Opinion of the Scientific Committee on Plants concerning the non-inclusion of Fenthion in annex I of Directive 91/414/EEC (Opinion expressed by the SCP on 2 October 1998)

Terms of Reference

The draft Commission Directive proposing non-inclusion of fenthion in Annex 1 to Directive 91/414/EEC had been referred to the Scientific Committee on Plants for consultation with the following questions to the Committee:

1. Is it appropriate (and possible) to establish an ADI and an AOEL using the toxicological end point of mutagenicity? If so, which safety factor should be used to ensure human and animal safety?

2. If not, is it correct to use the endpoint of plasma cholinesterase inhibition to establish the ADI and AOEL and which safety factor should be used to ensure human and animal safety?

Background

The draft Commission Directive for the postponement of the inclusion of fenthion in Annex I to Directive 91/414/EEC concerning the placing of plant protection products on the market was submitted to the Committee for opinion. The Committee had been supplied with a dossier provided by Bayer AG, the monograph prepared by the Greek authorities, the results of the 'Peer Review' involving several Member States and the draft Commission Directive.

Fenthion is an oganophosphorous insecticide. It is cholinesterase inhibitor acting by contact, inhalation and as a stomach poison in larvae and adults. It is active against a broad spectrum of insect pests (Lepidoptera, Diptera, Coleoptera, Hemiptera).

The draft Directive proposed that authorisations on all crops other than olives and citrus should be withdrawn and that only bait applications, involving the partial treatment of a small proportion of trees, would continue to be authorised for a period of approximately three years. These authorisations would then be reviewed in the light of the submission and the evaluation of confirmatory data.

Opinion of the Committee

Following a review of the data submitted, the Committee decided to deal additionally with the following aspects:

1. Acceptability of the dietary risk assessment.

2. Relevance of the neurotoxicity and ocular toxicity to man.

3. Environmental aspects relating to degradation and mobility in soil, effects on bees and other non-target arthropods, aquatic organisms and birds.

Questions addressed to the Committee

1. Is it appropriate (and possible) to establish an ADI and an AOEL using the toxicological end point of mutagenicity? If so, which safety factor should be used to ensure human and animal safety?

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. It is not possible to derive accurately quantitative data as to the threshold of action and, consequently, it is not possible to use the test results to set a NOEL for such an effect.

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 currently available data provides some support that fenthion should be treated as a class III mutagen but the data is not definitive. There is an urgent need to repeat the bone marrow micronucleus assay to confirm the positive result observed at one time point.

The Committee was aware that the registrant has conducted two further mutagenicity studies **in vivo**. The results of one of the two tests (not available to the Committee) have been reported to be negative; the results of the other study are not yet available. Depending on these new results, the classification of fenthion concerning mutagenicity will have to be re-examined.

It is worth mentioning that the carcinogenicity study results (although somewhat dated and with some methodological limitations) are negative and no reproductive effects were noted in a two generation reproductive study and in a teratogenicity study.

2. If not, is it correct to use the endpoint of plasma cholinesterase inhibition to establish the ADI and AOEL and which safety factor should be used to ensure human and animal safety?

Fenthion is an organophosphorus insecticide that produces cholinesterase inhibition. There are two forms of cholinesterase enzymes in the human body: acetylcholinesterase (ACHE) and plasma cholinesterases (PCHE). The former enzyme is present in the nervous tissue, where it causes the cleavage of acetylcholine into choline and acetic acid, thereby terminating the cholinergic transmission at the synaptic terminals. The latter are a heterogeneous group of enzymes which are produced by the liver and released into plasma and are not considered to have any physiological function in the organism. Apart from the nervous tissue, ACHE is also present in erythrocytes where it has no known physiological function.

When a cholinesterase inhibitor enters into the body, it induces inhibition of the cholinesterase enzymes in blood and tissues. The level of ACHE inhibition in red blood cells mirrors, to some extent, the inhibition of ACHE in the nervous tissue and, accordingly, is used as an indicator (and a predictor) of the level of poisoning. Depending on the particular compounds and their mode of intake, symptoms and clinical signs of poisoning generally occur at an inhibition level in blood greater than 60-80% of the baseline value. PCHE is also inhibited, but this inhibition **per se** is not responsible for a clinical cholinergic syndrome or

any other adverse effects, as this enzyme has no relevant biological functions. Thus PCHE inhibition is considered to be an indicator of exposure (and intake) and not an indicator of effects. The inhibiting potency of a given compound against cholinesterase can be measured **in vitro** and is usually expressed as I_{50}, that is the concentration at which 50% of the enzyme activity is inhibited. Several organophosphorus compounds are stronger inhibitors of ACHE than PCHE (that is I_{50} ACHE < I_{50} PCHE) while others, such as for example, malathion, dichlorvos and diazinon, are stronger inhibitors of PCHE than ACHE (that is I_{50} ACHE > I_{50} PCHE). Based on results from human volunteers, exposed workers and the general population, fenthion behaves in man similarly to the latter group, inducing PCHE inhibition at dose levels lower than those which cause ACHE inhibition.

The toxicological dossier of fenthion, includes among other studies, an oral study in human volunteers, acute and subacute oral studies in rodents, a two-year carcinogenicity study in rats and mice, and a two-generation study in rats. Interestingly, the NOELs found in animal and human studies are of the same order of magnitude, similarly the animal NOELs from subacute studies are of the same order of magnitude as the NOELs from the long-term studies. This observation indicates that acetylcholinesterase inhibition is the critical toxic mechanism of fenthion or, in other words, no toxic effects other than cholinesterase inhibition need to be considered in identifying a NOEL (or a NOAEL) and setting an ADI. (for further discussion on other effects, see below).

The Committee considered it preferable to use the available human study to estimate the ADI, since the purpose of the ADI is to address the risk for man. The human study was conducted using two oral daily dosing levels of 0.02 and 0.07 mg/kg b.w. /day, administered for 4 weeks, The findings showed slight inhibition of PCHE at 0.07 mg/kg bw, no inhibition of PCHE at 0.02 mg/kg bw and no inhibition of ACHE at either of the two dose levels. The conclusion is that a NOEL is set at 0.02 mg/kg bw, while a NOAEL is set at 0.07 mg/kg bw, since PCHE inhibition is not considered an **adverse effect.** An ADI can thus be set at 0.007 mg/kg bw using a safety factor of ten.

It should be noted that the NOAEL of 0.07 mg/kg bw is the value obtained in a human study that did not test higher doses; therefore it can be argued that this value already contains an extra margin of safety of unknown size, represented by the dose interval that ranges from the NOAEL and the unknown, but surely higher, LOAEL.

Additional points raised by the Committee

HUMAN TOXICOLOGY

1. Acceptability of the dietary risk assessment.

For a discussion on the estimation of the ADI, see the question No. 2.

When the ADI is fixed at 0.007 mg/kg b.w., the daily dietary residue intake from citrus fruit, olives and olive oil for the general population is acceptable, using both the European and the Greek diets. The acute dietary risk assessment is also acceptable.

2. Relevance of the neurotoxicity and ocular toxicity to man.

The available hen studies on delayed neurotoxicity of fenthion have not provided a clear indication as to whether or not fenthion may act as a delayed neurotoxicant through the interaction with NTE (neurotoxic esterase), the nervous system enzyme believed to be responsible for the "delayed neuropathy". Moreover, limited studies in man have indicated the possibility that fenthion induces an "intermediate syndrome" characterised by signs and symptoms of neurotoxicity. It is therefore advisable to recommend further tests in animal on delayed neurotoxicity. In terms of risk for man, delayed neurotoxicity or the so called "intermediate syndrome", would in any case occur at high or very high doses which would also elicit an acute anticholinergic clinical syndrome. Consequently, the measures necessary to protect the users from acute toxic effects are also effective to protect against delayed neurotoxicity, should this effect be confirmed.

In addition to the toxic effects observed in animal studies with fenthion, ocular toxicity was also observed in rats orally administered with high doses. However, this effect appears to be species-specific as it was not evident in comparable studies in mice, dogs and Rhesus monkeys. No evidence of such an effect can be deduced from the acute poisoning reports in man or other human studies. This effect is, therefore, considered to be non-relevant for human risk assessment.

CONCLUSION ON TOXICOLOGY.

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.

ENVIRONMENTAL ASPECTS

1. Degradation and mobility in soil

The data supplied on degradation and mobility of fenthion and its metabolites indicate that no problem exists concerning the possibility of ground water contamination.

2. Ecotoxicology

2.1. Bees and other non-target arthropods

A very high acute risk for bees was identified on the basis of contact toxicity data (Annex VI triggers exceeded four-fold or more). Laboratory oral toxicity data and semi-field studies would be necessary in order to carry out a conclusive risk assessment.

Fenthion causes mortality of 100% when applied in the range of the bait applications rates. Annex VI triggers would be exceeded by a minimum of at least three fold, indicating a very high risk. Data on standard species are missing, as are data from semi-field and field tests under conditions of the bait applications. Under conditions of full cover applications, semi-field data showed 60-100% effects on two of the four species tested. Such effects are also likely to occur with bait applications in treated trees.

A conclusive assessment of the safety of the bait applications cannot be performed due to the absence of the following data:

- the attractiveness of the bait to a range of non-target organism species

- the stability, availability and toxicity of fenthion in the bait formulations over time.

Conclusion: A complete risk assessment for bees and other non-target arthropods would require additional data to that which were made available to the Committee, although the available data indicate a very high risk. It can be assumed, however, that in order to be effective against the target organism, the bait formulation containing the active ingredient must be sufficiently attractive and stable under field conditions in order to attract and kill target organisms over a relatively long period of time. In the absence of any other information, the same activity cannot be excluded for non-target organisms.

2.2. Aquatic organisms

Toxicity in the aquatic environment is extremely high, particularly for aquatic invertebrates (various endpoints < 0.1 µg/l) which is increased in formulation (< 0.01 µg/l). Very wide buffer zones (> 50 m) are proposed in the documentation supplied to the Committee. However, the basis for these exposure assessments remains uncertain, since two different spray drift models were used (the Dutch one for citrus and the German one for olives). In both cases, non-standard model parameters were used. Furthermore, exposure assessment assumed an even distribution of the bait application over the whole area. This scenario needs to be redefined, since the bait application would consist of spot or row treatment at roughly the full cover application rate over the treated area, with other areas left untreated. Spray drift from this 'spot' type of application cannot be calculated using the standard models which were derived from evenly distributed (full cover) applications.

No data are supplied for a possibly relevant metabolite (fenthion sulfoxide) which occurs in soil and sediments. Since fenthion is persistent in sediments under anaerobic conditions for up to 60 days, fenthion sulfoxide may be continuously produced (it is itself not stable) and present during this period. Both citrus and olives are permanent crops, and repeated applications are intended for each season. Therefore long-term exposure for benthic organisms must be assumed but cannot be properly assessed due to lack of data to evaluate these effects.

Conclusion: For conventional applications, even with buffer zones of 50 m severe acute effects on invertebrates could occur from spray drift from a treated area. The 'spot' method of bait application and the specific formulation type cannot be really addressed by any of the standard spray drift models. Accordingly, a risk assessment on the bait applications cannot be performed. Also, long-term risk from fenthion metabolites in the sediment cannot be assessed due to lack of data.

2.3. Birds

Due to the very high acute toxicity of fenthion to birds, fenthion is (outside the EU) also used as an avicide, e.g. against weaverbirds in Africa. Incidents of massive bird kills after aerial spraying of crops have been reported. Accordingly, aerial applications have been banned by the Greece in 1997 and have been found unacceptable through the review process, this conclusion is fully supported by the Committee. Furthermore, in light of the very high risk and the weight of evidence, the risk assessment should consider all the available toxicity data (Quelea quelea: LD50 1.3 mg/kg bw) rather than the value of 7.2 mg/kg bw (which was

chosen because it had been derived with a standard species). Hence, TER values should be 5.5 times lower than presented in the evaluation supplied to the Committee and would, accordingly, not satisfy the Annex VI criteria.

Lacking or inconsistent important data:

a) A semi-field study to determine acute risk under field conditions is missing. Such a study would also have to examine possible effects on nestlings in treated trees where they are likely to receive approximately similar exposure as under full cover applications.

b) There are no data on reproductive effects at sublethal doses, although the intended repeated applications are likely to expose birds repeatedly over a period of time during which bird species breed and rear their young, both inside and outside the treated areas (birds from outside are likely to forage in olive/citrus groves as well).

c) The issue of secondary poisoning has not been addressed. For example, in the absence of other information, it must be assumed that the baits are also attractive to non-target arthropods, and that non-target arthropods will be killed by exposure through contact with the bait. Hence, concentrations of dead arthropods below the treated trees could form an attractive, concentrated food source for foraging birds.

Conclusion: In view of the very high acute risk for birds, the lacking data on sublethal effects and other issues, it is not possible to conclude on the safety of the intended uses.

OVERALL CONCLUSION

Based on the conclusions of the human and environmental risk assessment, the Scientific Committee on Plants is of the opinion that it is not possible to complete a full assessment in the absence of data to prove that even the limited intended use as a bait application on citrus and olive is safe for human health and the environment. The Committee acknowledges that the development of an innovative technique of application, namely bait formulation including fenthion plus attractant on only a part of the crop, would be promising to achieve limited exposure of humans and the environment; however specific studies have to be made available on such a type of application before a conclusive evaluation can be made.

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