of fenthion. These residues could have resulted either from (a) previous treatments of the same site in earlier years (the Committee considers it unlikely that fenthion would be so persistent), (b) previous treatments of the same site in the same year, (c) drift from treatments in neighbouring areas. No information is available regarding any previous or neighbouring treatments. The residues measured after treatment on this site are presumably inflated by the pre-existing residues, but on the other hand, this will also happen sometimes in normal use. Another complication is that prior treatment or contamination presumably reduces insect density and consequently bird foraging activity. It is therefore possible that study 3 site 1 could either over-estimate or under-estimate avian exposure.

7) The efficiency of the methods for detecting mortality is uncertain.
The field studies included searches for carcasses in adjacent habitats, and also estimation of search efficiency. However, the information provided is not sufficient to evaluate the chance of false negatives, i.e. whether mortality might have occurred but not been detected. The reasons for this are: (a) the extent of the area searched outside the orchard is not stated, (b) it is not stated whether search efficiency was measured in the orchard, in the adjacent habitat, or both, (c) it is unclear whether dummy carcasses were placed in ways that simulate the behaviour of intoxicated birds, which are likely to hide deep in any available vegetation (Fryday et al. 1996), (d) it is uncertain how far birds might travel after being exposed before they became incapacitated. Therefore there is significant uncertainty regarding the true levels of mortality in the field studies.

8) The efficiency of the methods for detecting behavioural effects is uncertain
Responding to comments by Sweden, the RMS placed special emphasis on the lack of observed behavioural effects in the field study of bait application in olives. In the study of full cover applications to olives 19 carcases were found but only 17 birds were observed with abnormal behaviour. However, the true frequencies of mortalities and behavioural effects are unknown, so the proportion of each which were detected is uncertain. Consequently, lack of observed behavioural effects in the bait application study does not necessarily imply that mortality was absent.

9) The exposure of birds during breeding is uncertain

The Committee understands that it is proposed to apply the compound only between the second half of July and the end of August The Committee is uncertain to what extent this would prevent exposure of breeding birds, as no data have been provided on the actual timing of breeding (including late or repeat clutches) by birds in olive or citrus orchards.

If breeding birds were likely to be exposed, then the new 7 day toxicity study (showing reproductive and parental effects at 33 mg/kg diet but not at 10 mg/kg) may not be adequate to assess the risk of reproductive effects. This is because (a) field studies demonstrate the potential for residues to persist at non-negligible levels over periods greater than 7 days, and (b) the NOEC might be lower than 10 mg/kg for exposures greater than 7 days.

In order to provide some indication of the impact of these many uncertainties on the potential risk, the Committee explored their effect on acute risks in some approximate quantitative assessments. The results are presented in Appendix 1. While not definitive, the analyses suggested that the true level of mortality following bait applications is very uncertain and could vary widely between sites. At one extreme, it is possible that mortality would occur at very few or even no sites. At the other extreme, mortality could occur on many sites and might reach high levels on some sites. Because of the high level of uncertainty concerning residues and exposure, neither extreme can be ruled out. The lack of recorded mortality in the field studies for bait applications to olives is not inconsistent with these conclusions, because of the potential effects of (a) site to site variation in residues and exposure, (b) disturbance and (c) limitations in searching methods (as discussed above).

The Committee is aware that full-cover applications of fenthion have been used in olive orchards for many years. If there were reliable information on the frequency of bird mortality associated with these applications, this should be taken into account. However, it should be borne in mind that poisoning incidents are likely to be under-reported. Intoxicated birds are likely to seek cover (Fryday et al. 1996). Birds receiving sublethal dermal exposures may die of starvation, as shown in experiments with fenthion (Pope & Ward, 1972), and are also likely to seek cover before they succumb. The likelihood of casualties being found and reported is further reduced if the species involved are small in body size and therefore inconspicuous (Baillie et al. 1995), and if there is no well-publicised system for reporting and investigation of incidents.

The Committee notes that olive and citrus orchards may be used not only by local bird populations, but also by other species passing on migration from more northerly parts of Europe (da Prato and da Prato (1983), Cuadrado et al. (1989) and Cuadrado (1992)). Exposure to fenthion in olive and citrus orchards may therefore have wider significance than to the local resident bird population. Although present for shorter periods, migrating birds might experience more severe acute exposures if the energy demands of migration lead to greater or more rapid food intakes.

I.4 Conclusions

The Committee concludes that the risks to birds from the proposed uses of fenthion are very uncertain. Therefore, despite the proposed change of application method and the provision of new studies, the concerns raised in the Committee’s previous opinion remain unresolved.

The Committee would expect that the bait application presents less risk than the full cover application, and the available data are consistent with this. In principle, bait applications should generally use less pesticide although the degree of reduction achieved will vary in practice. However, the available data are not sufficient to estimate with confidence the size of reductions that would be expected in normal use.

Based on the available data, there is substantial uncertainty regarding the levels and frequency of avian mortality that would be caused by bait applications of fenthion to olives. Also, it is uncertain whether breeding birds would be present during these applications and, if so, whether reproductive effects would be expected.

The data provided for olives cannot be used to assess risk in citrus because residues and exposure would be different.

The Committee notes that some of the birds exposed to the use of fenthion in olive and citrus orchards may be migrants from more northerly parts of Europe.
In order to improve the risk assessment for birds in olives or citrus, the Committee would recommend monitoring residues and mortality in a larger number of field sites. If such studies are conducted, they should be designed to take account of the methodological issues and uncertainties identified by the Committee. Depending on the potential for exposure of breeding birds, further studies of reproductive toxicity might be desirable to complete the risk assessment.

II. Question 2

Considering the intended uses (bait uses in citrus and olive groves) does the Committee consider that the additional toxicological information alters its previous assessment?

<u>Opinion:</u>
The additional toxicological information does not alter the Committee's previous opinion regarding the mutagenic properties of fenthion. Available new data indicate that fenthion is unlikely to pose a risk of delayed neurotoxicity in humans.

<u>Scientific background on which the opinion is based:</u>

Fenthion has been classified as class III mutagen according to the EC classification system on the basis of an incomplete data set on mutagenicity and the presence of equivocally positive mutagenicity results in some tests. The data available at that time provided support for that classification of fenthion, but the data were not definitive. Note was taken of the results from carcinogenicity studies (although somewhat dated and with some methodological limitations), a two-generation reproduction study and a teratogenicity study. None of these studies indicated any adverse response to fenthion exposure characterised by their specific objectives. Nevertheless, more experiments were requested in order to clarify the uncertainties in the mutagenicity portion of the fenthion database.

Recent studies are *in vivo* studies for UDS in rat liver, micronuclei in mouse bone marrow cells and chromosomal aberrations in mouse bone marrow cells. Only the last was not available when this Committee previously reviewed questions regarding the toxicology of fenthion (1998). The micronucleus test showed a significant increase in micronuclei, whereas there were no significant increases in the endpoints investigated in the other two tests. The chromosomal aberration test was conducted using i.p. dose levels considerably in excess of the high dose in the micronucleus induction test. There appears to have been no provision in the scoring of damage for changes in chromosomal number (other than ploidy).

Mutagenicity testing is carried out to provide evidence on whether or not a substance is able to interfere with the cellular genome by inducing mutations. It provides qualitative results in vitro and in vivo that enable the classification of a substance as a strong mutagen, moderate or weak mutagen or non-mutagen. Mutagens can be DNA-reactive or not DNA-reactive. The current default assumption is that DNA-reactive mutagens have no threshold and consequently no NOAEL can be established for such substances. On the contrary, available data support the experience of concentrations or doses below which there is either no activity or no significant activity for substances that are not DNA-reactive. For these, it is possible to establish an NOAEL. This Committee has previously adopted this differential approach in the evaluation of aneugenic substances, specifically, the methyl benzimidazole carbamates carbendazim, benomyl and thiophanate-methyl.

When these principles are applied to fenthion, it is clear that evidence has been provided that is supportive of a mode of action that does not involve DNA-reactivity. The weight of evidence from mammalian cell culture experiments supports a lack of clastogenic activity for fenthion and this is borne out by the absence of a clastogenic effect in bone marrow cells of mice treated *in vivo*. Therefore the small increases in the proportion of micronucleated cells in two of three mouse bone marrow cell assays could have been due to aneuploidy rather than chromosomal breakage. Therefore the Committee confirms its previous opinion that the mutagenic properties of fenthion are not of concern for human risk assessment of this active substance.

Delayed polyneuropathy

A study on delayed neurotoxicity (Organophosphorous induced polyneuropathy, OPIDP) in hens was performed with fenthion. Hens received a single oral dose of fenthion (40 mg/kg bw), corresponding to about 1.5 times the unprotected LD_{50}. Animals were treated with atropine (50 mg/kg bw twice a day for 2 days). Despite antidote treatment, hens displayed typical acute cholinergic signs, which lasted 1-2 days with complete recovery within 1 week. This correlated with a 80-90% brain acetylcholinesterase (AChE) inhibition. Five (out of 20) hens died of cholinergic toxicity. No inhibition of neuropathy target esterase (NTE, the target of OPIDP) was found 24 or 48 hours after dosing. None of the treated animals developed clinical or morphological signs of OPIDP, whereas positive controls (tri-orthocresylphosphate treated hens) did develop OPIDP within two weeks. The Committee noted that the dose of fenthion was only 1.5 the unprotected LD_{50} and that humans are likely to survive comparatively higher doses than hens because of a more effective treatment that humans can receive (see opinion on fosthiazate). However, the lack of NTE inhibition at the tested dose and the fact that OPIDP was never reported in humans after severe poisoning with fenthion are reassuring in this respect. Therefore, it is concluded that fenthion is unlikely to cause OPIDP in humans.

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Acknowledgements

The Committee wishes to acknowledge the contribution of the working groups that prepared the initial draft opinion.

Toxicology: Prof. Maroni (Chairman) and Committee Members: Dr. Delcour-Firquet, Prof. Leszkowicz, Dr. Meyer, Dr Moretto, Prof. Petzinger, Prof. Savolainen, Prof. Silva Fernandes, Dr. Speijers, and invited experts Dr. Fait, Prof. Galli, Dr. McGregor.

Environment:
Prof. Hardy (Chairman) and Committee members: Mr. Koepp, Prof. Leszkowicz, Prof. Papadoupoulou-Mourkidou, Prof. Silva Fernandes, invited experts: Dr. Boesten, Dr. Carter, Prof. Forbes, Dr. Hart and Dr. Luttik.

Appendix – approximate risk assessments for bait applications of fenthion to olive orchards

I. Introduction

In order to provide some indication of the impact of the many uncertainties identified in the Opinion on Question 1, the Committee explored their effect in two types of approximate risk assessment.

II. Assessment using acute toxicity/exposure ratios (TERs)

The Committee calculated expected acute exposures using the measured residues from each of the field study sites, assuming that the food intake of small insectivorous birds (10 gram body weight) is approximately 10.3 g wet weight per day (estimated by the method presented in the Guidance Document on Risk Assessment for Birds and Mammals (2002[7]).

The exposure estimates were combined with data on toxicity to provide acute TERs for each sampling date in each field site. Luttik and Aldenberg (1995) summarised 45 LD50 values for 22 species (range 1 to 40 mg a.s./kg BW). 15 to 19 species have one or more LD50s that is lower than the predicted environmental concentration (PEC). With data on this many species, the usual practice of using the lowest LD50 and applying an uncertainty factor of 10 would result in a very conservative estimate of toxicity. The Committee therefore chose to calculate the TERs using the HD5 (5^{th} percentile of sensitivity distribution) of 1.37 mg/kg body weight as cited by Luttik and Aldenberg (1995). The results are presented in Table 1. Many of the TERs are below 1, indicating a potentially high risk of acute mortality.

Table 1: Acute TER values (HD_5 /$PEC_{insects}$) for fenthion based on measured residues in field studies 2 and 3 in olive orchards. Because between-species variation in toxicity has been accounted for by using the HD5 (see text), these TERs might be compared to a trigger of 1 rather than 10. Values below 1 (bold in Table) indicate a potentially high risk.

Number of study	Before treatment	After 1 day	After 3 days	After 5 days	After 10 days	Collecting Method
Study 2 site 1	8.8	**0.1**	**0.1**	**0.1**	**0.4**	Pounding funnels
Study 2 site 2	20.2	**0.1**	**0.2**	**0.3**	**0.4**	Pounding funnels
Study 3 site 1	**0.9**	**0.3**	**0.4**	**0.9**		Pounding funnels
Study 3 site 2	7.4	2.9	1.5	2.6		Pounding funnels

One third to one half of the residues at site 1 in study 3 appear to have resulted from earlier or contamination from neighbouring treatments. If this amount were excluded from the calculation (which may or may not be appropriate, depending on whether such residues would occur in normal use) then the TER on the day after treatment would be about 0.6 instead of 0.3.

7 http://europa.eu.int/comm/food/fs/sc/scp/out125_ppp_en.pdf

III. Influence of uncertainties on expected mortality

The Committee explored the influence of 2 sources of uncertainty.

1. *Variation in residues.* The residues found on insects from the two sites in Study 3 differed by nearly a factor of 10. This indicates that the range of variation between sites could be very large, although part of this was probably due to contamination from earlier or neighbouring treatments. If it is assumed that between-site variation in residues follows a lognormal distribution[8] (as is often assumed – e.g. Luttik, 2001) then based on 2 measurements the 90% confidence interval for the average day 1 residue would be 0.0001 – 1246 mg/kg. If it is assumed that the distribution is normal rather than lognormal the 90% confidence interval becomes –9 mg/kg (which is clearly impossible) to 14 mg/kg. If the pre-treatment residue of 1.59 mg/kg is deducted from the day 1 residue at site 1, the 90% confidence interval based on normal distribution becomes –5 to 8 mg/kg. The Committee does not regard any of these confidence intervals as accurate, but they demonstrate that having data from only 2 sites implies great uncertainty about the true average. In particular, it is likely that residues following bait application may sometimes exceed 10 mg/kg and reach levels similar to those observed in the full-cover study. Therefore the Committee explored the level of mortality expected given the measured levels of residues found in the full cover study as well as both sites in the bait application study (see below).

2. *Variation in use of orchards by birds.* There is no available information on the percentage of their diet that birds obtain in olive orchards. Therefore the Committee explored the effect of varying this percentage between 0 and 100%.

The potential importance of these uncertainties is illustrated in Figures 1 and 2, which show how the proportion of bird species suffering exposures exceeding their LD50 depends on the proportion of diet obtained in the treated crop (PT) and the concentration of fenthion on insects (C).

[8] No details were provided on the locations from which insects were sampled. The Committee has assumed in its assessment that each reported residue determination represents a pooled sample collected from a representative selection of locations within the orchard. If this is not the case (e.g. if insects were sampled only from treated trees) then a more complex assessment would be necessary, taking account of (a) variation in residues within the orchard, and (b) proportions of diet obtained by birds in locations with different residues (e.g. treated and untreated trees).

Figure 1. Relationship between proportions of birds' diets obtained in treated orchards (PT) and the proportion of bird species expected to ingest a dose exceeding their LD50, based on residues of 14.95 mg/kg, as measured at site 1 in study 2 (full cover application in olives)[9].

[9] Exposure was calculated assuming body weight of 10 g and daily food consumption of 10.33 g insects (wet weight). Proportion of species affected was calculated by comparing the exposure for each value of PT and C with the fitted cumulative distribution of LD50s of fenthion for 22 bird species obtained from the database described by Luttik and Aldenberg (1997). It is assumed that the distribution of toxicities for the tested species is representative of that for species exposed in olive orchards. Statistical tests show that the data closely follow a lognormal distribution. The ETX computer program was used to fit the cumulative distribution and confidence limits shown in Figures 1 and 2.

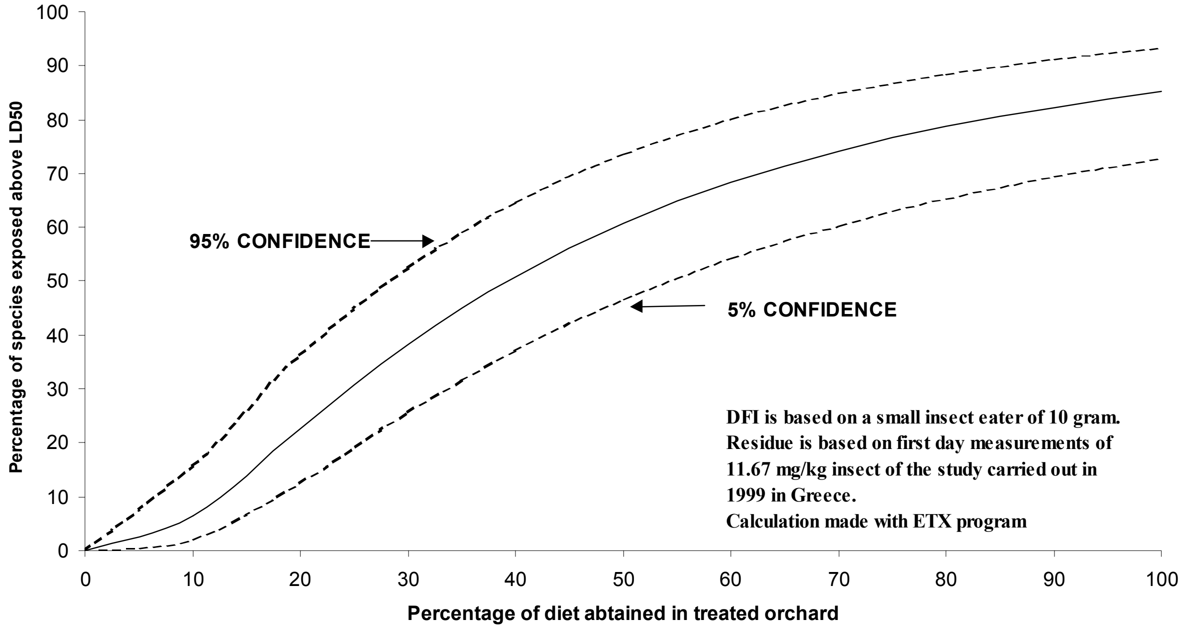
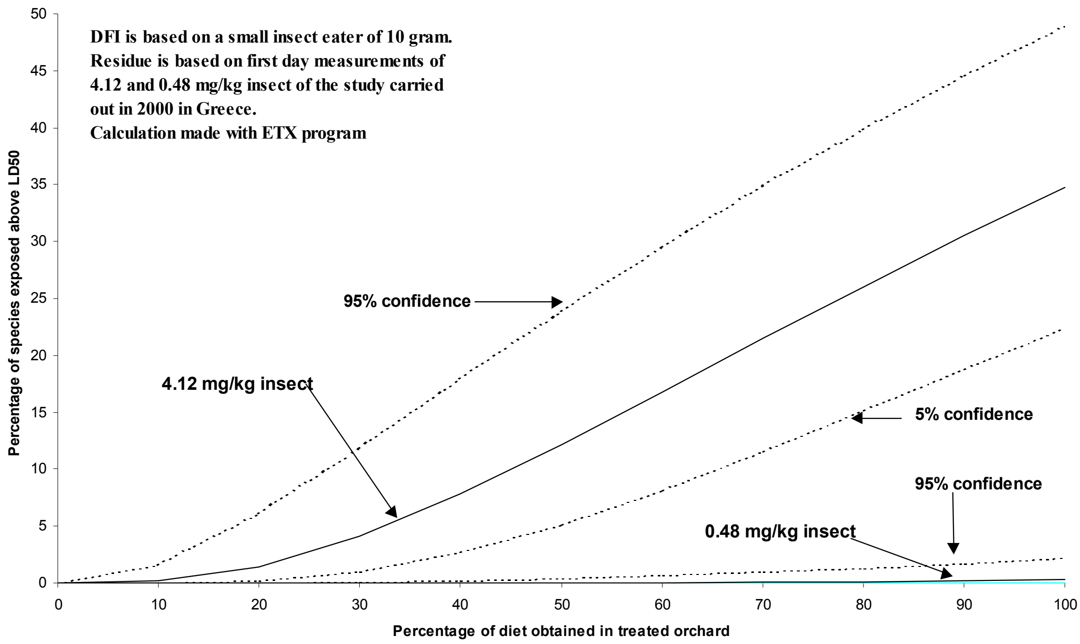

100
90
80
70
60
50
40
30
20
10
0
Percentage of species exposed above LD50
95% CONFIDENCE
5% CONFIDENCE
DFI is based on a small insect eater of 10 gram.
Residue is based on first day measurements of
11.67 mg/kg insect of the study carried out in
1999 in Greece.
Calculation made with ETX program
0
10
20
30
40
50
60
70
80
90
100
Percentage of diet abtained in treated orchard

Figure 2. Relationship between proportions of birds' diets obtained in treated orchards (PT) and the proportion of bird species expected to ingest a dose exceeding their LD50, based on residues of 0.48 and 4.12 mg/kg, as measured in study 3 (bait application in olives). See also footnote to Figure 1.



As already mentioned, there is no data on the proportion of their diet which birds obtain from olive orchards, nor what proportion of the diet will be contaminated by fenthion following bait application. However, it is within the bounds of possibility that on some sites the proportion could be very high. On such sites, the results to the right-hand sides of Figures 1 and 2 would apply.

The residue level assumed in Figure 1 is the measured value reported on the day after treatment in site 1 following full-cover application to olives (Study 2). However, as discussed above, residues on insects following bait applications are very uncertain and may sometimes exceed 10 mg/kg. In such cases, the expected mortalities for bait applications would be closer to those shown in Figure 1 than Figure 2.

The results in Figures 1 and 2 are consistent with the Committee's qualitative assessment (see main Opinion), that the true level of mortality following bait applications is very uncertain and could vary widely between sites. At one extreme, it is possible that mortality would be expected at very few or even no sites. At the other extreme, Figures 1 and 2 show that mortality could occur on many sites and might reach high levels (e.g. over 50% of species exceeding their LD50) on some sites. Because of the high level of uncertainty, neither extreme can be ruled out.

IV. Additional considerations

The Committee's calculations above assumed that birds do not selectively avoid insects contaminated with fenthion. However, in the 7-day dietary study with quail, intake of food treated with fenthion was reduced progressively over time for treatment levels of 33 and 100 mg/kg. Also, grackles were shown to avoid commercial turkey starter food treated with fenthion in a study by Grue (1982): in a 5-day exposure with no untreated food available, birds offered only food treated at 25 mg/kg food showed a 30% reduction in food intake over 5 days, compared to controls. All birds exposed at this level survived, but 67-100% mortality occurred at all higher treatment levels, from 30 to 400 mg/kg. It is likely that an avoidance response of this type would reduce exposure and risk to some degree, but the laboratory results for quail and grackles cannot be extrapolated with any certainty to the bird species, foods and concentrations that are relevant in olive orchards.

Furthermore, the results of field study 2 (full cover application to olives) shows that avoidance failed to prevent mortality at concentrations below 25 mg/kg - this could be caused by various mechanisms, including one or more of the following: (a) birds feeding quickly may ingest a lethal dose before the avoidance response operates, (b) the avoidance response may be slower or less effective in inexperienced birds (most of the mortality in study 2 involved fledglings), (c) the mortality may in fact have been caused by dermal rather than dietary exposure. There is evidence that at least in some circumstances, non-dietary routes of exposure are of similar or greater importance compared to dietary ones (e.g. Driver et al. 1991, Mineau 2001).