Conclusion regarding the peer review of the pesticide risk assessment of the active substance

benthiavalicarb

finalised: 12 July 2007

SUMMARY

Benthiavalicarb is a new active substance for which in accordance with Article 6 (2) of Council Directive 91/414/EEC[1] Belgium received an application from Kumiai Chemicals Industry Co Ltd for inclusion in Annex I to Directive 91/414/EEC. Complying with Article 6 of Directive 91/414/EEC, the completeness of the dossier was evaluated and confirmed by Commission Decision[2].

Following the agreement between the EU-Commission and the EFSA for the EFSA to organise a peer review of those new active substances for which the decision on the completeness of the dossier had been published after June 2002, the designated rapporteur Member State Belgium made available the report of its initial evaluation of the dossier on benthiavalicarb, hereafter referred to as the draft assessment report (DAR), which was received by EFSA on 13 April 2004.

The peer review was initiated on 10 May 2004 by dispatching the draft assessment report for consultation of the Member States and the notifier. Subsequently, the comments received on the DAR were examined by the rapporteur Member State and the need for additional data was agreed in an evaluation meeting on 16 December 2004. Remaining issues as well as further data made available by the notifier upon request were evaluated in a series of scientific meetings with Member State experts in April – May 2005.

A final discussion of the outcome of the consultation of experts took place with representatives from the Member States on 24 April 2007 leading to the conclusions as laid down in this report.

The conclusion was reached on the basis of the evaluation of the use as fungicide as proposed by the applicant which comprise foliar spraying to control *Phytophthora infestans and Plasmopara viticola* in grapes, tomatoes and potatoes. Due to the fact that the isopropyl ester, a variant of benthiavalicarb, is used in the formulated product, it should be noted that the evaluated data belong to the variant benthiavalicarb-isopropyl, unless otherwise specified.
Only the use of benthiavalicarb-isopropyl as a fungicide was evaluated.
The representative formulated products for the evaluation were "KIF-230 15% WG" and "KIF-230/Mancozeb 17.5/700 WG", both are water dispersible granules (WG).

[1] OJ No L 230, 19.8.1991, p. 1. Directive as last amended by OJ L 106, 24.4.2007, p.14
[2] OJ No L 11, 16.1.2003, p.52

Adequate methods are available to monitor all compounds given in the respective residue definition. None of them are enantioselective. The methods determine all 4 possible isomers, but the pairs of enantiomers only as a sum.
Sufficient analytical methods as well as methods and data relating to physical, chemical and technical properties are available to ensure that quality control measurements of the plant protection product are possible.

Benthiavalicarb-isopropyl has a low acute toxicity after oral, dermal and inhalatory exposure. It is neither a skin nor an eye irritant, while it is a skin sensitiser, therefore the classification as R43 "May cause sensitisation by skin contact" is proposed. Overall, benthiavalicarb-isopropyl is not genotoxic both *in-vivo* and *in-vitro* assays. Benthiavalicarb-isopropyl is proposed for classification as Carc. Cat. 3 R40, due to the occurrence of uterine tumours in rats. The relevant NOAEL is 9.9 mg/kg bw/day either for general toxicity or for carcinogenicity (LOAEL 250 mg/kg bw/day). Benthiavalicarb-isopropyl does not show reproductive toxicity potential: The relevant parental NOAEL is 10 mg/kg bw/day, the pup NOAEL is 67.2 mg/kg bw/day and the reproductive toxicity NOAEL is 702.5 mg/kg bw/day (highest dose tested).The lowest relevant developmental NOAEL is established at 20 mg/kg bw/day, based upon the increased ossification delay and the increased dwarfism incidence at the top dose in rats. The findings were both considered associated with treatment. During the written procedure, EFSA considered that the proposal for R63 might be justified due to the maternal NOAEL $\geq$ 20 mg/kg bw/day. The ADI is 0.1 mg/kg bw/day based on the NOAEL from the 2 year study in rats with an assessment factor of 100; the AOEL is 0.1 mg/kg bw/day derived from the rat teratogenicity study and an assessment factor of 100. The allocation of the ARfD was not deemed necessary based on the toxicological profile of benthiavalicarb-isopropyl. The operator exposure assessment shows estimated exposure levels below the AOEL (German model), even without the use of PPE; the estimated worker and bystander exposure for the worst case scenario represents about 48% and 1% of the AOEL, respectively.

The metabolism of benthiavalicarb was investigated in grapes, tomatoes and potatoes after a foliar treatment with radio-labelled benthiavalicarb-isopropyl. Potato metabolism was also studied after a soil treatment. In all crops investigated, benthiavalicarb-isopropyl was the major component of the terminal residue. A pH induced isomerisation of benthiavalicarb-isopropyl into the diastereomer KIF-230 S-L was observed in the tomato study. In general, only minor amounts of metabolites of benthiavalicarb-isopropyl were generated; and they were partially present as free metabolites but mainly conjugated with glucose. None of the metabolites identified in primary crops was found to be of a particular toxicological concern. A cleavage of the amide bond, as occurring in soil, was not observed in primary crop metabolism studies. However, no sufficient data are currently available to address the concern about a potential selective uptake of toxicologically relevant metabolites from soil.

Given the residue situation in crops that are relevant as animal feed items, no significant residues in livestock diet are expected. However, this assessment may have to be reviewed upon receipt of further data on investigation of residues in rotational crops potentially used as feed items.
Assessment of the safety of different consumers groups indicates that the intake of residues of benthiavalicarb-isopropyl (including potentially present residues of KIF230 S-D, KIF 230 S-L and KiF 230 R-D) resulting from the supported representative uses is well below the toxicological reference value for chronic exposure (ADI) for benthiavalicarb-isopropyl. Potential contribution from animal commodities and succeeding crops were not included in the calculations.
Nevertheless, it should be mentioned that for the uses with a combi-formulation (grapevines, tomatoes, potatoes) containing besides benthiavalicarb-isopropyl also mancozeb, the consumer risk assessment could not be completed, since no assessment with regard to mancozeb residues was carried out.

Benthiavalicarb-isopropyl is moderately persistent in soil under aerobic conditions. In the experiments performed with the ^{14}C-phenyl-benthiavalicarb-isopropyl four major soil transformation products were identified: M1; M3; M4 and M5. Bound residues reached a maximum of 58.2 % AR and mineralization was between 3.6 – 11.7 % AR at 120 d. No isomeric conversion of the active substance was observed in any of the experiments. Data from the parent study M5 was shown to be moderately persistent. The degradation of the transformation products M1, M3 and M4 was investigated in separated studies with three soils. M1 was shown to be low to moderately persistent, M3 low persistent and M4 very low persistent to moderate persistent in soil.
Under dark anaerobic conditions at 20 ºC benthiavalicarb-isopropyl was slightly more persistent than in aerobic ones. Transformation product M8 was found in higher amounts in anaerobic conditions and should be considered as a major soil anaerobic metabolite with respect to the ground water exposure assessment.
In the experiment performed with the ^{14}C-valyl-benthiavalicarb-isopropyl labelled experiment no metabolites were identified.
Photolysis is not expected to contribute to the degradation of benthiavalicarb-isopropyl in soil.
PEC soil were calculated by the RMS based on the worst case laboratory half life of 19.1 d and the representative uses with 50 % interception. Applicant provided a PEC soil calculation assuming no degradation between application and resulting in a more worse case with respect to the RMS proposal. Maximum amount observed of metabolites was applied to this worst case PEC soil for the parent to calculate maximum PEC soil of metabolites.
Batch adsorption / desorption studies show that benthiavalicarb-isopropyl is high to medium mobile, M1, M3 and M4 are medium mobile and M5 is medium to low mobile in soil. Benthiavalicarb-isopropyl may be considered stable to hydrolysis under most common environmental conditions. Photolysis may contribute to the environmental degradation of benthiavalicarb-isopropyl in acidic waters (pH 5: DT_{50} = 6.8 d). Benthiavalicarb-isopropyl is not readily biodegradable according the available study.
In water / sediment systems, benthiavalicarb-isopropyl partitions to the sediment where it breaks down to the metabolites M3, M4 and M5. No major metabolites were identified in the water phase.

Bound residues reached 40.6 % AR at the end of the study (100 d). Volatiles collected in the NaOH trap (presumably CO_2) reached maxima of 0.9 and 3.8 % AR at the end of the study (100 d). Benthiavalicarb-isopropyl degradation on the whole systems proceeded with half lives of 15 and 18.2 d. No isomeric conversion of the active substance was observed in any of the experiments.

PEC_{SW} of benthiavalicarb-isopropyl were calculated for the representative uses based on spray drift loadings. Worst case half life dissipation ($DT_{50\ diss.\ water}$ = 7.7 d) from the water sediment studies was used in this calculation. PEC_{SED} for the metabolites M3, M4 and M5 were calculated based on the lumped application rate without degradation between applications and the maximum percentage observed in the water sediment studies corrected for the molecular weight.

For the representative uses proposed and the scenarios modelled with FOCUS PEARL none of the concentration of the potential residue components exceeds the trigger value of 0.1 µg / L in ground water.

Benthiavalicarb-isopropyl is not expected to be transferred to the atmospheric compartment and potential for long range transport may be considered negligible.

No full risk assessment was conducted for the formulation containing mancozeb (KIF 230/Mancozeb 17.5/700 WG, representative uses in tomato, grapes and potato).

The risk to birds and mammals was assessed as low for the representative use of the formulation KIF-230 15% WG in tomatoes. The risk assessment for the formulation KIF-230/Mancozeb 17.5/700 WG is not completed since the toxicity of the second active substance mancozeb was not considered in the risk assessment. The risk assessment for aquatic organisms was based on endpoints from technical benthiavalicarb-isopropyl. Spray drift was considered as the only relevant route of entry into surface water. Therefore aquatic organisms would be exposed to the formulation and not to technical benthiavalicarb-isopropyl alone. However the endpoints observed in tests with benthiavalicarb-isopropyl formulated as KIF-230 15% WG are similar to technical active substance and given the large margin of safety based on endpoints for the technical active substance (TER values of more than one order of magnitude above the relevant Annex VI trigger values of 100 and 10) the risk to aquatic organisms is considered to be low for the representative uses of KIF-230 15% WG in tomatoes.

The risk assessment for the representative uses of the formulation KIF 230/Mancozeb 17.5/700 WG was also based on endpoints from technical benthiavalicarb-isopropyl without taking into account the toxicity of mancozeb. This is considered as not appropriate since the formulation KIF 230/Mancozeb 17.5/700 WG is about 3 orders of magnitude more toxic than the formulation KIF-230 15% WG. A high risk to aquatic organisms from the representative uses of KIF 230/Mancozeb 17.5/700 WG cannot be excluded. Benthiavalicarb-isopropyl partitions at high rates to the sediment but since the 21-d NOEC for daphnids is greater than 0.1 mg/L a test with sediment dwelling organisms is not triggered. The acute toxicity of the major metabolites in sediment KIF-230-M-3 and KIF-230-M-5 to daphnids is comparable to the acute toxicity of benthiavalicarb-isopropyl. Only the acute endpoint of KIF-230-M4 is lower than that of the parent. Since the metabolites occurred in the sediment phase of the water-sediment system at maximum levels markedly lower than that of benthiavalicarb-isopropyl the expert meeting considered the risk from the metabolites (including the metabolite KIF-230-M4) to sediment dwelling organisms as low.

The HQ values for the use of KIF-230/Mancozeb 17.5/700 WG in tomatoes/grapevine indicated a potential high risk to predatory mites. The risk to *T. pyri* needs to be addressed further. The RMS proposed a confirmatory data requirement after Annex I listing. The expert meeting on ecotoxicology agreed to the data requirement but concluded that these data should be made available before Annex I listing.

No effects of >30% on non-target arthropods were observed in tests with KIF-230 15% WG. However the tested dose was too low. Therefore a data requirement was set in the evaluation meeting for the applicant to provide studies at an application rate which covers the representative use (applying a MAF of 3.2). The data requirement was confirmed by the expert meeting.

The acute risk to earthworms was assessed as low for all representative uses evaluated. The long-term TER value of 2.9 for the representative use of KIF-230 15% WG in tomatoes was below the trigger of 5. Since the long-term endpoint (NOEC) is based on the highest tested dose and a high margin of safety was observed in the acute risk assessment the risk to earthworms was considered to be low by the RMS for all representative uses.

The risk from the major soil metabolites KIF-230-M1 and KIF-230-M3 to earthworms was assessed as low. The risk from the metabolites KIF-230-M1 and KIF-230-M3 was discussed in the expert meeting on ecotoxicology and considered to be low.

The risk to bees, other soil non-target macro-organisms, soil micro-organisms, non-target plants and biological methods of sewage treatment was assessed as low for all representative uses.

Key words: benthiavalicarb, benthiavalicarb-isopropyl, peer review, risk assessment, pesticide, fungicide

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BACKGROUND

In accordance with Article 6 (2) of Council Directive 91/414/EEC Belgium received an application from Kumiai Chemicals Industry Co Ltd for inclusion of the active substance benthiavalicarb in Annex I to Directive 91/414/EEC. Complying with Article 6 of Directive 91/414/EEC, the completeness of the dossier was evaluated and confirmed by Commission Decision.

Following the agreement between the EU-Commission and EFSA for EFSA to organise a peer review of those new active substances for which the completeness of the dossier had been officially confirmed after June 2002, the designated rapporteur Member State Belgium submitted the report of its initial evaluation of the dossier on benthiavalicarb, hereafter referred to as the draft assessment report (DAR), to the EFSA on 13 April 2004. This draft assessment report was distributed for consultation to the Member States and the notifier on 10 May 2004.

The comments received on the draft assessment report were evaluated and addressed by the rapporteur Member State. Based on this evaluation, representatives from Member States identified and agreed in an evaluation meeting on 16 December 2004 on data requirements to be addressed by the notifier as well as issues for further detailed discussion at expert level. A representative of the notifier as well as of the European Crop Protection Association (ECPA) was attending this meeting.

Taking into account the information received from the notifier addressing the request for further data, a scientific discussion of the identified data requirements and/or issues took place in expert meetings organised on behalf of the EFSA by the EPCO-Team at the Federal Office for Food Safety and Consumer Protection (BVL) in Braunschweig in April-May 2005. The reports of these meetings have been made available to the Member States electronically.

A final discussion of the outcome of the consultation of experts took place with representatives from Member States on 24 April 2007 leading to the conclusions as laid down in this report.

During the peer review of the draft assessment report and the consultation of technical experts no critical issues were identified for consultation of the Scientific Panel on Plant Health, Plant Protection Products and their Residues (PPR).

Following the agreement between the EU Commission and EFSA regarding the peer review of new active substances, this conclusion summarises the results of the peer review on the active substance and the representative formulation evaluated as finalised at the end of the examination period. A list of the relevant end points for the active substance as well as the formulation is provided in appendix 1.

The documentation developed during the peer review was compiled as a **peer review report** comprising of the documents summarising and addressing the comments received on the initial evaluation provided in the rapporteur Member State's draft assessment report:

- the comments received
- the resulting reporting table (rev. 1-2 of 22 December 2004)

as well as the documents summarising the follow-up of the issues identified as finalised at the end of the commenting period:

- the reports of the scientific expert consultation
- the evaluation table (rev. 3-1 of 24 April 2007)

Given the importance of the draft assessment report including its addendum (compiled version of April 2007 containing all individually submitted addenda) and the peer review report with respect to the examination of the active substance, both documents are considered respectively as background documents A and B to this conclusion.

By the time of the presentation of this conclusion to the EU-Commission, the rapporteur Member State has made available amended parts of the draft assessment report (Vol. 1, level 1-4, Vol. 3, B1, B2, B5-B7 and B9) which take into account mostly editorial changes. Since these revised documents still contain confidential information, the documents cannot be made publicly available. However, the information given can basically be found in the original draft assessment report together with the peer review report which both is publicly available.

THE ACTIVE SUBSTANCE AND THE FORMULATED PRODUCT

Benthiavalicarb is the ISO common name for [(*S*)-1-{[(1*R*)-1-(6-fluoro-1,3-benzothiazol-2-yl)ethyl]carbamoyl}-2-methylpropyl]carbamic acid (IUPAC). Due to the fact that the isopropyl ester, a variant of benthiavalicarb, is used in the formulated product, it should be noted that the evaluated data belong to the variant benthiavalicarb-isopropyl, unless otherwise specified.

Benthiavalicarb and benthiavalicarb-isopropyl, respectively, belong to the class of carbamate fungicides such as thiophanate and iprovalicarb. The mode of action of benthiavalicarb-isopropyl is to inhibit the incorporation of precursors required for phospholipid biosynthesis.

The representative formulated products for the evaluation were "KIF-230 15% WG" and KIF-230/Mancozeb 17.5/700 WG, both are water dispersible granules (WG).

The evaluated representative uses as fungicide comprise foliar spraying to control *Phytophthora infestans* and *Plasmopara viticola* in grapes, tomatoes and potatoes.

SPECIFIC CONCLUSIONS OF THE EVALUATION

1. Identity, physical/chemical/technical properties and methods of analysis

The minimum purity of benthiavalicarb-isopropyl as manufactured should not be less than 910 g/kg. At the moment no FAO specification exists.

The technical material contains two impurities, KIF-230-I-6[3] and KIF-230-I-12[4], which have to be regarded as toxicological relevant. The maximum content in the technical material should not be higher than 3.5 mg/kg and 14 mg/kg, respectively.

The assessment of the data package revealed no issues that need to be included as critical areas of concern with respect to the identity, physical, chemical and technical properties of benthiavalicarb-isopropyl or the respective formulations. However, a data gap concerning the spectra for the relevant impurity of KIF-230-I-6 was identified. Furthermore, it should be noted that no data are available whether or not the content of the relevant impurities in the formulations is increasing upon storage.

The main data regarding the identity of benthiavalicarb-isopropyl and its physical and chemical properties are given in appendix 1.

Sufficient test methods and data relating to physical, chemical and technical properties are available. Also adequate analytical methods are available for the determination of benthiavalicarb-isopropyl in the technical material and in the representative formulations as well as for the determination of the relevant impurities in the technical material.
Therefore, enough data are available to ensure that quality control measurements of the plant protection product are possible.

As a result of a question on a processing study posed by the residue meeting of experts the applicant in their letter dated 25 October 2006 made a case for the instability of the radiolabelled material used in the study. The case stated that the breakdown was as a result of self irradiation. This means that the radiolabelling of the compound makes it less stable than the unlabelled compound. Then this of course has implication for all studies that used radiolabelled material. As a result of this a new data gap was identified for the applicant to explain this issue. It was noted in the evaluation meeting on 26/04/07 that the rapporteur agreed that the issue should be raised in the conclusion but did not agree with the setting of a new data gap.

Adequate methods are available to monitor all compounds given in the respective residue definition, i.e. benthiavalicarb-isopropyl, its enantiomer and their diastereomers in food of plant origin; benthiavalicarb-isopropyl and its enantiomer in soil, water and air.

[3] KIF-230-I-6: 6,6'-difluoro-2,2'-dibenzothiazole
[4] KIF-230-I-12: bis(2-amino-5-fluorophenyl) disulfide

The methodology used is GC with PN detection or HPLC with MS/MS detection. None of them is enantioselective. It should be noted that the methods were validated by fortifying samples with benthiavalicarb-isopropyl and its diastereomer KIF-230S-L. Based on the fact that none of the methods are enantioselective, it is not possible to distinguish between the enantiomers. Therefore, the methods determine all 4 possible isomers, but the pair of enantiomers only as a sum.
Residues in food of plant origin can in principle be determined with a multi-method such as the German S19 method, but the validation was conducted only with pure benthiavalicarb-isopropyl. Therefore, no data are available to demonstrate that the condition of the S19 method would separate the signals for the diastereomers. The S19 multi-method is not enantio selective.

An analytical method for food of animal origin is not required due to the fact that no residue definition is proposed (see 3.2).

The discussion in the meeting of experts (EPCO 25, May 2005) on identity, physical and chemical properties and analytical methods was limited to the analytical methods for impurities in the technical material, some clarification concerning the relevant impurities and the minimum purity of benthiavalicarb.
It should be noted that the RMS had recently received studies to address the requirement on spectra for the relevant impurity KIF-230-I-6. The studies are summarised and accepted by the RMS in an addendum to the DAR (November 2006, B.2). However, this assessment was neither peer reviewed nor discussed in a meeting of experts.

2. Mammalian toxicology

Benthiavalicarb-isopropyl was discussed in a meeting of experts in May 2005 (EPCO experts' meeting 23). Although the major points of concerned were discussed, it was not possible to finalise the discussion on all the existing open points due to time restraints; hence a first round of written procedure was performed at the end of 2005 between EFSA and RMS. The RMS was asked for further information and clarifications in order to close the remaining open points. The revised discussion table was then circulated among all the participants into the meeting for consultation and final revisions.

The majority of the studies (and the most critical ones for the problem, i.e. the carcinogenicity studies), were performed with a batch which was less pure (88.6%) that the commercial batch, for which authorisation was sought. RMS considered that the existing database covered the human risk assessment well. Furthermore, according to the new production, the (mutagenic) impurities KIF-230-1-6 and KIF-230-1-12 are present at a level < LOQ.
The current specification of the two concerning mutagenic impurities was an order of magnitude lower than the originally proposed one, and should not give rise to further concern.

A concern was raised by EFSA with regard to isomeric conversion from R-L to S-L. The issue was discussed in a second round of toxicology experts' meeting in January 2007. An increase of isomer KIF-230S-L was observed in processed commodities (tomatoes, dry raisins), compared to benthiavalicarb-isopropyl. The maximum isomerisation was calculated to a maximum level of 41%. As the toxicological studies (on carcinogenicity) have been performed with benthiavalicarb-isopropyl (purity 98%) and a content of 4- 5% of the inactive optical isomer KIF-230S-L the isomer is covered. The RMS considered that there is no evidence that the S-L isomer is more toxic than the parent (R-L): considering the structure-activity relationship, supported by the absence of adverse effects in the acute oral toxicity study and the bacterial genotoxicity test, the expected toxicity of the KIF230S-L isomer is not greater than that of benthiavalicarb-isopropyl (KIF 230R-L) itself. The meeting agreed to the conclusion.

2.1. ABSORPTION, DISTRIBUTION, EXCRETION AND METABOLISM (TOXICOKINETICS)

Benthiavalicarb-isopropyl is extensively and rapidly absorbed (complete at the low dose, about 50% at the high dose). It is widely distributed, mainly in the gastro-intestinal tract, bile duct and urinary bladder. The metabolism is extensive for low dose administrations and limited following high dose administrations.

2.2. ACUTE TOXICITY

Benthiavalicarb-isopropyl has a low acute toxicity after oral, dermal and inhalatory exposure. It is neither a skin nor an eye irritant, while it is a skin sensitiser, therefore the classification as **R43 "May cause sensitisation by skin contact"** was proposed.

2.3. SHORT TERM TOXICITY

The relevant short term toxicity NOAEL of 14 mg/kg bw/day was set based upon the induced anaemia, liver effects and related clinicochemical findings in the 90 day rat study. In the dog, the NOAEL was based on a macrocytic hypochromic anaemia, increased γ-GT and ALP activities, with increased liver/adrenal weights and decreased thymus weights.

2.4. GENOTOXICITY

Various batches of Benthiavalicarb-isopropyl were tested. Two of them (G51-08 and G51-15) showed potential to induce mutations in S. typhimurium strain TA98. It was demonstrated that the mutagenic potential was caused by the presence of impurity KIF-230–I–6. In addition, batch G51-08 contained the genotoxic relevant impurity KIF-230–I–12.

The notifier provided a new five-batch analysis which was claimed to correspond with the impurity profile of the commercially manufactured active substance. The genotoxicity studies on this new set of batches demonstrated that the active substance was devoid of mutagenic activity.

It is of note that the two impurities, KIF-230–I–6 and KIF-230–I–12 were <LOQ in the new commercial batches.

A slight increase of polyploid cell incidence was detected in the in-vitro chromosome-aberration assay, in the absence of exogeneous metabolisation, but its toxicological significance remains questionable, as this may be a reflexion of cell toxicity, and no similar effect was observed when the test was performed in the presence of S9.
Other mechanistic or complementary studies, including the single cell gel assay (Comet-assay on lymphocytes), and the analysis of 8-OH DNA-adducts in liver cells, offered additional evidence that Benthiavalicarb-isopropyl is not genotoxic both *in-vivo* and *in-vitro*.

2.5. LONG TERM TOXICITY

The long-term effects of Benthiavalicarb-isopropyl were investigated in both rat and mouse.
The target organs for long term exposures in rodents were liver, kidney and thyroid.
At high doses, mice showed an increased incidence of hepatocellular adenomas, but at the upper end of the historical control range; the incidence of uterine adenocarcinomas was highly significantly increased in rats and was above maximal historical control value (8%).
The issue of endocrine disruption was discussed by the experts. It was considered unlikely that an endocrine disrupting potential was fully responsible for the tumour occurrence in the uterus, as oestradiol levels were increased during weeks 52 and 78 of the assay, but not at termination. The RMS considered that the carcinogenicity study was performed with a batch containing mutagenic impurities and, even if the level of these impurities was reduced to <LOQ in the commercial batch, the classification as **Carc. Cat. 3 (R40) "Limited evidence for carcinogenic effects"** was proposed. During the written procedure it was further specified that a threshold can be identified, and the relevant NOAEL of 9.9 mg/kg bw/day from the rat study was confirmed, (LOAEL 250 mg/kg bw/day) based upon the liver and kidney alterations, the associated clinicochemical modifications and the haematological disorders.

2.6. REPRODUCTIVE TOXICITY

Benthiavalicarb-isopropyl did not show reproductive toxicity potential: The relevant parental NOAEL was set at 10 mg/kg bw/day, the pup NOAEL at 67.2 mg/kg bw/day and the reproductive toxicity NOAEL was 702.5 mg/kg bw/day (highest dose tested).

The lowest relevant developmental NOAEL was established at 20 mg/kg bw/day, based upon the increased ossification delay and the increased dwarfism incidence at the top dose in rats. The findings were both considered associated with treatment. During the written procedure, EFSA considered that the proposal for Repr. Cat 3 (**R63)** might be justified due to the maternal NOAEL ≥ 20 mg/kg bw/day (at this level toxicity consists in 10% increased liver weight). The RMS did not agree as the incidence was low and the effects were not considered serious enough and maternal toxicity was suspected (abortions at this dose and also reduced bodyweight in the dam showing nanofoetuses).

2.7. NEUROTOXICITY

An acute and subacute neurotoxicity study was conducted. There is no indication of neurotoxicity in these studies. In the acute study, a weak decrease of motor activity was observed on day 1, but not at later stages. In the repeated feeding study, a toxicity NOAEL was established based at 174 mg/kg bw/day on a decreased body weight gain and decrease of motor activity at the next dose.

2.8. FURTHER STUDIES

Metabolites KIF-230–M4[5] and KIF-230–M5[6], and impurity KIF-230–I12 were more toxic than Benthiavalicarb-isopropyl.

Metabolite KIF-230-M5 is harmful by oral route, with an LD_{50} of 545 mg/kg bw, as well as impurity KIF-230–I12 (LD_{50} 840 mg/kg bw); metabolites KIF-230–M4, and impurities KIF-230–I6 and KIF-230–I12 were genotoxic in bacteria (TA98) (impurities KIF-230–I6 and KIF-230–I12 were present in the pilot batches, but at levels below the LOQ in the commercial batches for which authorisation is sought). Metabolite KIF-230-M1[7] is harmful by oral uptake (LD_{50} = 467 mg/kg b.w); metabolite KIF-230-M3[8] shows low acute toxicity via oral route (LD_{50} > 2000 mg/kg b.w).

Since KIF-230-M4 (methyl ketone derivative of the fluorobenzothiazol-moiety) is an environmental metabolite which was not recovered in the rat metabolism, the experts considered that further genotoxic tests including an *in-vitro* chromosome aberration study and an *in-vivo* micronucleus test might be necessary if the metabolite would be considered environmentally pertinent. However, it was concluded that M4 is not predicted to contaminate the groundwater (trigger not exceeded in any of the FOCUS scenarios), thus there's no environmental concern.

EFSA notes that this data requirement might be reconsidered in case the required study on succeeding crops shows an uptake of M4 from soil into plant parts relevant for human consumption or as a feed item.

During the EPCO meeting, the experts discussed the immunotoxic potential of benthiavalicarb-isopropyl. Regenerative anaemia was observed essentially in the 90-day dog study at doses of ≥ 40 mg/kg bw/day. In the 1 year dog study, some aspects of a potential immunotoxicity such as increased of β and γ globulin levels, thymus weight decrease at ≥40 mg/kg bw/day (also seen after 90 day) were noted.

The majority of the EPCO 23 experts concluded that there was no evidence for a specific immunotoxic property of the substance and that thymus weight decreases were related to general systemic toxicity. One MS still concern about the effect proposed further testing. The overall NOAEL for immunotoxic effects was set at 40 mg/kg bw/day (90 d, 1 y dog study).

[5] KIF-230-M4: 6-fluorobenzothiazol-2-yl methyl ketone
[6] KIF-230-M5: 1-(6-fluorobenzothiazol-2-yl) ethylamine
[7] KIF-230-M1: 6-fluoro-2-hydroxybenzothiazole
[8] KIF-230-M3: 1-(6-fluorobenzothiazol-2-yl) ethanol

2.9. MEDICAL DATA

Based on the reports of the medical surveillance on manufacturing plant personnel, observed effects were declared not to be related to the exposure to the active substance

2.10. ACCEPTABLE DAILY INTAKE (ADI), ACCEPTABLE OPERATOR EXPOSURE LEVEL (AOEL) AND ACUTE REFERENCE DOSE (ARFD)

ADI

The established ADI is 0.1 mg/kg bw/day based on the NOAEL from the 2 year study in rats with an assessment factor of 100. It was noted that the margin of security with the dose were tumours appeared in the rat (249.6 mg/kg bw/d) was about 2500. This was considered sufficient in terms of consumer risk assessment.

AOEL

The short-term systemic AOEL of 0.1 mg/kg bw/day was derived from the lowest NOAEL in the rat teratogenicity study and an assessment factor of 100 was applied. It was of note that the margin of security with the dose were tumours appeared in the rat (249.6 mg/kg bw/d) was about 2500. This was considered sufficient in terms of exposure risk assessment.

ARfD

As the compound was of low acute toxicity, and no meaningful neurotoxicity or reprotoxicity was observed, the establishment of an acute reference dose was not deemed necessary.

2.11. DERMAL ABSORPTION

The RMS proposed 16% (concentrate) and 70 % (dilution), based on an *in vitro* human study including skin residues, performed with benthiavalicarb-isopropyl formulated as KIF-230 15% WG. This worst case assumption was accepted by the experts.

2.12. EXPOSURE TO OPERATORS, WORKERS AND BYSTANDERS

The formulations of Benthiavalicarb-isopropyl, wettable granules containing either ~150 g/kg a.s. (KIF-230 15% WG) or ~17.5 g/kg a.s. in combination with Mancozeb ~700 g/kg ("KIF-230/Mancozeb 17.5/700", main formulation) are proposed to be used as fungicides in tomatoes, potatoes and grapes.

As for the combined formulation (benthiavalicarb-isopropyl + mancozeb), the risk assessment should be regarded as inconclusive. This is due to the fact that for instance there is no dermal absorption value for the combi-product, and there should be a discussion on the relevant AOEL to be used and a possible additional safety factor which might be considered (due to similar hazard profile). Finally, an agreement on whether additive or synergistic exposure is most appropriate to assume. As there is no harmonised approach to consider the combined toxicity or exposure has to be considered at MS level.

Operators

In the following table, only the assessment based on the use of the KIF-230 15% WG formulation is presented:

Model	Method	% of the AOEL No PPE	% of the AOEL With PPE*
German	$Tomatoes_{out}$ (tractor, field crops, 0.075 kg a.s./ha)	37.7	2.4
	$Tomatoes_{in}$ (hand-held, 0.075 kg a.s./ha)	34.2	5.0
	Potatoes (tractor, field crops 0.028 kg a.s./ha)	14.1	0.9
	Grapes (tractor, high crops 0.035 kg a.s./ha)	33.6	4.8
UK POEM	$Tomatoes_{out}$ (tractor mounted boom with hydraulic nozzles, 0.075 kg a.s./ha, cont. size 10 kg)	158	23
	$Tomatoes_{out}$ (tractor mounted boom with hydraulic nozzles, 0.075 kg a.s./ha, cont. size 5 kg)	166	23
	$Tomatoes_{in}$ (hand-held, 0.075 kg a.s./ha, cont. size 1 kg)	426	175
	Potatoes (tractor mounted boom with hydraulic nozzles 0.028 kg a.s./ha, cont. size 10 kg)	58	9
	Potatoes (tractor mounted boom with hydraulic nozzles 0.028 kg a.s./ha, cont. size 5 kg)	62	9
	Grapes (tractor drawn air assisted orchard sprayer 0.035 kg a.s./ha, cont. size 10 kg)	307	194
	Grapes (tractor drawn air assisted orchard sprayer 0.035 kg a.s./ha, cont. size 5 kg)	310	194

*German model: gloves when handling the concentrate and gloves, coveralls and boots during application;

UK POEM: gloves when handling the concentrate and during application

The operator exposure assessment shows estimated exposure levels below the AOEL (German model), even without the use of PPE, for all the uses considered.

Workers

The estimated worker exposure for the worst case scenario (high crops, grapes) represents about 48% of the AOEL.

Bystanders

The estimated for the worst case scenario (high crops, grapes) represents about 1% of the AOEL.

3. Residues

Benthiavalicarb (variant KIF 230 R-L) was discussed at EPCO experts' meeting for residues (EPCO 24) in May 2005. The RMS did not attend the discussion. A revised DAR was tabled in the meeting, but not all open points and data requirements had been addressed in this document. Later in the process the RMS submitted addenda on the outstanding points. These addenda had, however, not been peer reviewed and thus, no agreed consumer risk assessment could be presented in the discussion with representatives from the Member States and the European Commission in December 2006. Therefore it was recommended benthiavalicarb be discussed in an experts' meeting again. Eventually a second experts' discussion took place at the PRAPeR experts' meeting for residues (PRAPeR 15) in January 2007.

3.1. NATURE AND MAGNITUDE OF RESIDUES IN PLANT

3.1.1. PRIMARY CROPS

The metabolism of benthiavalicarb was investigated in grapes, tomatoes and potatoes after a foliar treatment with pure material of the variant benthiavalicarb-isopropyl (KIF 230 R-L) radio-labelled at the benzyl ring and the L-valyl side chain. Potato metabolism was also studied after a soil treatment.

The study in grapevines was carried out at a *ca* 3fold application rate (3 N rate) when compared to the notified representative GAP. At harvest (PHI 17 d), in mature grapes the total radioactive residue (TRR) amounted to 0.3 mg/kg, the TRR in vine leaves ranged between 18 and 23 mg/kg.
Benthiavalicarb-isopropyl was the major constituent of the terminal residue in both, leaves and grapes (94 and 96% TRR, respectively). No conversion of benthiavalicarb-isopropyl into its three isomers (KIF 230 R-D, S-L and S-D) was observed in the analysed leave samples, while grapes were not analysed for. The remaining radioactivity apart from benthiavalicarb-isopropyl was too low for any further identification. However, upon enzymatic treatment of the sample extracts with β -glucosidase the chromatographic profile did not change, indicating that no sugar conjugates of metabolites had been present. Due to the very low level of metabolites formed in grapes and leaves, it was not possible to deduce a metabolic pathway in grapevines.

In a study on tomato plants (1.3 N rate) the TRR on the fruits decreased slowly until harvest at maturity (PHI 56 d). At harvest, the TRR was 2.3 mg/kg in foliage and less than 0.01 mg/kg in the fruits. Benthiavalicarb-isopropyl was the major constituent of the total residue in both, tomato fruit and foliage (55% and 95 % of the TRR respectively). No conversion of benthiavalicarb-isopropyl into its diastereomer KIF 230 S-L was observed, the respective enantiomers KIF 230 S-D and R-D were not analysed for in the study. Up to 44% of total radioactivity in tomato fruits remained unknown as its very low amount (<0.003 mg/kg) made an identification extremely difficult. Thus, it was not possible to derive a metabolic pathway in tomatoes from this study.
In a second study on tomatoes, higher total residues were generated by individually treating selected fruits and leaves of tomato plants. After 14 days, only very little radioactivity (<0.01% TRR) was found in untreated fruits or leaves of the test plants, what suggests that residues of benthiavalicarb-

isopropyl are hardly translocated in the plant. Upon characterisation of the TRR in the treated leaves and fruits, 98% were identified as benthiavalicarb-isopropyl. The residual radioactivity could be attributed to the metabolites KIF230-M11 (0.1% TRR) and KIF230-M15 (up to 0.25% TRR) and to not further identified polar compounds (<1% TRR).
A slight isomerisation of benthiavalicarb-isopropyl into the S-L isomer (0.6% TRR) but also into the respective enantiomers R-D (0.24%) and S-D (0.12%) was observed in tomato fruits. The level of isomerisation was lower in tomato foliage. It was presumed that the acidic pH of the fruits (about pH 4) is one of the main factors that could explain the higher level of diastereomer KIF-230S-L present in the fruits. Upon investigating the impact of different pH-values on isomerisation, a tendency was observed that the rate of isomerisation from benthiavalicarb-isopropyl into the S-L diastereomer increased with a decrease of the pH-value.

In a study on potatoes, the plants received either a post-emergence soil application (*ca* 0.6 N of the intended foliar rate) or a foliar application (3.5 N rate).
Potato tubers harvested after a soil application (PHI 90 d) contained very low levels of radioactive residues (<0.001 mg/kg) and therefore no further characterisation of radioactivity was performed. As in the foliage of soil treated potato plants benthiavalicarb-isopropyl was recovered (*ca* 11% TRR at PHI 90 d), it was concluded that the compound is taken up from the soil. Upon hydrolysis with β – glucosidase, sugar conjugates of the phenyl-ring hydroxylated KIF-230 R-L and the de-fluorinated phenyl ring-hydroxylated KIF-230 R-L were identified amongst the residual 79% TRR in foliage. EPCO 24 has requested further clarification on the amounts and identity of residues generated in the soil-applied potato metabolism study. The addendum of July 2006, revised by the RMS in January 2007, was discussed by PRAPeR 15. Three main fractions, accounting together for 61% TRR and individually not exceeding 0.02 mg/kg, could be separated but attempts to further identify them failed. With reference to the currently applicable trigger values for identification of metabolites in food and feed items the meeting concluded that this information should be considered sufficient, and further that the uptake of residues (parent and metabolites) in potato plants following a soil application is not expected to reach significant levels under conditions as applied in the available metabolism study. However, the meeting noticed that this conclusion is not necessarily appropriate to be applied to crops that may grow as succeeding crops (refer to 3.1.2).
In foliar treated potato tubers (3.5 N rate) at harvest (PHI 14 d), the TRR amounted up to 0.014 mg/kg for both labels. About 4.7% of the TRR in foliar treated tubers was recovered as benthiavalicarb-isopropyl while *ca* 77 % TRR were unknown compounds. Further investigation of the unidentified fractions by enzymatic reaction with β-glucosidase indicated that glucose conjugates (22% TRR) were present in potato tubers after foliar treatment. In potato foliage the major part of the residue (90%TRR) was still present as benthiavalicarb-isopropyl. No isomeric conversion into KIF230 R-D, S-L and S-D was observed in the analysed foliage samples. Again, upon hydrolysis with β-glucosidase, sugar conjugates of the phenyl ring hydroxylated KIF-230 R-L and the de-fluorinated phenyl ring hydroxylated KIF-230 R-L were identified in the residual TRR in foliage.

The metabolic pathway of benthiavalicarb-isopropyl could be established in fruit and in root and tuber crops having received a foliar application. No major qualitative difference was observed between the two radio-labels in terms of the metabolic pattern generated in the tested crops. In all crops benthiavalicarb-isopropyl was the major component of the terminal residue. Only minor amounts of metabolites were present, partially as free metabolites but mainly conjugated with glucose. To conclude, the degradation of benthiavalicarb-isopropyl proceeds via ring hydroxylation and/or deflourination followed by sugar conjugation on the hydroxyl groups. A cleavage of the amide bond, as occurring in soil, was not observed in primary crop metabolism studies.
A slight isomerisation was observed in the tomato metabolism study. The occurrence of isomerisation of benthiavalicarb-isopropyl was attributed to the natural pH of the analysed plant material (pH induced isomerisation) and seemed to affect mainly the generation of the diastereomer KIF-230 S-L.

Supervised residue trial data on grapes, tomatoes and potatoes from Northern and Southern Europe were submitted and evaluated. The trials were supported by sufficiently validated analytical methods and scientifically acceptable storage stability data. The analytical methods used in the residue trials could not distinguish between benthiavalicarb-isopropyl and its enantiomer (KIF-230-S-D), neither could the two diastereomers of benthiavalicarb-isopropyl KIF 230 S-L and KIF230 R-D be separated. Thus, the residues analysed for were the sum of benthiavalicarb-isopropyl and potentially present KIF-230-S-D (referred to as benthiavalicarb in the following), and the sum of KIF 230 S-L and its enantiomer KIF230 R-D (referred to KIF 230 S-L in the following).
Residues in potato tubers were all below the LOQ (<0.01 mg/kg) for benthiavalicarb-isopropyl and KIF 230 S-L, respectively. Residues of benthiavalicarb-isopropyl up to 0.14 mg/kg and 0.21 mg/kg were found in tomatoes and grapes, respectively. In a few trials the presence of isomer KIF 230 S-L above LOQ level (0.01 mg/kg to 0.06 mg/kg) in the fruits was confirmed at the PHI defined in the cGAP.
The residue data base for tomato under outdoor conditions is limited, however as the more critical use was found to be the indoor use on tomatoes, the risk assessment and the proposed MRL rely on data from indoor trials and no further data for the outdoor use are required

If treated according to the representative GAP, significant residues (>0.1 mg/kg) are expected in tomatoes and grapes.
Since in soil metabolism the cleavage of the amide bond of benthiavalicarb-isopropyl led to the generation of the toxicologically significant metabolites M5, M4 and M1, the potential of an amide hydrolysis occurring also under processing conditions was noted by EPCO 24. The applicant submitted studies investigating the impact of different processing conditions on the nature of the residue, which were evaluated in the addenda of July 2006, November 2006 and January 2007 and discussed by PRAPeR 15. Formation of the metabolites of toxicological concern M5, M4 and M1 was not observed at the different pH's and temperatures tested. In one study M4 could be detected at a low level (3% TRR) but its presence was attributed to the not completely purified material used in this test. (degradation to M4 by self-irradiation - see chapter 1). In the other study, were the

experimental conditions chosen were more drastic, a slight isomerisation of the parent isomer to the S-L isomers was observed (*ca* 4%).

Processing of grapes and tomatoes was studied according to conditions applied in the commercial practice. Benthavalicarb-isopropyl and KIF 230 S-L were determined separately. Experts' request for additional information on technological specifications to the processing studies was addressed in the addendum of July 2006 and was considered by PRAPeR 15. In tomato and grape processing studies some significant levels of the S-L isomer (however the R-D enantiomer could not be separated from the S-L with the applied analytical method) were observed in processed fractions.

Even though not present above the LOQ in the raw tomatoes tested in processing studies, the diastereomer KIF 230 S-L was found after processing in puree and ketchup and in tomato pomace at significant levels. Also after processing of grapes into raisins significant levels of the diastereomer KIF 230 S-L were found in raisins. In raisins (after having been dried at 60 °C for 5 to 9 days) the level of KIF 230 S-L had increased disproportionate to what could be expected from concentration of initially present amounts in the unprocessed grapes. It is therefore believed that isomerisation may be caused by a combination of different parameters (pH, temperature and time of heat exposure; matrix effects). Altogether, processing of grapes into juice and wine as well as peeling, juicing and canning of tomatoes reduced the residue levels of benthiavalicarb-isopropyl and isomers, while residues concentrated in raisins and in tomato puree and ketchup.

Given the observed isomerisation into the diastereomer KIF 230 S-L (and possibly enantiomer KIF230 R-D) under processing conditions the residue for risk assessment and monitoring should be defined as sum of the diastereomers benthiavalicarb-isopropyl and KIF 230 S-L including their enantiomers (KIF-230-S-D and KIF-230 R-D) expressed as benthiavalicarb-isopropyl. The analytical methods used throughout the residue studies but also the analytical method validated for monitoring/enforcement purposes could not/cannot distinguish between the enantiomer (KIF-230-S-D) and benthiavalicarb-isopropyl and the diastereomers of benthiavalicarb-isopropyl KIF230 S-L and KIF 230 R-D. Therefore, even not definitely proven to be present, KIF-230-S-D and KIF 230 R-D should be included for formal reasons.

The experts' meeting on toxicology concluded that the stereo isomeric structure is not expected to be of any relevance for the toxicological activity of the molecules and thus the expected toxicity of the KIF230 S-L isomer (and consequentially the KIF 230 R-D- and KIF 230 S-D isomer) is not greater than that of bethiavalicarb (KIF 230 R-L) itself. Hence, PRAPeR 15 considered benthiavalicarb-isopropyl and all its existing isomers of as equally toxic and agreed the residue for risk assessment and monitoring purposes be defined as benthiavalicarb-isopropyl its enantiomer (KIF 230 S-D) and its diastereomers (KIF230 S-L and KIF 230 R-D).

3.1.2. SUCCEEDING AND ROTATIONAL CROPS

Benthiavalicarb-isopropyl is moderately persistent in soil, thus no studies in succeeding or rotational crops were submitted by the applicant. However, from the available data it is known that metabolites occur in soil, which were not found in primary crops and in rat metabolism and, in addition, they are deemed to be of toxicological concern (M1, M4, M5; more toxic than benthiavalicarb-isopropyl in

acute studies and genotoxic in-vitro, respectively, while M3 was not of particular toxicological concern) (refer to 4.1 and 2.8).

Concerns have been raised about the possibility of a selective uptake of these metabolites by succeeding crops. The available metabolism study in potatoes involving a soil application of benthiavalicarb-isopropyl is not sufficient to confidently exclude that these metabolites of toxicological concern could be found in succeeding crops due to the following reasons adduced by EPCO 24: 1) The application rate in the available soil-applied potato metabolism study is lower than the rate intended for foliar treatment of crops according to the notified critical GAP (cGAP) and hence the respective metabolites may have not been identified in the study even if they were possibly present, and 2) no other representative rotational/succeeding crops than root and tuber crops have been tested. PRAPeR 15 added to this conclusion that in the applicants considerations and argumentation to waive rotational crop testing, metabolite M5 is assumed to be already present at the time of application of the parent compound and afterwards declining with time, but this assumption was considered not appropriate because the peak concentration of metabolite M5 in soil is observed after 60 days.

Therefore, both experts' meetings EPCO 24 and PRAPeR 15 concluded that further data on succeeding crops are needed to fully address the concern about selective soil metabolites uptake and identified a data gap. The request of such study had been recommended by the Co-RMS earlier too.

3.2. NATURE AND MAGNITUDE OF RESIDUES IN LIVESTOCK

Of the crops notified for the use of benthiavalicarb, only potatoes are relevant as an animal feed item. Given the residue situation in potatoes (all trials <0.01 mg/kg), no significant residues in livestock diet are expected. According to current knowledge, metabolism and livestock feeding studies are not required. However, relevant feed items may be grown in rotation with crops treated with benthiavalicarb. Thus, this assessment may have to be reviewed upon receipt of further data on investigation of residues in rotational crops (if residue levels in these crops were shown to be relevant) (see 3.1.2)

3.3. CONSUMER RISK ASSESSMENT

Assessment of the safety of different consumers groups indicates that the intake of residues of benthiavalicarb-isopropyl (including enantiomer KIF230 S-D) and KIF 230 S-L (including enantiomer KIF230 R-D) resulting from the supported representative uses is well below the toxicological reference value for chronic exposure (ADI) of benthiavalicarb-isopropyl.

The experts' meeting on toxicology concluded that the stereo isomeric structure is not expected to be of any relevance for the toxicological activity of the molecules and thus the expected toxicity of the KIF230 S-L isomer (and consequentially the KIF 230 R-D- and KIF 230 S-D isomer) is not greater than that of benthiavalicarb-isopropyl (KIF 230R-L) itself.

PRAPeR 15 considered benthiavalicarb-isopropyl and all its existing isomers of as equally toxic and consider the sum of benthiavalicarb-isopropyl its enantiomer (KIF 230 S-D) and its diastereomers (KIF230 S-L and KIF 230 R-D) in the consumer risk assessment.

Potential contribution from animal commodities and succeeding crops were not included in the intake calculations, but as mentioned under points 3.1.2 and 3.2, it has currently not been assessed whether they are of any relevance (depended on data expected from the required rotational crop testing).
The chronic dietary exposure assessment has been based on the Theoretical Maximum Daily intake (TMDI) calculation using the WHO/ GEMS Food European diet for adult consumers, the German national diet for the 4-6 year old girl (1993) and UK consumption figures (PSD consumer exposure model 1999). Residues in grapes, tomatoes and potatoes were considered to be at the level of the respective proposed MRLs. Under these conditions the calculated TMDI were in all cases <2% of the ADI of benthiavalicarb- isopropyl.
Benthiavalicarb- isopropyl and its isomers are not acutely toxic and thus an acute risk assessment is not necessary.

Nevertheless, it should be mentioned that for the uses with the combi-formulation (grapevines, tomatoes, potatoes) containing besides benthiavalicarb also mancozeb, the consumer risk assessment could not be completed, since no assessment with regard to mancozeb residues was carried out.

3.4. PROPOSED MRLS

The results of supervised residue trials were analysed according to the statistical tools recommended for MRL setting by the current European guidelines (Doc 7039/VI/95). The proposed MRLs in accordance with the proposed residue definition are:

Table and wine grapes	0.3 mg/kg[9]
Tomatoes	0.3 mg/kg
Potatoes	0.02* mg/kg

4. Environmental fate and behaviour

Benthiavalicarb was discussed in the meeting of experts on fate and behaviour into the environment EPCO 21 (April 2005).

4.1. FATE AND BEHAVIOUR IN SOIL

4.1.1. ROUTE OF DEGRADATION IN SOIL

The route of degradation of benthiavalicarb-isopropyl in soil under dark aerobic conditions at 20 ºC was investigated in one study with four soils (pH $_{KCl}$ 4.2 – 7.2; OC 1.3 – 4.0 %; clay 10 – 29 %; 45 % MWHC) with benthiavalicarb-isopropyl either ^{14}C-labelled at the valyl moiety (only one soil) or at the phenyl ring. No metabolites were identified in the ^{14}C-valyl labelled experiment. Bound residues reached a maximum of 41.2 % AR after 59 d and then decreased to 26.5 % AR at the end of the

[9] Due to the amendment of the residue definition in the second discussion in a meeting of experts (PRAPeR 15) the highest residue (as the sum of isomers) in grapes has increased and therefore the initially proposed MRL of 0.2 mg/kg needs to be raised to 0.3 mg/kg. New proposal not peer reviewed but agreed between the RMS and EFSA.

experiment (365 d). Mineralization of the side chain was relatively high (44 % AR as CO_2 after 120 d). In the experiments performed with the ^{14}C-phenyl-benthiavalicarb-isopropyl four major soil transformation products were identified: M1 (max. 27. 7 % AR after 120 d); M3 (max. 12.3 % AR after 28 d); M4 (max. 9.8 % AR after 28 d) and M5 (max. 26.8 % after 58 d). Bound residues reached a maximum of 58.2 % AR and mineralization was between 3.6 – 11.7 % AR at 120 d. Selected sample were analysed with HPLC and a chiral stationary phase. No isomeric conversion of the active substance was observed in any of the experiments.

Degradation of ^{14}C-phenyl-benthiavalicarb-isopropyl in flooded soil under dark anaerobic conditions at 20 ºC was investigated in one soil (pH_{KCl} 6.6; OC 2.5 %; clay 10 %). The same metabolites found in the aerobic study were found in this one. Transformation product **M8**[10] (max. 9.0 % AR after 120 d), resulting from the acetylation of the metabolite M5, was found in higher amounts in anaerobic conditions than in the aerobic ones and should be considered as a major anaerobic metabolite with respect to the ground water exposure assessment.

A soil photolysis study is available. According the results of this study photolysis is not expected to contribute to the degradation of benthiavalicarb-isopropyl.

4.1.2. PERSISTENCE OF THE ACTIVE SUBSTANCE AND THEIR METABOLITES, DEGRADATION OR REACTION PRODUCTS

Rate of degradation of benthiavalicarb-isopropyl under dark aerobic conditions at 20 ºC was derived from the data obtained in the route studies. Benthiavalicarb-isopropyl is moderately persistent in soil under aerobic conditions ($DT_{50\ lab\ 20\ ºC}$ = 10.6– 19.1 d). Data from the parent study was employed to derive the degradation rates of the transformation product M5 ($DT_{50\ lab\ 20\ ºC}$ = 17.4 – 40.4 d).

The degradation of the transformation products M1, M3 and M4 was investigated in separated studies with three soils (pH_{KCl} 4.9 - 7.2; OC 1.4 – 4.5 %; clay 15 – 32 %; 45 % MWHC). M1 was shown to be low to moderately persistent in soil ($DT_{50\ lab\ 20\ ºC}$ = 4 – 27 d), M3 low persistent in soil ($DT_{50\ lab\ 20\ ºC}$ = 2 – 7 d) and M4 very low persistent to moderate persistent in soil ($DT_{50\ lab\ 20\ ºC}$ < 1 d; $DT_{90\ lab\ 20\ ºC}$ = 32 – 80.75 d).

Under dark anaerobic conditions at 20 ºC benthiavalicarb-isopropyl was slightly more persistent than in aerobic ones ($DT_{50\ anaerobic\ lab\ 20\ ºC}$ = 39.9 d).

PEC soil were calculated by the RMS based on the worst case laboratory half life of 19.1 d and the representative uses (tomatoes 6 x 0.75 g a.s. / ha, 7 d interval; grapes 6 x 35 g a.s. / ha, 7 d interval) with 50 % interception. These PEC soil were used for the ecotoxicological risk assessment. Applicant provided a PEC soil calculation assuming no degradation between application and resulting in a worst case with respect to the RMS proposal. Maximum amount observed of metabolites was applied to this worst case PEC soil for the parent to calculate maximum PEC soil of metabolites.

[10] **M8:** *N*-[1-(6-Fluorobenzothiazol-2-yl)ethyl]acetamide

4.1.3. MOBILITY IN SOIL OF THE ACTIVE SUBSTANCE AND THEIR METABOLITES, DEGRADATION OR REACTION PRODUCTS

Batch adsorption / desorption studies are available for parent benthiavalicarb-isopropyl and the soil metabolites M1, M3, M4 and M5. Parent benthiavalicarb-isopropyl was tested in five soils (pH $_{KCl}$ 4.8 – 7.2; OC 1.3-5.4 %; clay 1 – 20 %) and the metabolites in three soils (pH $_{KCl}$ 4.0 - 7.5; OC 0.8 – 4.7 %; clay 9 – 35 %). The results of these studies show that benthiavalicarb-isopropyl is high to medium mobile (K_{foc} = 121.3 – 258.2 mL / g), M1, M3 and M4 are medium mobile (M1: K_{foc} = 237.2 – 422.3 mL / g; M3: K_{foc} = 116.4 – 241.0 mL / g; M4: K_{foc} = 221.4 – 407.8 mL / g) and M5 is medium to low mobile in soil (K_{foc} = 494.4 – 787.3 mL / g).

4.2. FATE AND BEHAVIOUR IN WATER

4.2.1. SURFACE WATER AND SEDIMENT

A preliminary hydrolysis test was conducted at 50 ºC in sterile buffered solutions 4, 7 and 9 is available. Since degradation after 5 d was < 10 %, benthiavalicarb-isopropyl may be considered stable to hydrolysis under most common environmental conditions. However, some isomerisation (max. 2 % AR) was observed in the chiral carbon adjacent to the benzothiazol heterocycle.

Aqueous photolysis of ^{14}C-phenyl-benthiavalicarb-isopropyl was investigated in one study at 25 ºC under simulated sunlight (Xenon, filter cut off λ< 290 nm) with 12 h dark/light cycles for 30 d. Photolysis may contribute to the environmental degradation of benthiavalicarb-isopropyl in acidic waters (pH 5: DT_{50} = 6.8 d). In neutral or alkaline waters some photolysis occurs but to a much lesser extend (pH 7: DT_{50} = 516 d; pH 9: DT_{50} = 178 d). No metabolites above 10 % AR were identified in this study.

Benthiavalicarb-isopropyl is not readily biodegradable according the available study.

Dissipation and degradation of benthiavalicarb-isopropyl in water sediment was investigated in one study with two water/sediment systems (pH_{water}: 6.8 – 8.2; pH $_{sed\ KCl}$: 4.9 – 8.0; OC_{sed} 6.2 – 9.1 %; $clay_{sed}$ 19 %) at 20 ºC. Aerobic conditions were maintained in the water phase and anaerobic ones in the sediment. Benthiavalicarb-isopropyl partitions to the sediment where it breaks down to the metabolites M3 (max. 26.3% after 100 d, end of the study), M4 (max. 22.7 % AR after 30 d) and M5 (max. 11.9 % after 59 d). No major metabolites were identified in the water phase. Bound residues reached 40.6 % AR at the end of the study (100 d). Volatiles collected in the NaOH trap (presumably CO_2) reached maxima of 0.9 and 3.8 % AR at the end of the study (100 d). Benthiavalicarb-isopropyl degradation on the whole systems proceed with half lives of 15 and 18.2 d. Degradation of the sediment metabolite M4 was tentatively determined (only three points after maxima, DT_{50} = 67.6 d). It was not possible to determine the degradation rate for sediment metabolites M3 and M5 since maxima was reached at the end of the study or at one sampling point of it. Selected sample (14 DAT) were analysed with HPLC and a chiral stationary phase. No isomeric conversion of benthiavalicarb-isopropyl was observed in any of the experiments.

PEC_{SW} of benthiavalicarb-isopropyl were calculated for the representative uses based on spray drift loadings. Worst case half life dissipation ($DT_{50\ diss.\ water}$ = 7.7 d) from the water sediment studies was used in this calculation. PEC_{SED} for the metabolites M3, M4 and M5 was calculated based on the

lumped application rate without degradation between applications and the maximum percentage observed in the water sediment studies corrected for the molecular weight.

4.2.2. POTENTIAL FOR GROUND WATER CONTAMINATION OF THE ACTIVE SUBSTANCE THEIR METABOLITES, DEGRADATION OR REACTION PRODUCTS

Potential for ground water contamination was assessed by calculation of the 80th percentile annual average predicted concentration of parent benthiavalicarb-isopropyl and metabolites M1, M3, M4 and M5 in the leachate at 1m depth on the relevant FOCUS scenarios employing the FOCUS PEARL model. For the representative uses proposed and the scenarios modelled none of the concentration of the potential residue components exceeds the trigger value of 0.1 µg / L.

4.3. FATE AND BEHAVIOUR IN AIR

At 25 ºC the vapour pressure of benthiavalicarb-isopropyl is < 3 x 10^{-4} Pa and Henry's law constant is 8.72 x 10^{-3} Pa m^3/ mol indicating low volatility. Estimated half life in the atmosphere due to photochemical oxidative degradation is 2.3 h based on a OH radicals concentration of 1.5 x 10^6 OH· / cm^3. Therefore, benthiavalicarb-isopropyl is not expected to be transferred to the atmospheric compartment and potential for long range transport may be considered negligible.

5. Ecotoxicology

Benthiavalicarb-isopropyl was discussed at the EPCO experts' meeting for ecotoxicology (EPCO 22) in April 2005. No full risk assessment was conducted for the formulation containing mancozeb (KIF 230/Mancozeb 17.5/700 WG, representative uses in tomato, grapes and potato).

According to the new technical specification, the (mutagenic) impurities KIF-230-1-6 and KIF-230-1-12 are present at lower levels than in the original technical specifiction (< LOQ). The lower amounts of the two impurities in the new technical specification are not of ecotoxicological concern.

5.1. RISK TO TERRESTRIAL VERTEBRATES

The risk assessment for birds and mammals was conducted according to SANCO/4145/2000 for the representative uses in tomato and grapes (covering also the use in potatoes). The acute, short-term and long-term TER values for insectivorous and herbivorous birds and for herbivorous mammals were above the Annex VI trigger values indicating a low risk.

Since the $logP_{ow}$ of benthiavalicarb-isopropyl is < 3 a risk assessment for secondary poisoning of earthworm- and fish-eating birds is not required.

The acute LD_{50} values for the plant metabolites M-1 and M-5 were lower than the LD_{50} for benthiavalicarb-isopropyl by about one order of magnitude. No toxicity endpoints were available for birds. The risk from the plant metabolites to herbivorous birds and mammals is considered to be low

since the metabolites were found only at very low quantities in plant materials and tomato and potato foliage is not an attractive food source. Therefore the risk from plant metabolites to herbivorous birds and mammals is considered to be low.

The RMS conducted a risk assessment for the risk to birds and mammals from uptake of contaminated drinking water. The calculation based on PECsw values resulted in acute, short-term and long-term TER values far above the Annex VI trigger values of 10 and 5. The risk from uptake of contaminated drinking water was discussed in the expert meeting. It was noted that the risk assessment should have been conducted on the basis of a 5 fold dilution of the sprayed solution as suggested by the guidance document SANCO/4145/2000. If the risk assessment would have been conducted on the basis of a 5 fold dilution of the sprayed solution as suggested by the guidance document SANCO/4145/2000 all TER values would meet the trigger of 10 and 5 except the long-term TER for mammals. The expert meeting considered a long-term exposure as unlikely and the long-term risk to mammals from this exposure route as low

Overall it is concluded that the risk to birds and mammals is low for the representative uses in tomatoes of the formulation KIF-230 15% WG. The risk assessment for the formulation KIF 230/Mancozeb 17.5/700 WG is not completed since the toxicity of the second active substance mancozeb was not considered in the risk assessment.

5.2. RISK TO AQUATIC ORGANISMS

The toxicity of benthiavalicarb-isopropyl to the different groups of aquatic organisms was similar. The TER values for fish, daphnids and algae were calculated with endpoints observed in tests with technical benthiavalicarb-isopropyl. The TERs were more than one order of magnitude above the relevant Annex VI triggers of 100 and 10. However, only spray drift was considered as a route of entry into surface water and therefore the aquatic community would be exposed to the formulation and not only to the technical a.s.. Since the endpoints observed for benthiavalicarb-isopropyl formulated as KIF-230 15% WG are similar to technical benthiavalicarb-isopropyl it is assumed that the TERs are also similar and hence the risk to aquatic organisms from the representative use of KIF-230 15% in tomatoes is considered to be low.

The risk from the representative uses of the formulation KIF 230/Mancozeb 17.5/700 WG was calculated with endpoints from technical benthiavalicarb-isopropyl without taking into account the toxicity of mancozeb. This is considered as not appropriate since the formulation KIF 230/Mancozeb 17.5/700 WG is about 3 orders of magnitude more toxic than the formulation KIF-230 15%. A high risk to aquatic organisms from the representative uses of KIF 230/Mancozeb 17.5/700 WG cannot be excluded.

No major metabolite was found in the water phase of the water/sediment study. Benthiavalicarb-isopropyl partitions to the sediment reaching a maximum of 47.4 % of AR after 7 days. Since the 21-d NOEC to daphnids of 3 mg benthiavalicarb-isopropyl/L is greater than 0.1 mg/L a test with

sediment dwelling organisms is not triggered and the expert meeting decided that no testing with benthiavalicarb-isopropyl and sediment dwelling organism is required.

The acute toxicity of the major metabolites in sediment KIF-230-M-3 and KIF-230-M-5 to daphnids is comparable to the acute toxicity of benthiavalicarb-isopropyl. Only the acute toxicity of KIF-230-M4 is somewhat higher than that of the parent. Since the metabolites occurred in the sediment phase of the water-sediment system at maximum levels markedly lower than that of benthiavalicarb-isopropyl (26.3%, 22.7% and 11.9 % of AR) the expert meeting considered the risk from the metabolites to sediment dwelling organisms as low.

Since the $logP_{ow}$ of benthiavalicarb-isopropyl is < 3 no bioconcentration study with fish is triggered and the risk of bioaccumulation and biomagnification in aquatic food chains is considered to be low.

5.3. RISK TO BEES

The toxicity of benthiavalicarb-isopropyl to bees is low. The contact and oral LD_{50} values for technical benthiavalicarb-isopropyl and formulated as KIF-230 15% WG were >100 µg benthiavalicarb-isopropyl/bee. The acute contact and oral toxicity of the formulation KIF-230/Mancozeb/17.5/700 WG was >140 µg formulation/bee. The HQ values for the uses of KIF-230 15% WG in tomatoes and KIF-230/Mancozeb 17.5/700 WG in tomatoes and grapes were below the HQ trigger of 50 (0.8 and 14.3) indicating a low risk to bees. The risk assessment for the use of KIF-230/Mancozeb 17.5/700 WG in tomatoes and grapes covers also the risk for the use in potato where the product is applied at a lower application rate.
Overall it is concluded that the risk to bees is low for all representative uses.

5.4. RISK TO OTHER ARTHROPOD SPECIES

The formulations KIF-230 15% WG and KIF-230/Mancozeb 17.5/700 WG were tested in standard laboratory tests with *Typhlodromus pyri* and *Aphidius rhopalosiphi*.
The HQ values for *T. pyri* and *A. rhopalosiphi* were calculated as 22 and 1.07 for an application rate of 2000 g/ha indicating a potential high in-field risk for *T. pyri* from the use of KIF-230/Mancozeb 17.5/700 WG. The risk to *T. pyri* from the representative uses of KIF-230/Mancozeb17.5/700 WG needs to be addressed further. The RMS proposed a confirmatory data requirement after Annex I listing. The expert meeting agreed to the data requirement but concluded that these data should be made available before Annex I listing.

KIF-230 15% WG was tested with *T. pyri*, *A. rhopalosiphi*, *Poecilus cupreus* and *Chrysoperla carnea*. Mortality and sublethal effects were less than 30% at an application rate of 0.5 kg KIF-230 15% WG/ha. However the tests with KIF-230 15% WG were conducted at a rate equivalent to a single application. Therefore a data requirement was set in the evaluation meeting for the applicant to provide studies at an application rate which covers the representative use (applying a MAF of 3.2). The data requirement was confirmed by the expert meeting.

A high risk to non-target arthropods from the representative uses of KIF-230 15% WG and KIF-230/Mancozeb 17.5/700 WG cannot be excluded on the basis of the provided data.

5.5. RISK TO EARTHWORMS

The acute and long-term toxicity of benthiavalicarb-isopropyl and the acute toxicity of its metabolites KIF-230-M1 and KIF-230-M3 is low (>996 mg/kg). The endpoints were corrected with a factor of 2 since the log P_{ow} is >2. The acute TER values for the use of KIF-230 15 WG in tomato and of KIF-230/Mancozeb 17.5/700 WG resulted in TER values of more than two orders of magnitude above the Annex VI trigger of 10. The endpoint from the test with technical benthiavalicarb-isopropyl was used for the risk assessment. The test with the formulation KIF-230/Mancozeb 17.5/700 WG would result in a lower endpoint based on the content of active substance. However due to the large margin of safety observed in the risk assessment based on the toxicity of the technical active substance it is concluded that the acute risk to earthworms is low for all representative uses.

Chronic studies with earthworms were conducted with the formulation KIF-230 15% WG and KIF-230/Mancozeb 17.5/700 WG. No effects were observed at the highest tested doses of 5 kg product and 20 kg product/ha. The endpoint of 5 kg product/ha from the test with KIF-230 15% WG was used for the long-term risk assessment. The long-term TER values were calculated as 2.9 and 6.1 for the uses of KIF-230 15% WG in tomatoes and KIF-230/Mancozeb 17.5/700 WG in tomato and grapevine. Since the NOEC is based on the highest tested dose and a high margin of safety was observed in the acute risk assessment the risk to earthworms was considered to be low by the RMS. However the experts` meeting concluded that this assessment should be supported by a chronic earthworm study with high enough dose rates or a valid argumentation. The applicant informed the RMS that the formulation KIF-230 15% WG will not be longer commercialised. Therefore it was suggested by the RMS that the required data are submitted for national registration for formulations that will actually be put on the market. The combi-formulation KIF-230/Mancozeb 17.5/700 WG was tested at a higher application rate than KIF-230 15% WG and resulted in a higher NOEC for the formulation. During the evaluation meeting in December 2006 it was discussed whether it is possible to extrapolate from the endpoint observed in the long-term study with the combi-formulation KIF-230/Mancozeb 17.5/700 WG to the single-formulation KIF-230 15% WG in order to address the long-term risk. However the content of benthiavalicarb-isopropyl in the combi-product is less and the NOEC based on the content of benthiavalicarb-isopropyl would be lower than that from the test with the single formulation KIF-230 15% WG. Therefore the use of the endpoint from KIF-230/Mancozeb 17.5/700 WG would not lead to a TER above the trigger of 5.

The risk from the major soil metabolites KIF-230-M1 and KIF-230-M3 was assessed as low. No tests were conducted with the metabolites KIF-230-M4 and KIF-230-M5. The metabolites are intermediates of benthiavalicarb-isopropyl and the metabolites KIF-230-M1 and KIF-230-M3. The two metabolites would need to be more than 1000 times more toxic than the parent or the metabolites KIF-230-M1 and KIF-230-M3 to pose a higher risk to earthworms. Therefore it was concluded by the

expert meeting that the risk from the metabolites of benthiavalicarp-isorpropyl to earthworms is low for all represenatative uses evaluated.

5.6. RISK TO OTHER SOIL NON-TARGET MACRO-ORGANISMS

Not required since the DT_{90} for benthiavalicarb-isopropyl and its soil metabolites KIF-230-M1, KIF-230-M3, KIF-230-M4 are less than 100 days. The DT_{90} value for the metabolite KIF-230-M5 was in the range of 57.7 – 134.1 days. Since the metabolite is an intermediate of benthiavalicarb-isopropyl and the metabolite KIF-230-M3 and the risk to earthworms and soil micro-organisms was assessed as low for the parent and KIF-230-M3 no studies with the metabolite KIF-230-M5 and other soil macro-organisms were considered necessary.

5.7. RISK TO SOIL NON-TARGET MICRO-ORGANISMS

No effects >25% on soil respiration and nitrification were observed in tests with technical benthiavalicarb-isopropyl at dose rates of up to 2.647 mg/kg (more than 10 times the PECsoil for the use of KIF-230 15% WG in tomatoes) and with the metabolites KIF-230-M1 and KIF-230-M3 at a dose of 0.25 mg/kg (about 5 times and 10 times the PEC value for the use of KIF-230 15% WG in tomatoes).

No tests were conducted with the metabolites KIF-230-M4 and KIF-230-M5. The metabolites are intermediates of benthiavalicarb-isopropyl and the metabolites KIF-230-M1 and KIF-230-M3 and no effects of > 25% were observed in tests with benthiavalicarb-isopropyl and the metabolites KIF-230-M1 and KIF-230-M3 at a concentration of about 5-10 times the PEC. Although not quantified it is considered likely that the risk from KIF-230-M4 and KIF-230-M5 to soil micro-organisms is low.

5.8. RISK TO OTHER NON-TARGET-ORGANISMS (FLORA AND FAUNA)

Screening tests were conducted with the metabolites KIF-230-M1, -M3, -M4 and M-5 showing that the fungicidal activity of the metabolites is low. No herbicidal effects were observed in a test with *Amaranthus retroflexus, Chenopodium album, Cyperus iria, Digitaria sangunialis, Echinochloa crus-galli* and *Polygonum lapthifolium* at an application rate of 4000 g benthiavalicarb-isopropyl/ha. The risk to non-target plants is considered to be low for the representative uses evaluated.

5.9. RISK TO BIOLOGICAL METHODS OF SEWAGE TREATMENT

No inhibitory effect on respiration of activated sludge was observed up to the highest tested concentration of 100 mg benthiavalicarb-isopropyl/L. It is not expected that the concentration of benthiavalicarb-isopropyl would reach this concentration in sewage treatment plants when used according to the GAPs. Hence the risk to biological methods of sewage treatment is considered to be low for the representative uses evaluated.

6. Residue definitions

Soil

Definitions for risk assessment: benthiavalicarb-isopropyl, M1, M3, M4, M5

Definitions for monitoring: benthiavalicarb-isopropyl and its enantiomer.

Water

Ground water

Definitions for exposure assessment: benthiavalicarb-isopropyl, M1, M3, M4, M5, (M8 in case of anaerobic conditions)

Definitions for monitoring: benthiavalicarb-isopropyl and its enantiomer.

Surface water

Definitions for risk assessment: benthiavalicarb-isopropyl

Definitions for monitoring: benthiavalicarb-isopropyl and its enantiomer.

Air

Definitions for risk assessment: benthiavalicarb-isopropyl

Definitions for monitoring: benthiavalicarb-isopropyl and its enantiomer.

Food of plant origin

Definitions for risk assessment: benthiavalicarb-isopropyl its enantiomer and their diastereomers expressed as benthiavalicarb-isopropyl (based on available data limited to foliar application in fruit and root/tuber crops)

Definitions for monitoring: benthiavalicarb-isopropyl, its enantiomer and their diastereomers expressed as benthiavalicarb-isopropyl (based on available data limited to foliar application in fruit and root/tuber crops)

Food of animal origin

Definitions for risk assessment: not proposed, not required[11]

Definitions for monitoring: not proposed, not required

[11] Assessment might need to be reviewed upon receipt of the required data on rotational crops

Overview of the risk assessment of compounds listed in residue definitions for the environmental compartments

Soil

Compound (name and/or code)	**Persistence**	**Ecotoxicology**
benthiavalicarb-isopropyl	moderately persistent in soil ($DT_{50\ lab\ 20\ °C}$ = 10.6– 19.1 d)	The risk to earthworms and soil micro-organisms was assessed as low
M1	low to moderately persistent ($DT_{50\ lab\ 20\ °C}$ = 4 – 27 d)	The risk to earthworms and soil micro-organisms was assessed as low
M3	low persistent ($DT_{50\ lab\ 20\ °C}$ = 2 – 7 d)	The risk to earthworms and soil micro-organisms was assessed as low
M4	very low persistent to moderate persistent in soil ($DT_{50\ lab\ 20\ °C}$ < 1 d; $DT_{90\ lab\ 20\ °C}$ = 32 – 80.75 d)	The risk to earthworms is considered to be low
M5	moderately persistent ($DT_{50\ lab\ 20\ °C}$ = 17.4 – 40.4 d)	The risk to earthworms is considered to be low
M8	No data, only relevant for uses for which anaerobic conditions may be expected	No data available, no data required.

Ground water

Compound (name and/or code)	Mobility in soil	> 0.1 µg / L 1m depth for the representative uses (at least one FOCUS scenario or relevant lysimeter)	Pesticidal activity	Toxicological relevance	Ecotoxicological relevance
benthiavalicarb-isopropyl	medium mobile (K_{foc} = 121.3 – 258.2 mL / g)	FOCUS: Trigger not exceeded for any of the representative uses and scenarios simulated.	Yes	Yes	yes
M1	medium mobile (K_{foc} = 237.2 – 422.3 mL / g)	FOCUS: Trigger not exceeded for any of the representative uses and scenarios simulated.	No	Higher acute toxicity than benthiavalicarb isopropyl (harmful by oral uptake, LD_{50} = 467 mg/kg b.w)	The risk to sediment dwelling organisms was considered to be low in the surface water risk assessment
M3	medium mobile (K_{foc} = 116.4 – 241.0 mL / g)	FOCUS: Trigger not exceeded for any of the representative uses and scenarios simulated.	No	Low acute toxicity (comparable to benthiavalicarb isopropyl): LD_{50}>2000 mg/kg bw	The risk to sediment dwelling organisms was considered to be low in the surface water risk assessment
M4	medium mobile (K_{foc} = 221.4 – 407.8 mL / g)	FOCUS: Trigger not exceeded for any of the representative uses and scenarios simulated.	No	Higher toxicity than benthiavalicarb-isopropyl; genotoxic *in vitro*	The risk to sediment dwelling organisms was considered to be low in the surface water risk assessment

Compound (name and/or code)	Mobility in soil	> 0.1 µg / L 1m depth for the representative uses (at least one FOCUS scenario or relevant lysimeter)	Pesticidal activity	Toxicological relevance	Ecotoxicological relevance
M5	medium to low mobile (K_{foc} = 494.4 – 787.3 mL / g)	FOCUS: Trigger not exceeded for any of the representative uses and scenarios simulated.	No	Higher toxicity than benthiavalicarb-isopropyl	The risk to sediment dwelling organisms was considered to be low in the surface water risk assessment
M8	No data, only relevant for uses for which anaerobic conditions may be expected				

Surface water and sediment

Compound (name and/or code)	Ecotoxicology
benthiavalicarb-isopropyl (water and sediment)	See point 5.2.
M3 (sediment only)	The risk to sediment dwelling organisms is considered to be low
M4 (sediment only)	The risk to sediment dwelling organisms is considered to be low
M5 (sediment only)	The risk to sediment dwelling organisms is considered to be low

Air

Compound (name and/or code)	Toxicology
benthiavalicarb-isopropyl	Not acutely toxic via inhalation

LIST OF STUDIES TO BE GENERATED, STILL ONGOING OR AVAILABLE BUT NOT PEER REVIEWED

- Spectra for the relevant impurity KIF-230-I-6 according to Directive 94/37/EC. (RMS had received and evaluated the recently submitted studies in an addendum to the DAR, November 2006; the assessment was neither peer reviewed nor discussed (relevant for all uses evaluated; data gap identified by the meeting of experts, refer to chapter 1)
- In a letter dated 25 of October 2006 the applicant made case to address the formation of a breakdown product. This case stated that the instability was as a result of self irradiation. The applicant must explain how self irradiation causes instability of the molecule and address any consequences for the radiolabelled studies. (relevant for all uses evaluated data gap identified by EFSA April 2007; date of submission unknown; refer to chapter 1)
- Data on succeeding crops to fully address the concern about selective uptake of soil metabolites identified as being of toxicological concern (M1, M4, M5) (relevant for the uses in tomatoes, potatoes; date of submission unknown, data gap identified by the meeting of experts, refer to chapter 3); in case M4 is found, further genotoxicity tests including an in-vitro chromosome aberration study and an *in-vivo* micronucleus test might be considered
- A risk assessment for terrestrial vertebrates and aquatic organisms for the representative uses of KIF 230/Mancozeb 17.5/700 WG taking into consideration the toxicity of mancozeb (relevant for the representative uses of KIF 230/Mancozeb 17.5/700 WG in tomato, grapevine and potato; identified in the evaluation meeting in December 2004 and confirmed in the EPCO experts` meeting in April 2005; no submission date proposed by the applicant).
- A long-term study with earthworms and the formulation KIF-230 15% WG or a valid argumentation to address concerns with regard to long-term risk to earthworms (relevant for the outdoor use of KIF 230 15% WG in tomato; data gap identified in the EPCO experts` meeting in April 2005; no submission date proposed by the applicant, RMS suggested that the data should be submitted at national level after Annex I inclusion)
- A higher tier study with *Typhlodromus pyri* and the formulation KIF-230/Mancozeb 17.5/700 WG (relevant for the uses of KIF-230/Mancozeb 17.5/700 WG in tomato, grapevine and potato; data requirement identified by the RMS and confirmed in the EPCO experts` meeting in April 2005; no submission date proposed by the applicant)
- A study with *T. pyri* and *A. rhopalosiphi* at a dose rate high enough to cover the representative uses of KIF-230 15% WG (applying a MAF of 3.2) (relevant for the outdoor use of KIF-230 15% WG in tomato; data requirement identified in the evaluation meeting in December 2004 and confirmed by the EPCO experts` meeting in April 2005; no submission date proposed by the applicant).

CONCLUSIONS AND RECOMMENDATIONS

Overall conclusions

The conclusion was reached on the basis of the evaluation of the use as fungicide as proposed by the applicant which comprise foliar spraying to control *Phytophthora infestans and Plasmopara viticola* in grapes, tomatoes and potatoes. Due to the fact that the isopropyl ester, a variant of benthiavalicarb, is used in the formulated product, it should be noted that the evaluated data belong to the variant benthiavalicarb-isopropyl, unless otherwise specified.

Only the use of benthiavalicarb-isopropyl as a fungicide was evaluated.

The representative formulated products for the evaluation were "KIF-230 15% WG" and "KIF-230/Mancozeb 17.5/700 WG", both are water dispersible granules (WG).

Adequate methods are available to monitor all compounds given in the respective residue definition. None of them is enantioselective. The methods determine all 4 possible isomers, but the pairs of enantiomers only as a sum.

Sufficient analytical methods as well as methods and data relating to physical, chemical and technical properties are available to ensure that quality control measurements of the plant protection product are possible.

Benthiavalicarb-isopropyl has a low acute toxicity after oral, dermal and inhalatory exposure. It is neither a skin nor an eye irritant, while it is a skin sensitiser, therefore the classification as **R43** "May cause sensitisation by skin contact" is proposed. Overall, benthiavalicarb-isopropyl is not genotoxic both *in-vivo* and *in-vitro* assays. Benthiavalicarb-isopropyl is proposed for classification as **Carc. Cat. 3 R40**, due to the occurrence of uterine tumours in rats. The relevant NOAEL is 9.9 mg/kg bw/day either for general toxicity or for carcinogenicity (LOAEL 250 mg/kg bw/day). Benthiavalicarb-isopropyl does not show reproductive toxicity potential: The relevant parental NOAEL is 10 mg/kg bw/day, the pup NOAEL is 67.2 mg/kg bw/day and the reproductive toxicity NOAEL is 702.5 mg/kg bw/day (highest dose tested).The lowest relevant developmental NOAEL is established at 20 mg/kg bw/day, based upon the increased ossification delay and the increased dwarfism incidence at the top dose in rats. The findings were both considered associated with treatment. During the written procedure, EFSA considered that the proposal for **R63** might be justified due to the maternal NOAEL $\geq$ 20 mg/kg bw/day. The ADI is 0.1 mg/kg bw/day based on the NOAEL from the 2 year study in rats with an assessment factor of 100; the AOEL is 0.1 mg/kg bw/day derived from the rat teratogenicity study and an assessment factor of 100. The allocation of the ARfD was not deemed necessary based on the toxicological profile of benthiavalicarb-isopropyl. The operator exposure assessment shows estimated exposure levels below the AOEL (German model), even without the use of PPE; the estimated worker and bystander exposure for the worst case scenario represents about 48% and 1% of the AOEL, respectively.

The metabolism of benthiavalicarb was investigated in grapes, tomatoes and potatoes after a foliar treatment with radio-labelled benthiavalicarb-isopropyl. Potato metabolism was also studied after a

soil treatment. In all crops investigated, benthiavalicarb-isopropyl was the major component of the terminal residue. A pH induced isomerisation of benthiavalicarb-isopropyl into the diastereomer KIF-230 S-L was observed in the tomato study. In general, only minor amounts of metabolites of benthiavalicarb-isopropyl were generated; and they were partially present as free metabolites but mainly conjugated with glucose. None of the metabolites identified in primary crops was found to be of a particular toxicological concern. A cleavage of the amide bond, as occurring in soil, was not observed in primary crop metabolism studies. However, no sufficient data are currently available to address the concern about a potential selective uptake of toxicologically relevant metabolites from soil.

Given the residue situation in crops that are relevant as animal feed items, no significant residues in livestock diet are expected. However, this assessment may have to be reviewed upon receipt of further data on investigation of residues in rotational crops potentially used as feed items.

Assessment of the safety of different consumers groups indicates that the intake of residues of benthiavalicarb-isopropyl (including potentially present residues of KIF230 S-D, KIF 230 S-L and KiF 230 R-D) resulting from the supported representative uses is well below the toxicological reference value for chronic exposure (ADI) for benthiavalicarb-isopropyl. Potential contribution from animal commodities and succeeding crops were not included in the calculations.

Nevertheless, it should be mentioned that for the uses with a combi-formulation (grapevines, tomatoes, potatoes) containing besides benthiavalicarb-isopropyl also mancozeb, the consumer risk assessment could not be completed, since no assessment with regard to mancozeb residues was carried out.

Benthiavalicarb-isopropyl is moderately persistent in soil under aerobic conditions ($DT_{50\ lab\ 20\ °C}$ = 10.6– 19.1 d). In the experiments performed with the ^{14}C-phenyl-benthiavalicarb-isopropyl four major soil transformation products were identified: M1 (max. 27. 7 % AR after 120 d); M3 (max. 12.3 % AR after 28 d); M4 (max. 9.8 % AR after 28 d) and M5 (max. 26.8 % after 58 d). Bound residues reached a maximum of 58.2 % AR and mineralization was between 3.6 – 11.7 % AR at 120 d. Selected sample were analysed with HPLC and a chiral stationary phase. No isomeric conversion of the active substance was observed in any of the experiments. Data from the parent study was employed to derive the degradation rates of the transformation product M5 ($DT_{50\ lab\ 20\ °C}$ = 17.4 – 40.4 d). The degradation of the transformation products M1, M3 and M4 was investigated in separated studies with three soils. M1 was shown to be low to moderately persistent ($DT_{50\ lab\ 20\ °C}$ = 4 – 27 d), M3 low persistent ($DT_{50\ lab\ 20\ °C}$ = 2 – 7 d) and M4 very low persistent to moderate persistent in soil ($DT_{50\ lab\ 20\ °C}$ < 1 d; $DT_{90\ lab\ 20\ °C}$ = 32 – 80.75 d).

Under dark anaerobic conditions at 20 ºC benthiavalicarb-isopropyl was slightly more persistent than in aerobic ones ($DT_{50\ anaerobic\ lab\ 20\ °C}$ = 39.9 d). Transformation product M8 was found in higher amounts in anaerobic conditions and should be considered as a major soil anaerobic metabolite with respect to the ground water exposure assessment.

In the experiment performed with the ^{14}C-valyl-benthiavalicarb-isopropyl labelled experiment no metabolites were identified. Bound residues reached a maximum of 41.2 % AR after 59 d and then

decreased to 26.5 % AR at the end of the experiment (365 d). Mineralization of the side chain was relatively high (44 % AR as CO_2 after 120 d).

Photolysis is not expected to contribute to the degradation of benthiavalicarb-isopropyl in soil.

PEC soil were calculated by the RMS based on the worst case laboratory half life of 19.1 d and the representative uses (tomatoes 6 x 0.75 g a.s. / ha, 7 d interval; grapes 6 x 35 g a.s. / ha, 7 d interval) with 50 % interception. Applicant provided a PEC soil calculation assuming no degradation between application and resulting in a worst case with respect to the RMS proposal. Maximum amount observed of metabolites was applied to this worst case PEC soil for the parent to calculate maximum PEC soil of metabolites.

Batch adsorption / desorption studies show that benthiavalicarb-isopropyl is high to medium mobile (K_{foc} = 121.3 – 258.2 mL / g), M1, M3 and M4 are medium mobile (M1: K_{foc} = 237.2 – 422.3 mL / g; M3: K_{foc} = 116.4 – 241.0 mL / g; M4: K_{foc} = 221.4 – 407.8 mL / g) and M5 is medium to low mobile in soil (K_{foc} = 494.4 – 787.3 mL / g).

According the available hydrolysis study, benthiavalicarb-isopropyl may be considered stable to hydrolysis under most common environmental conditions. Photolysis may contribute to the environmental degradation of benthiavalicarb-isopropyl in acidic waters (pH 5: DT_{50} = 6.8 d). Benthiavalicarb-isopropyl is not readily biodegradable according the available study.

In water / sediment systems, benthiavalicarb-isopropyl partitions to the sediment where it breaks down to the metabolites M3 (max. 26. 3% after 100d, end of the study), M4 (max. 22.7 % AR after 30 d) and M5 (max. 11.9 % after 59 d). No major metabolites were identified in the water phase. Bound residues reached 40.6 % AR at the end of the study (100 d). Volatiles collected in the NaOH trap (presumably CO_2) reached maxima of 0.9 and 3.8 % AR at the end of the study (100 d). Benthiavalicarb-isopropyl degradation on the whole systems proceeded with half lives of 15 and 18.2 d. No isomeric conversion of the active substance was observed in any of the experiments.

PEC_{SW} of benthiavalicarb-isopropyl were calculated for the representative uses based on spray drift loadings. Worst case half life dissipation ($DT_{50\ diss.\ water}$ = 7.7 d) from the water sediment studies was used in this calculation. PEC_{SED} for the metabolites M3, M4 and M5 were calculated based on the lumped application rate without degradation between applications and the maximum percentage observed in the water sediment studies corrected for the molecular weight.

For the representative uses proposed and the scenarios modelled with FOCUS PEARL none of the concentration of the potential residue components exceeds the trigger value of 0.1 µg / L in ground water.

Benthiavalicarb-isopropyl is not expected to be transferred to the atmospheric compartment and potential for long range transport may be considered negligible.

The risk to birds and mammals was assessed as low for the representative use of the formulation KIF-2230 15% WG in tomatoes. The risk assessment for the formulation KIF-230/Mancozeb 17.5/700 WG is not completed since the toxicity of the second active substance mancozeb was not considered in the risk assessment. The risk assessment for aquatic organisms was based on endpoints from technical benthiavalicarb-isopropyl. Spray drift was considered as the only relevant route of entry into surface water. Therefore aquatic organisms would be exposed to the formulation and not to technical

benthiavalicarb-isopropyl alone. However the endpoints observed in tests with benthiavalicarb-isopropyl formulated as KIF-230 15% WG are similar to technical active substance and the risk to aquatic organisms is considered to be low for the representative uses of KIF-230 15% WG in tomatoes.

A high risk to aquatic organisms from the representative uses of KIF 230/Mancozeb 17.5/700 WG cannot be excluded since the formulation KIF 230/Mancozeb 17.5/700 WG is about 3 orders of magnitude more toxic compared to the formulation KIF-230 15% WG. A full risk assessment for the representative uses of KIF 230/Mancozeb 17.5/700 WG is required.

The HQ values for the use of KIF-230/Mancozeb 17.5/700 WG in tomatoes/grapevine indicated a potential high risk to predatory mites. The risk to *T. pyri* needs to addressed further. The expert meeting on ecotoxicology agreed to the data requirement and concluded that these data should be made available before Annex I listing.

No effects of >30% were observed in tests with KIF-230 15% WG. However the tested dose was too low and a data requirement was set in the evaluation meeting for the applicant to provide studies at an application rate which covers the representative use (applying a MAF of 3.2). The data requirement was confirmed by the expert meeting.

The acute risk to earthworms was assessed as low for all representative uses evaluated. The long-term TER value of 2.9 for the representative use of KIF-230 15% WG in tomatoes was below the trigger of 5. Since the long-term endpoint (NOEC) is based on the highest tested dose and a high margin of safety was observed in the acute risk assessment the risk to earthworms was considered to be low by the RMS for all representative uses.

The risk from the major soil metabolites KIF-230-M1 and KIF-230-M3 to earthworms was assessed as low. The risk from the metabolites KIF-230-M1 and KIF-230-M3 was discussed in the expert meeting on ecotoxicology and considered to be low.

The risk to bees, other soil non-target macro-organisms, soil micro-organisms, non-target plants and biological methods of sewage treatment was assessed as low for all representative uses.

Particular conditions proposed to be taken into account to manage the risk(s) identified

- None

Critical areas of concern

- As for the combined formulation (benthiavalicarb-isopropyl + mancozeb), the operator, worker, bystander and consumer risk assessment should be regarded as inconclusive.
- The risk assessment for birds and mammals and aquatic organisms for the representative uses of the formulation KIF-230/Mancozeb 17.5 WG was based on the toxicity of benthiavalicarb-isorpropyl alone. The toxicity of mancozeb was not taken into account. A high risk to birds and mammals and aquatic organisms cannot be excluded for the formulation KIF 230/Mancozeb 17.5/700 WG (representative uses in tomato, grapes and potato) on the basis of the risk assessments provided.

- The risk to predatory mites from the representative uses of KIF 230/Mancozeb 17.5/700 WG needs to be addressed further.
- The tests with non-target arthropods and the formulation KIF 230 15% WG were conducted at dose rates too low to cover the representative uses.

APPENDIX 1 – LIST OF ENDPOINTS FOR THE ACTIVE SUBSTANCE AND THE REPRESENTATIVE FORMULATION

(Abbreviations used in this list are explained in appendix 2)

Appendix 1.1: Identity, Physical and Chemical Properties, Details of Uses, Further Information

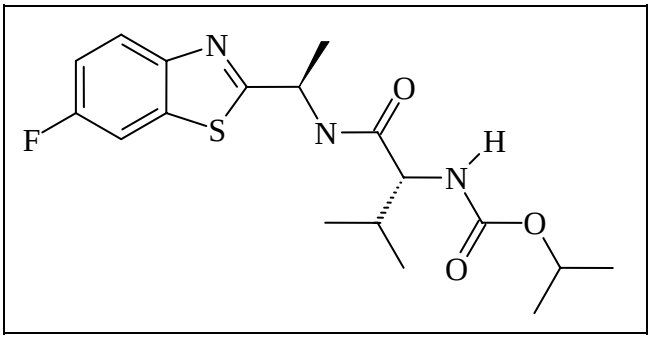
Active substance (ISO Common Name) ‡	Benthiavalicarb (ISO provisionally approved) The given data belong to the variant benthiavalicarb-isopropyl, unless specified otherwise
Function (e.g. fungicide)	Fungicide

Rapporteur Member State	Belgium
Co-rapporteur Member State	--

Identity (Annex IIA, point 1)

Chemical name (IUPAC) ‡	Isopropyl [(*S*)-1-{[(*R*)-1-(6-fluoro-1,3-benzothiazol-2-yl) ethyl]carbamoyl}-2-methylpropyl]carbamate
Chemical name (CA) ‡	1-methylethyl [(1S)-1-[[[(1R)-1-(6-fluoro-2-benzothiazolyl)ethyl]amino]carbonyl]-2-methylpropyl] carbamate
CIPAC No ‡	744 (benthiavalicarb) 744.204 (benthiavalicarb-isopropyl)
CAS No ‡	413615-35-7 (benthiavalicarb) 177406-68-7 (benthiavalicarb-isopropyl)
EEC No (EINECS or ELINCS) ‡	Not assigned
FAO Specification ‡ (including year of publication)	Not available
Minimum purity of the active substance as manufactured ‡ (g/kg)	910 g/kg (commercial plant)
Identity of relevant impurities (of toxicological, environmental and/or other significance) in the active substance as manufactured (g/kg)	KIF-230-I-6: < 3.5 mg/kg KIF-230-I-12: < 14 mg/kg
Molecular formula ‡	$C_{18}H_{24}FN_3O_3S$
Molecular mass ‡	381.47

‡ Endpoints identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Structural formula ‡	

Physical-chemical properties (Annex IIA, point 2)

Melting point (state purity) ‡	153.1 °C and 169.5 °C (polymorphism) (99.96%)
Boiling point (state purity) ‡	No boiling point could be determined due to decomposition (99.96%)
Temperature of decomposition	ca. 240 °C at atmospheric pressure (102 kPa) (99.96%)
Appearance (state purity) ‡	White powdered solid, odourless (99.96%)
Relative density (state purity) ‡	1.25 at 20.5 °C (99.96%)
Surface tension	63.1 mN/m at 22 °C (90% saturated solution)
Vapour pressure (in Pa, state temperature) ‡	< 3.0×10^{-4} Pa at 25 °C
Henry's law constant (Pa m^3 mol^{-1}) ‡	< 8.72×10^{-3} Pa.m^3.mol^{-1} at 20-25 °C
Solubility in water ‡ (g/L or mg/L, state temperature)	pH 5, 20 °C: 10.96 mg/L pH 9, 20 °C: 12.76 mg/L pH ≈ 6.3 (distilled water), 20 °C: 13.14 mg/L
Solubility in organic solvents ‡ (in g/L or mg/L, state temperature)	Solubility at 20 °C (g/L) heptane 2.15×10^{-2} xylene 0.501 1,2-dichloroethane 11.5 methanol 41.7 acetone 25.4 ethyl acetate 19.4
Partition co-efficient (log POW) ‡ (state pH and temperature)	pH 5, 20-25 °C: 2.63 (range 2.37 – 2.93) pH 9, 20-25 °C: 2.62 (range 2.36 – 2.90) pH unadjusted (distilled water), 20-25 °C: 2.56 (range 2.28 – 2.86)

‡ Endpoints identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Hydrolytic stability (DT_{50}) ‡ (state pH and temperature)	pH 4, 50 °C: hydrolytically stable pH 7, 50 °C: hydrolytically stable pH 9, 50 °C: hydrolytically stable
Dissociation constant ‡	No dissociation occurs in pH range 1.12 – 12.81
UV/VIS absorption (max.) ‡ (if absorption > 290 nm state ε at wavelength)	Neutral: λ_{max} 219 nm; ε = 24424 $L.mol^{-1}.cm^{-1}$ at λ 292.5 nm : ε = 1298 $L.mol^{-1}.cm^{-1}$
Photostability (DT_{50}) ‡ (aqueous, sunlight, state pH)	pH 5, 25 °C: DT_{50} = 6.8 d pH 7, 25 °C: DT_{50} = 516 d pH 9, 25 °C: DT_{50} = 178 d
Quantum yield of direct phototransformation in water at Σ > 290 nm ‡	≤ 0.0014
Flammability ‡	Not highly flammable; not auto-flammable
Explosive properties ‡	No explosive properties

‡ Endpoints identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

List of representative uses evaluated*

Crop and/or situation	Member State or Country	Product name	F G or I	Pests or Group of pests controlled	Formulation		Application				Application rate per treatment			PHI (days)	Remarks:
					Type	Conc. of a.s.	method kind	growth stage & season	number min max	interval between applications (min)	kg as/hl min max	water l/ha min max	kg as/ha min max		
(a)			(b)	(c)	(d-f)	(i)	(f-h)	(j)	(k)					(l)	(m)
Tomato	France Italy Portugal Spain	KIF-230 15% WG	F	*Phytophthora infestans*	WG	150 KIF-230	spray	From first symptoms of the disease	6	7	0.0075-0.030 KIF-230	250-1000	0.075 KIF-230	7	0.5 kg product /ha [1]
Tomato	France Italy Portugal Spain	KIF-230 15% WG	I	*Phytophthora infestans*	WG	150 KIF-230	spray	From first symptoms of the disease	6	7	0.0075-0.030 KIF-230	250-1000	0.075 KIF-230	3	0.5 kg product /ha
Tomato	France Italy Portugal Spain	KIF-230/ Mancozeb 17.5/ 700 WG	F	*Phytophthora infestans*	WG	17.5 KIF-230 + 700 mancozeb	spray	From first symptoms of the disease	6	7	0.0035-0.014 KIF-230 0.140-0.56 mancozeb	250-1000	0.035 KIF-230 1.400 mancozeb	7	2.0 kg product /ha [2]
Tomato	France Italy Portugal Spain	KIF-230/ Mancozeb 17.5/ 700 WG	I	*Phytophthora infestans*	WG	17.5 KIF-230 + 700 mancozeb	spray	From first symptoms of the disease	6	7	0.0035-0.014 KIF-230 0.140-0.56 mancozeb	250-1000	0.035 KIF-230 1.400 mancozeb	3	2.0 kg product /ha [2]

‡ Endpoints identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Crop and/or situation	Member State or Country	Product name	F G or I	Pests or Group of pests controlled	Formulation		Application				Application rate per treatment			PHI (days)	Remarks:
					Type	Conc. of a.s.	method kind	growth stage & season	number min max	interval between applications (min)	kg as/hl min max	water l/ha min max	kg as/ha min max		
(a)			(b)	(c)	(d-f)	(i)	(f-h)	(j)	(k)					(l)	(m)
Grapes (wine and table)	France, Germany Greece, Italy, Luxembourg, Portugal, Spain	KIF-230/ Mancozeb 17.5/ 700 WG	F	*Plasmopara viticola*	WG	17.5 KIF-230 + 700 mancozeb	spray	From first symptoms of the disease	6	10	0.0029-0.035 KIF-230 0.117-1.400 mancozeb	100-1200	0.035 KIF-230 1.400 mancozeb	28	2 kg product/ha [2]
Potato	Austria Belgium France Germany Greece Italy, Spain Sweden, UK	KIF-230/ Mancozeb 17.5/ 700 WG	F	*Phytophthora infestans*	WG	17.5 KIF-230 + 700 mancozeb	spray	From first symptoms of the disease	6	7	0.003-0.014 KIF-230 ~0.112-0.560 mancozeb	200-1000	0.028 KIF-230 1.120 mancozeb	7	1.6 kg product/ha [2]

[1] A high risk and or data gaps were identified in section 5

[2] The toxicity of the second active substance (mancozeb) was not considered in the risk assessment for terrestrial vertebrates and aquatic organisms and therefore a high risk to these groups of organisms cannot be excluded for the representative uses of KIF-230/Mancozeb 17.5/700 WG. A data gap was identified for non-target arthropods in section 5.

Remarks:	*	Uses for which risk assessment could not been concluded due to lack of essential data are marked grey	(h)	Kind, *e.g.* overall, broadcast, aerial spraying, row, individual plant, between the plants - type of equipment used must be indicated
	(a)	For crops, the EU and Codex classifications (both) should be used; where relevant, the use situation should be described (*e.g.* fumigation of a structure)	(i)	g/kg or g/L
			(j)	Growth stage at last treatment (BBCH Monograph, Growth Stages of Plants,

‡ Endpoints identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

	(b)	Outdoor or field use (F), glasshouse application (G) or indoor application (I)		1997, Blackwell, ISBN 3-8263-3152-4), including where relevant, information on season at time of application
	(c)	*e.g.* biting and suckling insects, soil born insects, foliar fungi, weeds		
	(d)	*e.g.* wettable powder (WP), emulsifiable concentrate (EC), granule (GR)	(k)	The minimum and maximum number of application possible under practical conditions of use must be provided
	(e)	GCPF Codes - GIFAP Technical Monograph No 2, 1989		
	(f)	Method, *e.g.* high volume spraying, low volume spraying, spreading, dusting, drench	(l)	PHI - minimum pre-harvest interval
	(g)	All abbreviations used must be explained	(m)	Remarks may include: Extent of use/economic importance/restrictions

‡ Endpoints identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Appendix 1.2: Methods of Analysis

Analytical methods for the active substance (Annex IIA, point 4.1)

Technical as (principle of method)	Chiral HPLC-UV
Impurities in technical as (principle of method)	(chiral) HPLC-UV headspace GC-FID Karl Fischer
Plant protection product (principle of method)	KIF-230 15% WG Benthiavalicarb-isopropyl: chiral HPLC-UV KIF-230/Mancozeb 17.5/700 WG Benthiavalicarb-isopropyl: chiral HPLC-UV Mancozeb: CS_2-evolution + iodometry ETU: HPLC-UV

Analytical methods for residues (Annex IIA, point 4.2)

Food/feed of plant origin (principle of method and LOQ for methods for monitoring purposes)	GC-NPD, LOQ = 0.01 mg/kg (for each pair of enantiomers) (commodities with high water content)
Food/feed of animal origin (principle of method and LOQ for methods for monitoring purposes)	Not required
Soil (principle of method and LOQ)	Enforcement method CLE 535/83: LC-MS/MS LOQ = 0.01 mg/kg for each pair of enantiomers
Water (principle of method and LOQ)	Enforcement method CLE 535/81-06R: LC-MS/MS LOQ = 0.1 µg/L for each pair of enantiomers (drinking water, surface water)
Air (principle of method and LOQ)	Enforcement method CLE 535/82-02R: GC-NPD LOQ = 0.75 µg/m³ for each pair of enantiomers (ambient air, warm air)
Body fluids and tissues (principle of method and LOQ)	Not required

Classification and proposed labelling (Annex IIA, point 10)

with regard to physical/chemical data	None

‡ Endpoints identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Appendix 1.3: Impact on Human and Animal Health

Absorption, distribution, excretion and metabolism in mammals (Annex IIA, point 5.1)

Rate and extent of absorption ‡	Rapid (<48h); efficient (89-97%) at low dose, less efficient (41-54%) at high dose
Distribution ‡	Widely distributed
Potential for accumulation ‡	Apparent accumulation after repeated administration, most probably due to recruitment of valine
Rate and extent of excretion ‡	Rapid, within 48h: 73-81% (low dose) and 80-86% (high dose); means (48h):12% urine/cage wash , 65% faeces; evidence of biliary excretion, enterohepatic circulation
Metabolism in animals ‡	Extensive (low dose) to low (high dose) metabolisation; major metabolite B11 (glucuronic acid conjugate of hydroxylated derivative); limited cleavage of the amide bond of the valyl-moiety
Toxicologically significant compounds ‡ (animals, plants and environment)	Benthiavalicarb-isopropyl; impurities KIF-230–I6, and –I12 (only pilot and some tox batches) and metabolites M1 M4 and M5

Acute toxicity (Annex IIA, point 5.2)

Rat LD_{50} oral ‡	>5000 mg/kg b.w.
Rat LD_{50} dermal ‡	>2000 mg/kg b.w.
Rat LC_{50} inhalation ‡	>4.6 mg/L air
Skin irritation ‡	Not irritant
Eye irritation ‡	Not irritant
Skin sensitization ‡ (test method used and result)	Maximisation test, sensitiser **Xi R43**

Short term toxicity (Annex IIA, point 5.3)

Target / critical effect ‡	Rat: Liver (↑weight, γGT), RBC (anaemia); Dog: liver/adrenal (↑weight), thymus (↓weight), RBC (anaemia)
Lowest relevant oral NOAEL / NOEL ‡	14 mg/kg b.w./d (90d rat)
Lowest relevant dermal NOAEL / NOEL ‡	300 mg/kg b.w./d
Lowest relevant inhalation NOAEL / NOEL ‡	No data, not required

‡ Endpoints identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Genotoxicity ‡ (Annex IIA, point 5.4)

.....	*In-vitro:* negative in Ames, TK, UDS, clastogenicity (equivocal indication of polyploidisation) *In-vivo:* negative in UDS, micronucleus. Overall no genotoxic potential

Long term toxicity and carcinogenicity (Annex IIA, point 5.5)

Target/critical effect ‡	Liver (rat, mouse); thyroid (rat, mouse); diverse organs at MTD (mouse)
Lowest relevant NOAEL / NOEL ‡	9.9 mg/kg b.w./d
Carcinogenicity ‡	Uterine adenocarcinoma (rat); liver adenoma, carcinoma, hepatoblastoma (mouse) at MTD **Carc. Cat. 3 (R40)** (uterine tumours in rat)

Reproductive toxicity (Annex IIA, point 5.6)

Reproduction target / critical effect ‡	2G rat: parents: ↑liver weight •pups: ↑liver weight, ↓spleen/thymus weight
Lowest relevant reproductive NOAEL / NOEL ‡	NOAEL parental: 10 mg/kg b.w./d NOAEL pups: 67.2 mg/kg b.w./d NOAEL reprotox: 702.5 (highest dose)
Developmental target / critical effect ‡	Rat: •maternal: ↑adrenal/liver weight •developmental: ↑thymic remnants
Lowest relevant developmental NOAEL / NOEL ‡	NOAEL maternal (rat):: 10 mg/kg b.w./d; NOAEL developmental (rabbit): 20 mg/kg b.w./d

Neurotoxicity / Delayed neurotoxicity ‡ (Annex IIA, point 5.7)

(i) Delayed neurotoxicity:	Not required
(ii) Acute and subchronic neurotoxicity: NOAEL (28d, neurotoxicity rat):	no meaningful neurotoxic effects 174 mg/kg b.w./d (↓bw gain, slight ↓motor activity, probably due to general toxicity)

‡ Endpoints identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Other toxicological studies ‡ (Annex IIA, point 5.8)

(1) mode of action of carcinogenicity *Thyroid* (i) 14d (diet), rat/mouse and (ii) 16 week (diet), mouse *Uterus:* (iii) 8 weeks (diet), rat: *Liver:* (iv) 8/10 weeks (diet), rat (initiation/promotion assay) (v) 7d (gavage), rat/mouse *In-vitro*: (vi) transformation assay in 3T3 (2) oxidative damage in liver cells (vii) 14d (iet), rat/mouse (3) acute oral toxicity (viii) and genotoxicity (ix) of metabolites/impurities	(i) ↑UDP-GT, ↑T_4, no effect on T_3/TSH on wk2 (ii) weak ↑TSH on wk16, not on wk 2, 4, 8 (iii) ↑aromatase in liver, not in uterus/ovary, no effect on serum oestradiol, progesterone, luteneisating hormone (iv) no initiating but phenobarbital-like promotion potency (v) induction of CYP450 enzymes, suggesting a PB-like effect; however in rat (not in mouse) also slight induction of CYP1A1 (AHC type of induction) (vi) slight colony-forming potential ('promotion'-type) (vii) no increase of 8-OhdG in liver cell DNA (viii) Metabolites KIF-230–M1 and –M5, and impurity KIF-230–I12 were more acutely toxic than benthiavalicarb-isopropyl (ix) Metabolites KIF-230–M4, and impurities KIF-230–I6 and –I12 were genotoxic in bacteria (TA98); Impurities KIF-230–I6 and –I12 were present in the pilot batches, but not in the commercial batches for which authorisation is sought.

Medical data ‡ (Annex IIA, point 5.9)

.....	Based on the reports of the medical surveillance on manufacturing plant personnel, observed effects were declared not to be related to the exposure to the active substance

Summary (Annex IIA, point 5.10)

	Value	Study	Safety factor
ADI ‡	0.1	2 yr rat	100
AOEL ‡	0.1	terato rat	100
ARfD (acute reference dose) ‡	Not allocated, not necessary	-	-

Dermal absorption (Annex IIIA, point 7.3)

In-vitro penetration study (rat, human)	Low dose: 70%; high dose: 16%

‡ Endpoints identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Acceptable exposure scenarios (including method of calculation)

Operator	Below the AOEL (<37%) without PPE (German model, all scenarios considered); below the AOEL for potatoes (<62%, no PPE), tomatoes (tractor mounted application, 23%, with PPE), above the AOEL for grapes (194% with PPE) and tomatoes (hand held application, 175%, with PPE) (UK POEM)
Workers	48% of the AOEL
Bystanders	1% of the AOEL

Classification and proposed labelling (Annex IIA, point 10)

with regard to toxicological data	Xn R43; Carc. Cat. 3 R40, R63?* Skin sensitiser Limited evidence of a carcinogenic effect

* During the written procedure, EFSA, supported by some MSs, considered that the proposal for Repr. Cat 3 (**R63)** might be justified due to the maternal NOAEL ≥ 20 mg/kg bw/day in rabbit (at this level toxicity consists in 10% increased liver weight). The RMS did not agree as the incidence was low and the effects were not considered serious enough and maternal toxicity was suspected (abortions at this dose and also reduced bodyweight in the dam showing nanofoetuses). The issue was not discussed in an experts' meeting.

‡ Endpoints identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Appendix 1.4: Residues

Metabolism in plants (Annex IIA, point 6.1 and 6.7, Annex IIIA, point 8.1 and 8.6)

Plant groups covered	Grapes, tomatoes (F), potatoes (R)
Rotational crops	A rotational crop study is required to fully address the concern about selective uptake of soil metabolites identified as being of toxicological concern (M1, M4, M5).
Plant residue definition for monitoring	Sum of Benthiavalicarb-isopropyl (KIF-230 R-L), and its enantiomer (KIF-230 S-D) and diastereomers (KIF-230 S-L and KIF-230 R-D) expressed as benthiavalicarb-isopropyl.
Plant residue definition for risk assessment	Sum of Benthiavalicarb-isopropyl (KIF-230 R-L), and its enantiomer (KIF-230 S-D) and diastereomers (KIF-230 S-L and KIF-230 R-D) expressed as benthiavalicarb-isopropyl.
Conversion factor (monitoring to risk assessment)	None

Metabolism in livestock (Annex IIA, point 6.2 and 6.7, Annex IIIA, point 8.1 and 8.6)

Animals covered	None
Animal residue definition for monitoring	Not required
Animal residue definition for risk assessment	Not required
Conversion factor (monitoring to risk assessment)	None
Metabolism in rat and ruminant similar (yes/no)	No investigation
Fat soluble residue: (yes/no)	No, according to log P*ow* value < 3

Residues in succeeding crops (Annex IIA, point 6.6, Annex IIIA, point 8.5)

.....	A rotational crop study is required to fully address the concern about selective uptake of soil metabolites identified as being of toxicological concern (M1, M4, M5).

Stability of residues (Annex IIA, point 6 introduction, Annex IIIA, point 8 introduction)

.....	Residues of benthiavalicarb-isopropyl (both isomers KIF-230R-L and KIF-230S-L) in tomato fruit , grape berries and potato tuber can be considered as stable under frozen storage conditions for 8 months (tomato) and 1 year (grapes and potatoes).

‡ Endpoints identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Regarding the stability of the residues in grapes under frozen storage conditions, an important degradation of the residue level (24%) occurred from day 0 within the first month of storage. In the second part of the storage period (from 34 days to 395 days), the residue level can be considered as stable in grapes.

Residues from livestock feeding studies (Annex IIA, point 6.4, Annex IIIA, point 8.3)

Intakes by livestock ≥ 0.1 mg/kg diet/day:	Ruminant: no	Poultry: no	Pig: no
Muscle	-	-	-
Liver	-	-	-
Kidney	-	-	-
Fat	-	-	-
Milk	-	-	-
Eggs	-	-	-

Feeding studies are not required considering that non significant residues (<0.01 mg/kg) in the total diet (as received) may occur on the basis of the 1 x dose rate.

‡ Endpoints identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Summary of critical residues data (Annex IIA, point 6.3, Annex IIIA, point 8.2)

Crop	Northern or Mediterranean Region	Trials results relevant to the critical GAP [mg/kg] (a)	Recommendation/comments	MRL	STMR (b)
Table and wine grapes	NE	*Sum of all isomers expressed as benthiavalicarb-isopropyl:* 0.02, 0.03, 4 x 0.04, 3 x 0.05, 0.06, 2 x 0.08, 2 x 0.09, 2 x 0.12, 0.13, 0.15, 0.27 - *KIF-230R-L (incl. KIF-230S-D):* 0.049, 0.013, 0.022, 0.120, 0.076, 0.06, 0.09, 0.03, 0.08, 0.04, 0.13, 0.21, 0.04, 0.03, 0.04, 0.03, 0.03, 0.11, 0.07 - *KIF-230S-L (incl. KIF-230R-D):* <0.01, <0.01, <0.01, <0.01, <0.01, 0.02, 0.03, <0.01, <0.01, <0.01, 0.02, 0.06, <0.01, 0.01,<0.01, <0.01, <0.01, <0.01, <0.01	19 trials are available for the North of EU. Trials were performed in accordance with the critical GAP following 6 foliar spray applications at a rate of 0.035 kg a.s./ha with an interval of 9 to 11 days between each application. Decay curves are given with last sampling 28 days after last application. Commodities which were analysed were the berries, juice, raisin, must and wine.	0.3[12]	0.05

[12] Due to the amendment of the residue definition in the second discussion in a meeting of experts (PRAPeR 15) the highest residue (as the sum of isomers) in grapes has increased and therefore the initially proposed MRL of 0.2 mg/kg needs to be raised to 0.3 mg/kg. New proposal not peer reviewed but agreed between the RMS and EFSA.

‡ Endpoints identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Crop	Northern or Mediterranean Region	Trials results relevant to the critical GAP [mg/kg] (a)	Recommendation/comments	MRL	STMR (b)
Table and wine grapes	SE	*Sum of all isomers expressed as benthiavalicarb-isopropyl:* 2 x <0.02, 0.02, 3 x 0.03, 3 x 0.04, 2 x 0.05, 2 x 0.06, 0.07, 0.08, 2 x 0.09, 0.11, 0.16 *- KIF-230R-L (incl. KIF-230S-D):* <0.01, 0.023, 0.047, 0.040, 0.038, 0.070, 0.023, 0.08, 0.03, 0.14, 0.05, 0.08, 0.01, 0.06, 0.02, 0.03, 0.10, 0.03, <0.01 *- KIF-230S-L (incl. KIF-230R-D)*: <0.01, <0.01, <0.01, <0.01, <0.01, <0.01, <0.01, <0.01, 0.01, <0.01, 0.02, <0.01, <0.01, <0.01, <0.01, <0.01, <0.01, 0.01, <0.01, <0.01	19 trials are available for the South of EU. Trials were performed in accordance with the critical GAP following 6 foliar spray applications at a rate of 0.035 kg a.s./ha with an interval of 9 to 11 days between each application. Decay curves are given with last sampling 28 days after last application. Commodities which were analysed were the berries, juice, raisin, must and wine.		

‡ Endpoints identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Crop	Northern or Mediterranean Region	Trials results relevant to the critical GAP [mg/kg] (a)	Recommendation/comments	MRL	STMR (b)
Tomatoes	Indoor NE and SE	*Sum of all isomers expressed as benthiavalicarb-isopropyl:* 0.05, 0.06, 0.07, 0.09, 0.10, 2 x 0.12, 0.15, 0.23, 0.26 *-KIF-230R-L (incl. KIF-230S-D)*: 0.114, 0.039, 0.139, 0.25, 0.05, 0.22, 0.11, 0.06, 0.092, 0.08 *-KIF-230S-L (incl. KIF-230R-D)*: <0.01, <0.01, <0.01, <0.01, <0.01, 0.01, <0.01, <0.01, <0.01, <0.01	Trials are available for the North and South of Europe under greenhouse conditions. Trials were made following 6 spray applications at the rate of 0.075 kg a.s./ha with a 7 day spray interval. The last application occurred 3 days before harvest.	0.3	0.1
	NE (Outdoor)	No residue trial provided.			
	SE (Outdoor)	*Sum of all isomers expressed as benthiavalicarb-isopropyl:* 2 x <0.02, 0.02 *-KIF-230R-L (incl. KIF-230S-D)*: 0.013, <0.01, <0.01: incomplete data base *-KIF-230S-L (incl. KIF-230R-D)*: <0.01, <0.01, <0.01: incomplete data base.	Trials are available for the South of Europe under field conditions. Trials were made following 6 spray applications at the rate of 0.075 kg a.s./ha with a 7 day spray interval. The last application occurred 7 days before harvest.		

‡ Endpoints identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Crop	Northern or Mediterranean Region	Trials results relevant to the critical GAP [mg/kg] (a)	Recommendation/comments	MRL	STMR (b)
Potatoes	NE	*Sum of all isomers expressed as benthiavalicarb-isopropyl:* 10 x < 0.02 *-KIF-230R-L (incl. KIF-230S-D)*: <0.01,<0.01, <0.01, <0.01, <0.01, <0.01, <0.01, <0.01, <0.01, <0.01 mg/kg *-KIF-230S-L (incl. KIF-230R-D)*: <0.01, <0.01, <0.01, <0.01, <0.01, <0.01, <0.01, <0.01, <0.01, <0.01 mg/kg	10 trials are available for the North and the South of EU. Potatoes were treated by foliar spray application 6 to 12 fold in Southern Europe and 9 to 12 fold in Northern Europe at a rate of 0.028 kg a.s./ha. The spray interval was 7 days and the last application was carried out 3 or 7 days before harvest.	0.02* mg/kg	0.02
	SE	*Sum of all isomers expressed as benthiavalicarb-isopropyl:* 10 x < 0.02 *-KIF-230R-L (incl. KIF-230S-D)*: <0.01, <0.01, <0.01, <0.01, <0.01, <0.01, <0.01, <0.01, <0.01, <0.01 mg/kg *-KIF-230S-L (incl. KIF-230R-D)*: <0.01, <0.01, <0.01, <0.01, <0.01, <0.01, <0.01, <0.01, <0.01, <0.01 mg/kg			

(a) Numbers of trials in which particular residue levels were reported *e.g.* 3 x <0.01, 1 x 0.01, 6 x 0.02, 1 x 0.04, 1 x 0.08, 2 x 0.1, 2 x 0.15, 1 x 0.17
(b) Supervised Trials Median Residue *i.e.* the median residue level estimated on the basis of supervised trials relating to the critical GAP
*) LOQ

‡ Endpoints identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Consumer risk assessment (Annex IIA, point 6.9, Annex IIIA, point 8.8)

ADI	0.1 mg/kg b.w./day
TMDI (European Diet) (% ADI)	*Provisional calculation pending the results of the succeeding crops data requirement* -European adults (1.33 %), -German 4-6 years old girl (0.51 %), -Children and infant from UK (0.64 % and 0.54 % respectively)
NEDI (% ADI)	-UK adults: 0.57 %, -UK children: 0.56 %, -UK infants: 0.44 %
Factors included in NEDI	Processing factors for table/wine grapes and tomatoes: see table here below.
ARfD	Not allocated.
Acute exposure (% ARfD)	Not applicable.

Processing factors (Annex IIA, point 6.5, Annex IIIA, point 8.4)

Crop/processed crop	Number of studies	Transfer factor (Range)
Table/Wine grapes	8	
Juice		0.56 (0.37 - 1.0)
Raisin		2.7 (1.2 - 5.5)
Must		1.1 (0.45 - 1.7)
Red and white wine		0.89 (0.5 - 1.6)
Tomatoes	2*	
Peeled tomatoes		0.18 (0.12 / 0.25)
Juice		0.52 (0.39 / 0.66)
Wet pomace		1.7 (0.58 / 2.8)
Dry pomace		10 (6 / 14)
Puree		1.2 (0.58 / 1.7)
Ketchup		1.4 (1.1 / 1.7)
Canned tomatoes		0.24 (0.16 / 0.33)

* Of the 4 studies submitted were only 2 considered for calculation of the transfer factor.

‡ Endpoints identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Proposed MRLs (Annex IIA, point 6.7, Annex IIIA, point 8.6)

Table/wine grapes	0.3 mg/kg[13]
Tomatoes	0.3 mg/kg
Potatoes	0.02*mg/kg

*) LOQ

[13] Due to the amendment of the residue definition in the second discussion in a meeting of experts (PRAPeR 15) the highest residue (as the sum of isomers) in grapes has increased and therefore the initially proposed MRL of 0.2 mg/kg needs to be raised to 0.3 mg/kg. New proposal not peer reviewed but agreed between the RMS and EFSA.

‡ Endpoints identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Appendix 1.5: Fate and Behaviour in the Environment

Route of degradation (aerobic) in soil (Annex IIA, point 7.1.1.1.1)

Mineralization after 100 days ‡	44.8 % after 120 d, [14C-valyl]-label (n= 1) 3.6-11.7 % after 120 d, [14C-benzyl]-label (n= 4)
Non-extractable residues after 100 days ‡	36.3 % after 120 d, [14C-valyl]-label (n= 1) 22.5-58.2 % after 120 d, [14C-benzyl]-label (n= 4)
Relevant metabolites - name and/or code, % of applied ‡ (range and maximum)	[14C-benzyl]-label experiment M-1 max level of 9.8-27.7% at day 58-120 (n= 4) M-3 max level of 2.2-12.3 % at day 28 (n= 4) M-4 max level of 7.6-9.8% at day 28 (n= 4) M-5 max level of 12.1-26.8% at day 28-58 (n= 4) no metabolite in the [14C-valyl]-label experiment

Route of degradation in soil - Supplemental studies (Annex IIA, point 7.1.1.1.2)

Anaerobic degradation ‡	Mineralisation 0.5 % after 120 d Non-extractable residues 25.5 % after 120 d Metabolites Sum M-1 and M-3 15.5 % at 120 d M-4 11.9 % at 120 d M-5 9.9 % at 120 d M-8 9.0 % at 120 d Benzyl label
Soil photolysis ‡	Similar route of degradation was observed under dark and light conditions Mineralisation 1.8 % after 30 d Non-extractable residues 32.8 % after 30 d Metabolites M-1 12.1 % at 30 d M-3 3.8 % at 30 d M-4 3.5% at 30 d M-5 5.1 % at 30 d Benzyl label

‡ Endpoints identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Rate of degradation in soil (Annex IIA, point 7.1.1.2, Annex IIIA, point 9.1.1)

Method of calculation	Laboratory: first order kinetics
Laboratory studies ‡ (range or median, with n value, with r^2 value)	**Benthiavalicarb-isopropyl** DT_{50lab} (20°C, aerobic): 10.6-19.1 d, mean = 14.3 d (n= 4, r^2 = 0.98-0.99) Metabolite M5: DT_{50lab} (20°C, aerobic): 17.4-40.4 d, mean = 29.4 d (n= 4, r^2 = 0.86-0.98) Metabolite M1: DT_{50lab} (20°C, aerobic): 4-27 d, mean = 13.7 d (n= 3, r^2 = 0.79-0.99) Metabolite M3: DT_{50lab} (20°C, aerobic): 2-7 d, mean = 5.3 d (n= 3, r^2 = 0.97-0.99) Metabolite M4: DT_{50lab} (20°C, aerobic): 0.07-0.57 d, mean = 0.25 d (n= 3, r^2 = 0.68-0.96) **Benthiavalicarb-isopropyl** DT_{90lab} (20°C, aerobic): 35.3-63.3 d, mean = 47.3 d (n= 4, r^2 = 0.98-0.99) Metabolite M5: DT_{90lab} (20°C, aerobic): 57.7-134.1 d, mean = 97.6 d (n= 4, r^2 = 0.86-0.98) Metabolite M1: DT_{90lab} (20°C, aerobic): 13-91d, mean = 46 d (n= 3, r^2 = 0.79-0.99) Metabolite M3: DT_{90lab} (20°C, aerobic): 15-24 d, mean = 21 d (n= 3, r^2 = 0.97-0.99) Metabolite M4: DT_{90lab} (20°C, aerobic): 0.23-1.89 d, mean = 0.82 d (n= 3, r^2 = 0.68-0.96) (Biexponential) DT_{50lab} (10°C, using a Q10 value of 2.2, aerobic): 23.3-42.0 d mean = 31.46 d DT_{50lab} (20°C, anaerobic): 39.9 d (n= 1, r^2= 0.99)
	Degradation in the saturated zone: no data submitted and no data required.
Field studies ‡ (state location, range or median with n value)	Not required: DT_{50} a.s. and metabolites less than 60 days
	DT_{90f}: Not required
Soil accumulation and plateau concentration ‡	Not required

‡ Endpoints identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Soil adsorption/desorption (Annex IIA, point 7.1.2)

K_f /K_{oc}	K_{oc}: **Benthiavalicarb-isopropyl** 121.3-258.2 (mean 180.56, $^1/_n$= 0.84-0.93, 5 soils)
K_d	M-1 237.2-422.3 (mean 299.6, $^1/_n$=0.76-0.78, 3 soils), M-3 116.4-241.0 (mean 168.7, $^1/_n$= 0.79-0.82, 3 soils), M-4 221.4-407.8 (mean 296.8, $^1/_n$= 0.82-0.91, 3 soils), M-5 494.4-787.3 (mean 618.1, $^1/_n$= 0.73-0.79, 3 soils)
	K_f: **Benthiavalicarb-isopropyl** 0.8-6.5 (mean 4.1, 5 soils) M-1 3.4-11.2 (mean 7.1, 3 soils), M-3 1.9-5.5 (mean 3.9, 3 soils), M-4 3.3-10.4 (mean 6.9, 3 soils), M-5 4.6-23.2 (mean 16.6, 3 soils)
pH dependence (yes / no) (if yes type of dependence)	No
	For FOCUS gw modelling – K_{oc}: **Benthiavalicarb-isopropyl**, mean 180.56, $^1/_n$= 0.78 K_{oc}: M-1, mean 299.6, $^1/_n$= 0.88 K_{oc}: M-3, mean 168.7, $^1/_n$= 0.81 K_{oc}: M-1, mean 296.8, $^1/_n$= 0.85 K_{oc}: M-1, mean 618.1, $^1/_n$= 0.76

Mobility in soil (Annex IIA, point 7.1.3, Annex IIIA, point 9.1.2)

Column leaching ‡	Not required
Aged residues leaching ‡	Not required
Lysimeter/ field leaching studies ‡	Not required

‡ Endpoints identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

PEC (soil) (Annex IIIA, point 9.1.3)

Parent

Benthiavalicarb-isopropyl	DT_{50} (d): 19.1 days
Method of calculation	Kinetics: 1st order
	representative worst case from lab studies.
Application rate	Crop: tomatoes
	50% plant interception
	6 applications of 75 g a.s./ha at interval of 7 days

$PEC_{(s)}$ (mg/kg)		Single application Actual	Single application Time weighted average	Multiple application Actual	Multiple application Time weighted average
Initial		0.050	-	0.174	-
Short term	4h	0.048	0.049	0.168	0.171
	2d	0.046	0.048	0.162	0.168
	4d	0.043	0.047	0.151	0.162
Long term	7d	0.039	0.044	0.135	0.154
	28d	0.018	0.031	0.063	0.109
	50d	0.008	0.023	0.028	0.080
	100d	0.001	0.013	0.005	0.047

Benthiavalicarb-isopropyl	DT_{50} (d): 19.1 days
Method of calculation	Kinetics: 1st order
	representative worst case from lab studies.
Application rate	Crop: tomatoes and grapes
	50% plant interception
	6 applications of 35 g a.s./ha at interval of 7 days

$PEC_{(s)}$ (mg/kg)		Single application Actual	Single application Time weighted average	Multiple application Actual	Multiple application Time weighted average
Initial		0.023	-	0.082	-
Short term	24h	0.023	0.023	0.080	0.081

‡ Endpoints identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

$PEC_{(s)}$ (mg/kg)		Single application Actual	Single application Time weighted average	Multiple application Actual	Multiple application Time weighted average
	2d	0.022	0.023	0.077	0.080
	4d	0.020	0.022	0.071	0.077
Long term	7d	0.018	0.021	0.064	0.073
	28d	0.008	0.015	0.030	0.052
	50d	0.004	0.011	0.013	0.038
	100d	0.001	0.006	0.002	0.022

Metabolites M1, M3, M4, M5 Method of calculation	Following the assumption that there is no degradation of benthiavalicarb-isopropyl between applications, worst case PEC_s values for the soil metabolites M-1, M-3, M-4 and M-5 can be calculated based on the seasonal application of active substance (450 g a.s./ha), the maximal percentages of the compounds found in the soil metabolism study (28, 12, 9.8 and 27%, respectively) and the correction for the molecular weights (169, 197, 195 and 196, respectively)
Application rate	Crop: tomatoes 50% plant interception 450 g a.s./ha (6 applications of 75 g a.s./ha at interval of 7 days)

$PEC_{(s)}$ (mg/kg)	Single application Actual	Single application Time weighted average	Multiple application Actual	Multiple application Time weighted average
Worst case PEC	-	-	M1= 0.04 M3 = 0.02 M4 = 0.02 M5 = 0.04	-

‡ Endpoints identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Metabolites M1, M3, M4, M5 Method of calculation	Following the assumption that there is no degradation of benthiavalicarb-isopropyl between applications, worst case PEC_s values for the soil metabolites M-1, M-3, M-4 and M-5 can be calculated based on the seasonal application of active substance (450 g a.s./ha), the maximal percentages of the compounds found in the soil metabolism study (28, 12, 9.8 and 27%, respectively) and the correction for the molecular weights (169, 197, 195 and 196, respectively)
Application rate	Crop: tomatoes and grapes 50% plant interception 210 g a.s./ha (6 applications of 35 g a.s./ha at interval of 7 days)

$PEC_{(s)}$ (mg/kg)	Single application Actual	Single application Time weighted average	Multiple application Actual	Multiple application Time weighted average
Worst case PEC	-	-	M1= 0.02 M3 = 0.009 M4 = 0.007 M5 = 0.02	x

Route and rate of degradation in water (Annex IIA, point 7.2.1)

Hydrolysis of active substance and relevant metabolites (DT_{50}) ‡ (state pH and temperature)	50 °C at pH 4, 7 and 9: hydrolytic stability (<10 % hydrolysis after 5 d)
Photolytic degradation of active substance and relevant metabolites ‡	Xenon light source with UV filter; Photolysis rate (assuming first order kinetics): pH 5: k = 0.0934 d-1; DT_{50} = 6.8 d (disregarding 15-day result); pH 7: k = 0.0013 d-1; DT_{50} = 516 d pH 9: k = 0.0036 d-1; DT_{50} = 178 d No Major photolysis products (> 10% of applied radioactivity)

‡ Endpoints identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Readily biodegradable (yes/no)	Not readily biodegradable; 2-3% of the theoretical max value CO2 formed after 28 d
Degradation in water/sediment	
- DT_{50} water ‡	4.4-7.7 days
- DT_{90} water ‡	14.7-25.6 days (1st order, r2= not given, n= 2)
- DT_{50} whole system ‡	18.215.0 days
- DT_{90} whole system ‡	60.3-49.9 days (1st order, r2= not given, n= 2)
Mineralization	3.8-0.9 %AR (at 100 d, study end, n= 2)
Non-extractable residues	40.6-36.4 % AR (at 100 d, study end, n= 2)
Distribution in water / sediment systems (active substance) ‡	Maximum of 47.4-32.6 %AR in sediment after 7days. DT_{50} in sediment 26.9-16.4 days (DT90 82.4-38.2 days, 1st order, r2= not given, n= 2)
Distribution in water / sediment systems (metabolites) ‡	Water: Metabolite M-3: max of 3.3-6.1% (30-100 days, n= 2) Other metabolites at level < 3%AR Sediment: Metabolite M-3: max of 7.7-26.3% (100 days, n= 2) Metabolite M-4: max of 18.0-22.7% (59-30 days, DT_{50} 67.6-62.0 days, 1st order, r^2= not given, n= 2) Metabolite M-5: max of 9.3-11.9% (59 days, n= 2)

PEC (surface water) (Annex IIIA, point 9.2.3)

WG containing 15% benthiavalicarb-isopropyl
Parent

Benthiavalicarb-isopropyl	DT_{50} (d): 7.7 days
Method of calculation	Kinetics: 1st order representative worst case from sediment water study
Application rate	Crop: tomatoes Number of applications: 6 Interval (d): 7 days Application rate(s): 75 g as/ha Depth of water body: 30 cm
Main routes of entry	2.77 % drift from 1 metre

‡ Endpoints identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

PEC$_{(sw)}$ (µg / l)		Single application Actual	Single application Time weighted average	Multiple application Actual	Multiple application Time weighted average
Initial		0.69	0.66	4.2	4.0
Short term	4h	0.63	0.66	3.8	4.0
	2d	0.58	0.63	3.5	3.8
	4d	0.48	0.58	2.9	3.5
Long term	7d	0.37	0.52	2.2	3.1
	14d	0.20	0.40	1.2	2.4
	21d	0.11	0.31	0.6	1.9
	28d	0.06	0.25	0.3	1.5
	42d	0.02	0.18	0.1	1.0

Maximum concentration just after last application, Initial PEC after 1 appl. X $(1-e^{-nki})/(1-e^{-ki})$: 1.4 µg/L

WG containing 1.75% benthiavalicarb-isopropyl and 70% mancozeb (PEC for benthiavalicarb-isopropyl)

Benthiavalicarb-isopropyl	DT_{50} (d): 7.7 days
Method of calculation	Kinetics: 1st order
	representative worst case from sediment water study
Application rate	Crop: tomatoes and **grapes**
	Number of applications: 6
	Interval (d): 7 days
	Application rate(s): 35 g as/ha
	Depth of water body: 30 cm
Main routes of entry	8.02 % drift from 3 meters

PEC$_{(sw)}$ (µg/L)		Single application Actual	Single application Time weighted average	Multiple application Actual	Multiple application Time weighted average
Initial		0.94	0.90	5.6	5.4
Short term	24h	0.86	0.90	5.1	5.4
	2d	0.78	0.86	4.7	5.1
	4d	0.65	0.79	3.9	4.7

‡ Endpoints identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

PEC$_{(sw)}$ (µg/L)		Single application Actual	Single application Time weighted average	Multiple application Actual	Multiple application Time weighted average
Long term	7d	0.50	0.70	3.0	4.2
	14d	0.27	0.53	1.6	3.2
	21d	0.14	0.42	0.86	2.5
	28d	0.08	0.34	0.46	2.0
	42d	0.02	0.24	0.13	1.5

Maximum concentration just after last application, Initial PEC after 1 appl. X $(1-e^{-nki})/(1-e^{-ki})$: 1.9 µg/L

PEC (sediment)

Parent

Metabolites M-3, M-4, M-5 Method of calculation	Partitioning to top 1 cm layer of sediment, 0.8 kg/dm3 entry route as for surface water, pattern of decline reflecting that measured in the sediment/water study
Application rate	Crop: **tomatoes** Number of applications: 6 Interval (d): 7 days Application rate(s): a.s.: 450 g/ha Metabolite M-3: 61 g /ha, assuming max of 26.3%, Metabolite M-4: 52 g/ha, assuming max of 22.7% Metabolite M-5: 28 g, assuming max of 11.9% Depth of sediment body: 1 cm correction for the molecular weights of the metabolites (381.47, 197, 195 and 196, respectively for a.s., M3, M4 and M5)
Main routes of entry	2.77 % drift from 1 meter

‡ Endpoints identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

PEC$_{(sed)}$ (µg/kg)	Single application Actual	Single application Time weighted average	Multiple application Actual	Multiple application Time weighted average
Initial (considering 6 applications at t 0)	a.s.: 150 µg/kg M-3: 21µg/kg M-4: 18 µg/kg M-5: 10 µg/kg	Not relevant	Not relevant	Not relevant

WG containing 1.75% benthiavalicarb-isopropyl and 70% mancozeb (PEC for benthiavalicarb-isopropyl)

Metabolites M-3, M-4, M-5 Method of calculation	Partitioning to top 1 cm layer of sediment, 0.8 kg/dm3 entry route as for surface water, pattern of decline reflecting that measured in the sediment/water study
Application rate	Crop: tomatoes and **grapes** Number of applications: 6 Interval (d): 7 days Application rate(s): a.s.: 210 g/ha Metabolite M-3: 28 g /ha, assuming max of 26.3% Metabolite M-4: 48 g/ha, assuming max of 22.7% Metabolite M-5: 13 g, assuming max of 11.9% Depth of sediment body: 1 cm correction for the molecular weights of the metabolites (381.47, 197, 195 and 196, respectively for a.s., M3, M4 and M5)
Main routes of entry	8.02 % drift from 3 meter,

PEC$_{(sed)}$ (µg/kg)	Single application Actual	Single application Time weighted average	Multiple application Actual	Multiple application Time weighted average
Initial (considering 6 applications at t 0)	a.s.: 210 µg/kg M-3: 28 µg/kg M-4: 25 µg/kg M-5: 13 µg/kg	Not relevant	Not relevant	Not relevant

‡ Endpoints identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

PEC (ground water) (Annex IIIA, point 9.2.1)

Method of calculation and type of study (*e.g.* modelling, monitoring, lysimeter)	Modelling using FOCUS model(s), with appropriate FOCUS gw scenarios, according to FOCUS guidance. Model(s) used: PEARL Scenarios (list of names): Chateaudun, Piacenza, Porto, Seville, Thiva Crop: tomatoes parent: Mean DT_{50lab} = 14 d; mean K_{oc} = 180 l/kg; $^1/_n$= 0.88 M-1: Mean DT_{50lab} = 13 d; mean K_{oc} = 299 l/kg; $^1/_n$= 0.77 M-3: Mean DT_{50lab} = 5 d; mean K_{oc} = 169 l/kg; $^1/_n$= 0.81 M-4: Mean DT_{50lab} = 0.25d; mean K_{oc} = 297 l/kg; $^1/_n$= 0.85 M-5: Mean DT_{50lab} = 29 d; mean K_{oc} = 618 l/kg; $^1/_n$= 0.76
Application rate	Application rate: 75 g a.s./ha. No. of applications: 6 Time of application: spring-summer Other uses at lower application rates (6 x 35 g a.s./ha in grapes, 6 x 28 g a..s./ha in potatoes) were not mentioned in this table (the PEC were < 0.000 µg/L)
$PEC_{(gw)}$	
Maximum concentration	Not applicable
Average annual concentration (Results quoted for modelling with FOCUS gw scenarios, according to FOCUS guidance)	Annual average concentrations (80th percentile) according to FOCUS guidance: active substance, M-1, M-3, M-4, M-5: < 0.000 µg/L (see detailed results in table below)

‡ Endpoints identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

PEC(gw) - FOCUS modelling results

Model /Crop	Scenario	Parent (µg/L)	Metabolite (µg/L)			
			M-1	M-3	M-4	M-5
	Chateaudun	0.000	0.000	0.000	0.000	0.000
	Piacenza	0.000	0.000	0.000	0.000	0.000
	Porto	0.000	0.000	0.000	0.000	0.000
	Seville	0.000	0.000	0.000	0.000	0.000
	Thiva	0.000	0.000	0.000	0.000	0.000

Fate and behaviour in air (Annex IIA, point 7.2.2, Annex III, point 9.3)

Direct photolysis in air ‡	Not studied - no data requested
Quantum yield of direct phototransformation	Active substance: ϕ: ≤ 0.0014 in water
Photochemical oxidative degradation in air ‡	DT_{50} of 2.334 hours derived by the Atkinson method of calculation
Volatilization ‡	Not available

PEC (air)

Method of calculation	Not required, based on vapour pressure (<3.0 x 10-4 Pa at 25ºC), dimensionless Henry's Law Constant (8.72 x 10-3 Pa.m3/mole)

$PEC_{(a)}$

Maximum concentration	Negligible

Definition of the Residue (Annex IIA, point 7.3)

Relevant to the environment	**Soil** Definitions for risk assessment: benthiavalicarb-isopropyl, M1, M3, M4, M5 Definitions for monitoring: benthiavalicarb-isopropyl and its enantiomer. **Water** **Ground water** Definitions for exposure assessment:

‡ Endpoints identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

	benthiavalicarb-isopropyl, M1, M3, M4, M5 Definitions for monitoring: benthiavalicarb-isopropyl and its enantiomer. **Surface water** Definitions for risk assessment: benthiavalicarb-isopropyl Definitions for monitoring: benthiavalicarb-isopropyl and its enantiomer. **Air** Definitions for risk assessment: benthiavalicarb-isopropyl Definitions for monitoring: benthiavalicarb-isopropyl and its enantiomer.

Monitoring data, if available (Annex IIA, point 7.4)

Soil (indicate location and type of study)	No data provided - none requested
Surface water (indicate location and type of study)	No data provided - none requested
Ground water (indicate location and type of study)	No data provided - none requested
Air (indicate location and type of study)	No data provided - none requested

Classification and proposed labelling (Annex IIA, point 10)

with regard to fate and behaviour data	Candidate for R53 May cause long-term adverse effect to the aquatic environment

‡ Endpoints identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Appendix 1.6: Effects on non-target Species

Effects on terrestrial vertebrates (Annex IIA, point 8.1, Annex IIIA, points 10.1 and 10.3)

Acute toxicity to mammals ‡	LD_{50} (rat) > 5000 mg a.s./kg b.w.
Reproductive toxicity to mammals ‡	NOAEL (rabbit) = 20 mg a.s./kg b.w./d
Acute toxicity to birds ‡	LD_{50} (*Colinus virginianus*) > 2000 mg a.s./kg b.w.
Dietary toxicity to birds ‡	LC_{50} (*Colinus virginianus*) > 937 mg a.s./kg b.w./d
Reproductive toxicity to birds ‡	NOEL (*Colinus virginianus*, 24 weeks) = 105 mg a.s./kg b.w./d

Toxicity/exposure ratios for terrestrial vertebrates (Annex IIIA, points 10.1 and 10.3)

Application rate (kg a.s./ha)	Crop	Category (*e.g.* insectivorous bird)	Time-scale	TER	Annex VI Trigger
6 x 0.075 kg a.s./ha	tomato	medium herbivorous bird	acute	212	10
			short term	164	10
			long term	35	5
		insectivorous bird	acute	493	10
			short term	414	10
			long term	46	5
		medium herbivorous mammal	acute	1440	10
			long term	18	5
6 x 0.035 kg a.s./ha	tomato	medium herbivorous bird	acute	455	10
			short term	352	10
			long term	74	5
		insectivorous bird	acute	1057	10
			short term	888	10
			long term	99	5
		medium herbivorous mammal	acute	3087	10
			long term	39	5
6 x 0.035 kg a.s./ha	grapevine	insectivorous bird	acute	1057	10
			short term	888	10
			long term	99	5
		small herbivorous mammal	acute	756	10
			long term	8.4	5

‡ Endpoints identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Toxicity data for aquatic species (most sensitive species of each group) (Annex IIA, point 8.2, Annex IIIA, point 10.2)

Group	Test substance	Time-scale	Endpoint	Toxicity (mg/L)
Laboratory tests				
‡*Oncorhynchus mykiss*	Active substance	96 h	LC_{50}	> 10 mg a.s./L
‡*Oncorhynchus mykiss*	Active substance	28 d	NOEC based on weight	1.0 mg a.s./L
			NOEC based on length	3.2 mg a.s./L
‡*Oncorhynchus mykiss*	KIF-230 15% WG	96 h	LC_{50}	> 100 mg formulation/L
‡*Oncorhynchus mykiss*	KIF-230/ Mancozeb 17.5/700 WG	96 h	LC_{50}	0.307 mg formulation/L
‡*Cyprinus carpio*	Active substance	96 h	LC_{50}	> 10 mg a.s./L
‡*Lepomis macrochirus*	Active substance	96 h	LC_{50}	> 10 mg a.s./L
‡*Daphnia magna*	Active substance	48 h	EC_{50}	> 10 mg a.s./L
‡*Daphnia magna*	Active substance	21 d	NOEC	3.0 mg a.s./L
‡*Daphnia magna*	KIF-230-M-3	48 h	EC_{50}	55.3 mg M-3/L
‡*Daphnia magna*	KIF-230-M-4	48 h	EC_{50}	6.28 mg M-4/L
‡*Daphnia magna*	KIF-230-M-5	48 h	EC_{50}	> 10 mg M-5/L
‡*Daphnia magna*	KIF-230 15% WG	48 h	EC_{50}	> 100 mg formulation/L
‡*Daphnia magna*	KIF-230/ Mancozeb 17.5/700 WG	48 h	EC_{50}	0.302 mg formulation/L
‡*Pseudokirchneriella subcapitata*	Active substance	72 h	E_bC_{50} E_rC_{50}	> 10 mg a.s./L > 10 mg a.s./L
‡*Pseudokirchneriella subcapitata*	KIF-230 15% WG	72 h	E_bC_{50} E_rC_{50}	28.0 mg formulation/L > 100 mg formulation/L
‡*Pseudokirchneriella subcapitata*	KIF-230/ Mancozeb 17.5/700 WG	72 h	E_bC_{50} E_rC_{50}	0.162 mg formulation/L > 1.0 mg formulation/L

Microcosm or mesocosm tests
Not required.

‡ Endpoints identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Toxicity/exposure ratios for the most sensitive aquatic organisms (Annex IIIA, point 10.2)

Application rate (kg a.s./ha)	Crop	Organism	Time-scale	Distance (m)	TER	Annex VI Trigger
6 x 0.075 kg a.s./ha	tomato	*Oncorhynchus mykiss*	acute	1	7143	100
			chronic	1	714	10
		Daphnia magna	acute	1	7143	100
			chronic	1	2143	10
		Pseudokirchneriella subcapitata	acute	1	7143	10
6 x 0.035 kg a.s./ha	grapevine	*Oncorhynchus mykiss*	acute	3	5263	100
			chronic	3	526	10
		Daphnia magna	acute	3	5263	100
			chronic	3	1579	10
		Pseudokirchneriella subcapitata	acute	3	5263	10

Bioconcentration

Bioconcentration factor (BCF) ‡	Not required.
Annex VI Trigger:for the bioconcentration factor	Not required.
Clearance time (CT_{50})	Not required.
(CT_{90})	Not required.
Level of residues (%) in organisms after the 14 day depuration phase	Not required

Effects on honeybees (Annex IIA, point 8.3.1, Annex IIIA, point 10.4)

Acute oral toxicity ‡	LD_{50} > 100 µg a.s./bee (from studies with a.s. and with formulation KIF-230 15 % WG) LD_{50} > 140 µg KIF-230/Mancozeb 17.5/700 WG/bee
Acute contact toxicity ‡	LD_{50} > 100 µg a.s./bee (from studies with a.s. and with formulation KIF-230 15 % WG) LD_{50} > 140 µg KIF-230/Mancozeb 17.5/700 WG /bee

‡ Endpoints identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Hazard quotients for honey bees (Annex IIIA, point 10.4)

Application rate (kg as/ha)	Crop	Route	Hazard quotient	Annex VI Trigger
Laboratory tests				
75 g a.s./ha	tomato	oral	0.8	50
		contact	0.8	50
2000 g KIF-230/ Mancozeb 17.5/700 WG/ha	tomato grapevine	oral	14.3	50
		contact	14.3	50

Field or semi-field tests
Not required.

Effects on other arthropod species (Annex IIA, point 8.3.2, Annex IIIA, point 10.5)

Species	Stage	Test Substance	Dose (kg as/ha)	Endpoint	Effect	Annex VI Trigger
Laboratory tests ‡						
‡*Typhlodro-mus pyri*	protonymhs	KIF-230 15%WG	0.5 kg/ha	corrected mortality reproductive ability	- 5.7 % 110 %	30 %
‡*Typhlodro-mus pyri*	protonymhs	KIF-230/ Mancozeb 17.5/700 WG	0 – 1.0 kg/ha	LR_{50} (7 d) reproductive ability	0.29 kg/ha 0 % HQ = 22	 2
‡*Aphidius rhopalosiphi*	adult females	KIF-230 15%WG	0.5 kg/ha	corrected mortality reproductive ability	0 % 71 %	30 %

‡ Endpoints identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Species	Stage	Test Substance	Dose (kg as/ha)	Endpoint	Effect	Annex VI Trigger
‡*Aphidius rhopalosiphi*	adult females	KIF-230/ Mancozeb 17.5/700 WG	6.0 kg/ha	LR_{50} (48 h) reproductive ability	> 6.0 kg/ha 90.4 % HQ = 1.07	 2
‡*Poecilus cupreus*	adults	KIF-230 15%WG	0.5 kg/ha	corrected mortality reduction in food uptake	0 % 29.4 %	30 %
‡*Chrysoperla carnea*	larvae	KIF-230 15%WG	0.5 kg/ha	corrected mortality reproductive ability	- 4.3% 111%	30 %

Corrected mortality: Negative values indicate a slight positive effect of the treatments in comparison with the control group.
Reproductive ability: Values above 100 % indicate a positive effect of the treatment in comparison with the control group.

Field or semi-field tests
Not required.

Effects on earthworms (Annex IIA, point 8.4, Annex IIIA, point 10.6)

Acute toxicity ‡	LC_{50} (*Eisenia foetida*, 14 d) > 1000 mg a.s./kg substrate $LC_{50, corr}$ (*Eisenia foetida*, 14 d) > 500 mg a.s./kg substrate LC_{50} (*Eisenia foetida*, 14 d) > 996 mg M-1/kg substrate $LC_{50, corr}$ (*Eisenia foetida*, 14 d) > 498 mg M-1/kg substrate LC_{50} (*Eisenia foetida*, 14 d) > 996 mg M-3/kg substrate $LC_{50, corr}$ (*Eisenia foetida*, 14 d) > 498 mg M-3/kg substrate LC_{50} (*Eisenia foetida*, 14 d) = 910.7 mg KIF-

‡ Endpoints identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

	230/Mancozeb 17.5/700 WG/kg substrate $LC_{50, corr}$ (*Eisenia foetida*, 14 d) = 455 mg KIF-230/Mancozeb 17.5/700 WG/kg substrate
Reproductive toxicity ‡	NOEC (*Eisenia foetida*, 56 d) = 5 kg KIF-230 15% WG/ha $NOEC_{corr}$ (*Eisenia foetida*, 56 d) = 2.5 kg KIF-230 15% WG/ha NOEC (*Eisenia foetida*, 56 d) = 20 kg KIF-230/Mancozeb 17.5/700 WG/ha $NOEC_{corr}$ (*Eisenia foetida*, 56 d) = 10 kg KIF-230/Mancozeb 17.5/700 WG/ha

Toxicity/exposure ratios for earthworms (Annex IIIA, point 10.6)

Application rate (kg as/ha)	Crop	Time-scale	TER	Annex VI Trigger
6 x 0.075 kg a.s./ha active substance	tomato	acute	2874	10
6 x 0.075 kg a.s./ha metabolite M-1	tomato	acute	12450	10
6 x 0.075 kg a.s./ha metabolite M-3	tomato	acute	24900	10
6 x 0.035 kg a.s./ha active substance	tomato grapevine	acute	6098	10
6 x 0.035 kg a.s./ha metabolite M-1	tomato grapevine	acute	24900	10
6 x 0.035 kg a.s./ha metabolite M-3	tomato grapevine	acute	55333	10
6 x 0.075 kg a.s./ha active substance (based on the formulation KIF-230 15 % WG)	tomato	long term	2.9	5
6 x 0.035 kg a.s./ha active substance (based on the formulation KIF-230 15 % WG)	tomato grapevine	long term	6.1	5

‡ Endpoints identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Effects on soil micro-organisms (Annex IIA, point 8.5, Annex IIIA, point 10.7)

Nitrogen mineralization ‡	a.s.: less than 25 % deviation from control in 28 days at 0.5294 mg a.s./kg soil and 2.647 mg a.s./kg soil KIF-230-M-1: less than 25 % deviation from control in 28 days at 0.25 mg M-1/kg soil KIF-230-M-3: less than 25 % deviation from control in 28 days at 0.25 mg M-3/kg soil
Carbon mineralization ‡	a.s.: less than 25 % deviation from control in 28 days at 0.5294 mg a.s./kg soil and 2.647 mg a.s./kg soil KIF-230-M-1: less than 25 % deviation from control in 28 days at 0.25 mg M-1/kg soil KIF-230-M-3: less than 25 % deviation from control in 28 days at 0.25 mg M-3/kg soil

Classification and proposed labelling (Annex IIA, point 10)

with regard to ecotoxicological data	R 52/53	Harmful to aquatic organisms, may cause long-term adverse effect to the aquatic environment

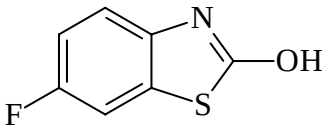
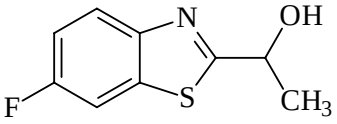
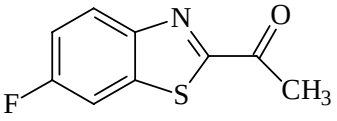
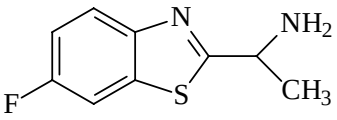
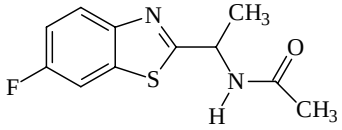
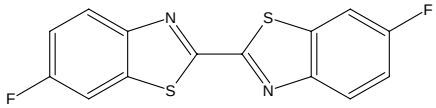
‡ Endpoints identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

APPENDIX 2 – ABBREVIATIONS USED IN THE LIST OF ENDPOINTS

ADI	acceptable daily intake
AOEL	acceptable operator exposure level
ARfD	acute reference dose
a.s.	active substance
bw	body weight
CA	Chemical Abstract
CAS	Chemical Abstract Service
CIPAC	Collaborative International Pesticide Analytical Council Limited
d	day
DAR	draft assessment report
DM	dry matter
DT_{50}	period required for 50 percent dissipation (define method of estimation)
DT_{90}	period required for 90 percent dissipation (define method of estimation)
ε	decadic molar extinction coefficient
EC_{50}	effective concentration
EEC	European Economic Community
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINKS	European List of New Chemical Substances
EMDI	estimated maximum daily intake
EU	European Union
FAO	Food and Agriculture Organisation of the United Nations
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
GAP	good agricultural practice
GCPF	Global Crop Protection Federation (formerly known as GIFAP)
GS	growth stage
h	hour(s)
ha	hectare
hL	hectolitre
HPLC	high pressure liquid chromatography or high performance liquid chromatography
ISO	International Organisation for Standardisation
IUPAC	International Union of Pure and Applied Chemistry
K_{oc}	organic carbon adsorption coefficient
L	litre
LC	liquid chromatography
LC-MS	liquid chromatography-mass spectrometry
LC-MS-MS	liquid chromatography with tandem mass spectrometry
LC_{50}	lethal concentration, median

LD_{50}	lethal dose, median; dosis letalis media
LOAEL	lowest observable adverse effect level
LOD	limit of detection
LOQ	limit of quantification (determination)
µg	microgram
mN	milli-Newton
MRL	maximum residue limit or level
MS	mass spectrometry
NESTI	national estimated short term intake
NIR	near-infrared-(spectroscopy)
nm	nanometer
NOAEL	no observed adverse effect level
NOEL	no observed effect level
PEC	predicted environmental concentration
PEC_A	predicted environmental concentration in air
PEC_S	predicted environmental concentration in soil
PEC_{SW}	predicted environmental concentration in surface water
PEC_{GW}	predicted environmental concentration in ground water
PHI	pre-harvest interval
pK_a	negative logarithm (to the base 10) of the dissociation constant
PPE	personal protective equipment
ppm	parts per million (10^{-6})
ppp	plant protection product
r^2	coefficient of determination
RPE	respiratory protective equipment
STMR	supervised trials median residue
TER	toxicity exposure ratio
TMDI	theoretical maximum daily intake
UV	ultraviolet
WHO	World Health Organisation
WG	water dispersible granule
yr	year

APPENDIX 3 – USED COMPOUND CODE(S)

Code/Trivial name	Chemical name	Structural formula
M1	6-Fluoro-2-hydroxybenzothiazole	
M3	1-(6-Fluorobenzothiazol-2-yl)ethanol	
M4	6-Fluorobenzothiazol-2-yl methyl ketone	
M5	1-(6-Fluorobenzothiazol-2-yl)ethylamine	
M8: *N*-[1-(6-Fluorobenzothiazol-2-yl)ethyl]acetamide	*N*-[1-(6-Fluorobenzothiazol-2-yl)ethyl]acetamide	
KIF-230-I-6	6,6'-difluoro-2,2'-dibenzothiazole	
KIF-230-I-12	bis(2-amino-5-fluorophenyl) disulfide