CLH report

Proposal for Harmonised Classification and Labelling

**Based on Regulation (EC) No 1272/2008 (CLP Regulation),
Annex VI, Part 2**

International Chemical Identification:

benthiavalicarb-isopropyl (ISO); isopropyl [(S)-1-{[(R)-1-(6-fluoro-1,3-benzothiazol-2-yl)ethyl]carbamoyl}-2-methylpropyl]carbamate

EC Number: -

CAS Number: 177406-68-7

Index Number: -

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Version number: 1.3 **Date: 22 January 2021**

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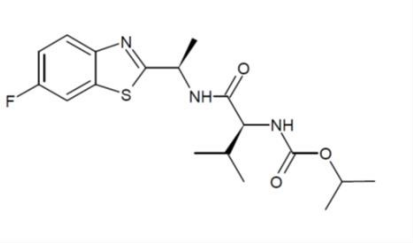
1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 1: Substance identity and information related to molecular and structural formula of the substance

Name(s) in the IUPAC nomenclature or other international chemical name(s)	IUPAC: Isopropyl [(S)-1-{[(R)-1-(6-fluoro-1,3-benzothiazol-2-yl) ethyl]carbamoyl}-2-methylpropyl]carbamate CA: 1-methylethyl [(1S)-1-[[[(1R)-1-(6-fluoro-2-benzothiazolyl)ethyl]amino]carbonyl]-2-methylpropyl] carbamate
Other names (usual name, trade name, abbreviation)	Producer's development code number: KIF-230, KIF-230R-L (which is the pure active substance, the active optical isomer)
ISO common name (if available and appropriate)	-
EC number (if available and appropriate)	-
EC name (if available and appropriate)	-
CAS number (if available)	177406-68-7
Other identity code (if available)	CIPAC number: 744.204
Molecular formula	$C_{18}H_{24}FN_3O_3S$
Structural formula	
SMILES notation (if available)	-
Molecular weight or molecular weight range	381.47g/mol
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	*confidential information (Volume 4 of RAR)*
Description of the manufacturing process and identity of the source (for UVCB substances only)	*n.a.*
Degree of purity (%) (if relevant for the entry in Annex VI)	*≥ 93% (w/w)*

1.2 Composition of the substance

Table 2: Constituents (non-confidential information)

Constituent (Name and numerical identifier)	Concentration range (% w/w minimum and maximum in multi-constituent substances)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)
benthiavalicarb-isopropyl CAS no: 177406-68-7	94.9 – 100%	None	Skin Sens. 1 – H317 Carc. 2 – H351 Aquatic Chronic 2 – H411

Table 3: Impurities (non-confidential information) if relevant for the classification of the substance

Impurity (Name and numerical identifier)	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)	The impurity contributes to the classification and labelling
KIF-230-I-6 6,6'-difluoro-2,2'-dibenzothiazole CAS no not available	0.0-0.00035			
KIF-230-I-12 bis(2-amino-5-fluorophenyl) disulfide CAS no not available	0.0 – 0.0015			
Toluene CAS no: 108-88-3	0.0 - 0.1	Flam. Liq 2 - H225 Skin Irrit. 2 – H315 Asp. Tox. 1 – H304 STOT SE 3 – H336 STOT RE 2 – H373 Repr. 2 – H361d	n.a.	No

Table 4: Additives (non-confidential information) if relevant for the classification of the substance

Additive (Name and numerical identifier)	Function	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)	The additive contributes to the classification and labelling
none	-	-	-	-	-

Table 5: Test substances (non-confidential information) (this table is optional)

Identification of test substance	Purity	Impurities and additives (identity, %, classification if available)	Other information	The study(ies) in which the test substance is used
The presented information demonstrates that the current EU specification in terms of impurities content is covered by the profiles of benthiavalicarb-isopropyl technical material as used in safety testing (confidential information in Volume 4 of RAR).				

2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 6:

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	No current Annex VI entry										
Dossier submitters proposal		benthiavalicarb-isopropyl (ISO); isopropyl [(S)-1-{[(R)-1-(6-fluoro-1,3-benzothiazol-2-yl)ethyl]carbamoyl}-2-methylpropyl]carbamate	-	177406-68-7	Carc. 2 Skin Sens. 1 Aquatic Chronic 2	H351 H317 H411	GHS08 GHS07 GSH09 Wng	H351 H317 H411			
Resulting Annex VI entry if agreed by RAC and COM		benthiavalicarb-isopropyl (ISO); isopropyl [(S)-1-{[(R)-1-(6-fluoro-1,3-benzothiazol-2-yl)ethyl]carbamoyl}-2-methylpropyl]carbamate	-	177406-68-7	Carc. 2 Skin Sens. 1 Aquatic Chronic 2	H351 H317 H411	GHS08 GHS07 GSH09 Wng	H351 H317 H411			

Table 7: Reason for not proposing harmonised classification and status under standard consultation

Hazard class	Reason for no classification	Within the scope of standard consultation
Explosives	Data conclusive but not sufficient for classification	Yes
Flammable gases (including chemically unstable gases)	Hazard class not applicable	No
Oxidising gases	Hazard class not applicable	No
Gases under pressure	Hazard class not applicable	No
Flammable liquids	Hazard class not applicable	No
Flammable solids	Data conclusive but not sufficient for classification	Yes
Self-reactive substances	Data lacking	Yes
Pyrophoric liquids	Hazard class not applicable	No
Pyrophoric solids	Data conclusive but not sufficient for classification	Yes
Self-heating substances	Data conclusive but not sufficient for classification	Yes
Substances which in contact with water emit flammable gases	Data conclusive but not sufficient for classification	Yes
Oxidising liquids	Hazard class not applicable	No
Oxidising solids	Data conclusive but not sufficient for classification	Yes
Organic peroxides	Hazard class not applicable	No
Corrosive to metals	Data conclusive but not sufficient for classification	Yes
Acute toxicity via oral route	Data conclusive but not sufficient for classification	Yes
Acute toxicity via dermal route	Data conclusive but not sufficient for classification	Yes
Acute toxicity via inhalation route	Data conclusive but not sufficient for classification	Yes
Skin corrosion/irritation	Data conclusive but not sufficient for classification	Yes
Serious eye damage/eye irritation	Data conclusive but not sufficient for classification	Yes
Respiratory sensitisation	Data lacking	Yes
Skin sensitisation	Harmonised classification is proposed	Yes
Germ cell mutagenicity	Data conclusive but not sufficient for classification	Yes
Carcinogenicity	Harmonised classification is proposed	Yes
Reproductive toxicity	Data conclusive but not sufficient for classification	Yes
Specific target organ toxicity-single exposure	Data conclusive but not sufficient for classification	Yes
Specific target organ toxicity-repeated exposure	Data conclusive but not sufficient for classification	Yes
Aspiration hazard	Hazard class not applicable	No
Hazardous to the aquatic environment	Harmonised classification proposed	Yes
Hazardous to the ozone layer	Data lacking	No

3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

Benthiavalicarb-isopropyl is not currently listed in Annex VI of Regulation (EC) 1272/2008.

4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

Benthiavalicarb-isopropyl is an active substance in the meaning of Regulation EC 1107/2009, therefore, is subject to harmonised classification and labelling according to Article 36 CLP Regulation, and justification is not required.

5 IDENTIFIED USES

Benthiavalicarb-isopropyl is an active substance used in plant protection products as a fungicide against *Peronosporales* fungi, except *Pythium* spp and *Phytophthora infestans* in potato crops.

6 DATA SOURCES

This CLH Report is mainly based on the available data from the Renewal Assessment Report (RAR, 2018/2019) developed in accordance with Regulation 1107/2009 and the Regulation (EC) No. 844/2012 by the Polish CA.

7 PHYSICOCHEMICAL PROPERTIES

Table 8: Summary of physicochemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
Physical state at 20°C and 101,3 kPa	Powdered solid, Munsell colour designation N9.5/90.0%R (white)	Takeuchi, 2000 Report Nr 2000-003	Visual assessment at 25°C KIF-230R-L pure a.s. Purity: 99.96%
	Solid, free flowing powder. White, opaque in colour	O'Connor, 2001 Report Nr 131/451) (amended 2003)	Visual assessment at 25°C KIF-230 technical grade. Purity: 94.0% as KIF-230R-L
Melting/freezing point	153.1ºC and 169.5ºC (polymorphism)	Takeuchi, 2000 Report Nr 2000-003	OECD 102 with KIF-230R-L pure a.s. Purity: 99.96%
Boiling point	Boiling point could not be determined due to decomposition Decomposition occurred at 240ºC (510 K) at 102 kPa and 322ºC (595 K) at 7.9 kPa	Mullee, 2000a Report Nr 131/428A	ASTM E537-86. Differential scanning calorimetry / Reduced pressure distillation. Method complies with OECD 103 with KIF-230R-L pure a.s. Purity: 99.96%
Relative density	1.25 at 20.5 ± 0.5ºC	Mullee, 2000b Report Nr 131/428B	OECD 109 with KIF-230R-L pure a.s. Purity: 99.96%
	1.25 at 20.5 ± 0.5ºC	O'Connor & Mullee, 2001a Report Nr 131/450	EEC A.3; OPPTS 830.7300 with KIF-230 technical grade. Purity:94.0% as KIF-230R-L
Vapour pressure	<3.0 x 10^{-4} Pa at 25ºC	Bates, 1999 Report Nr 535/41-D2141 (amended 2003)	OECD 104 with KIF-230R-L pure a.s. Purity: 100%
Surface tension	63.1 mN/m of a 9.69 x 10-3 g/l at 22.0 ± 0.5°C	Tremain, 2002 Report Nr 131/486	EEC A5 with KIF-230 technical grade. Purity: 94.0% as KIF-230R-L
Water solubility	pH 5: 10.96 mg/L at 20°C pH unadjusted: 13.14 mg/L at 20°C	Bates, 1999 Report Nr 535/41-	EEC A.6; OECD 105 with KIF-230R-L pure a.s. Purity: 100%

Property	Value	Reference	Comment (e.g. measured or estimated)
	pH 9: 12.76 mg/L at 20°C	D2141 (amended 2003)	
Partition coefficient n-octanol/water	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 (distill H_2O), 20-25 °C: 2.56 (range 2.28 – 2.86)	Bates, 1999 Report Nr 535/41-D2141 (amended 2003)	EEC A.8 / OECD 117 with KIF-230R-L pure a.s. Purity: 100%
Henry's law constant	4.53 x 10-3 Pa.m3.mol-1 (20°C)	Peeters, 2015 Report Nr WP15017	Calculation. Purity considered: 100% KIF-230R-L
Flash point	Not required (melting point > 40°C)	/	/
Flammability	Not highly flammable	Tremain, 2001d Report Nr 131/452	EEC A.10 with KIF-230technical grade. Purity: 94.0% as KIF-230R-L
Explosive properties	Non-explosive	Tremain, 2001d Report Nr 131/452	EEC A.14 with KIF-230 technical grade. Purity: 94.0% as KIF-230R-L
Self-ignition temperature	Does not have a self-ignition temperature below its melting temperature	Tremain, 2001d Report Nr 131/452	EEC A.16 with KIF-230 technical grade. Purity: 94.0% as KIF-230R-L
Oxidising properties	Non-oxidising	Tremain, 2002 Report Nr 131/486	EEC A17 with KIF-230 technical grade. Purity: 94.0% as KIF-230R-L
Granulometry	Not available	/	/
Stability in organic solvents and identity of relevant degradation products	At 20°C: Acetone 25.4g/L Xylene 0.501g/L Heptane $2.15x10^{-2}$g/L Ethyl acetate 19.4g/L 1,2-Dichloroethane 11.5 g/L Methanol 41.7 g/L	Mullee, 2000c Report Nr 131/428C	OECD 105 with KIF-230R-L pure a.s. Purity: 99.96%
Dissociation constant	No dissociation in the range pH 1.12 – 12.81 at 20°C	Takeuchi, 2000 Report Nr 2000-003	OECD 112 with KIF-230R-L pure a.s. Purity: 99.96%
Viscosity	Not applicable for solid substance		

8 EVALUATION OF PHYSICAL HAZARDS

8.1 Explosives

Table 9: Summary table of studies on explosive properties

Method	Results	Remarks	Reference
EEC A.14: 1) BAM fall hammer test 2) BAM friction test	1) and 2) No sign of ignition or explosion on impact and friction. No strong exothermic	KIF-230 technical grade Purity: 94.0%	Tremain, 2001d DRAR Volume 3 CA B2 Report Nr 131/452

Method	Results	Remarks	Reference
3) the Koenen steel tube test.	decomposition was observed. 3) Flame decrease and self-extinguished.	as KIF-230R-L	

8.1.1 Short summary and overall relevance of the information provided on explosive properties

One study was performed in accordance with EEC A.14 (Tremain, 2001d). The test substance was therefore subjected to: 1) BAM fall hammer test which is a test of mechanical sensitivity with respect to shock, 2) BAM friction test which is a test of mechanical sensitivity with respect to friction, and 3) the Koenen steel tube test which is a test of thermal sensitivity. The three tests were repeated three to six times and each time they were all negative.

8.1.2 Comparison with the CLP criteria

According to requirements of CLP regulation substance shall not be classified as explosive if there are no chemical groups associated with explosive properties (given in Table A6.1 in Appendix 6 of the UN RTDG, Manual of Tests and Criteria) present in the molecule.

Based on chemical structure, there are no chemical groups associated with explosive properties present in the benthiavalicarb-isopropyl There are unsaturated C-C links present, but they are found only in the benzothiazole group, which has no explosive properties. Additionally, even though EEC A.14 is not included in the recommended test series for the classification of explosive properties under CLP, the test was still designed in order to identify explosive properties and the results can be considered as sufficiently valid to indicate no potential for explosive properties.

8.1.3 Conclusion on classification and labelling for explosive properties

Benthiavalicarb-isopropyl is not classified for explosive properties under CLP regulation.

8.2 Flammable gases (including chemically unstable gases)

Hazard class is not applicable (benthiavalicarb-isopropyl is not a gas).

8.3 Oxidising gases

Hazard class is not applicable (benthiavalicarb-isopropyl is not a gas).

8.4 Gases under pressure

Hazard class is not applicable (benthiavalicarb-isopropyl is not a gas).

8.5 Flammable liquids

Hazard class is not applicable (benthiavalicarb-isopropyl is not a liquid).

8.6 Flammable solids

Table 10: Summary table of studies on flammable solids

Method	Results	Remarks	Reference
EEC A.10	Not highly flammable:	KIF-230 technical grade Purity: 94.0% as KIF-230R-L	Tremain, 2001d DRAR Volume 3 CA B2 Report Nr 131/452

8.6.1 Short summary and overall relevance of the provided information on flammable solids

One study performed in accordance with EEC A.10 is available: a pile of active substance melted, then ignited, extinguished itself after 15 seconds failing to propagate combustion in the preliminary screening test. The result shows that benthiavalicarb-isopropyl is to be regarded as not highly flammable.

8.6.2 Comparison with the CLP criteria

Benthiavalicarb-isopropyl was not readily combusted in the study following the EEC A10 method (Tremain, 2001d) and no sign of ignition was found in the BAM friction test (EEC A14 method, Tremain, 2001d) showing that the substance does not cause or contribute to fire through friction.

The method used for classification purposes according to CLP criteria is the UN Test N.1 described in the UN RTDG, Manual of Tests and Criteria (7th revision). However, as reflected in the ECHA Guidance on Information Requirements and Chemical Safety Assessment (R.7.1.10.3), if the result of an A.10 method indicates that classification as a flammable solid does not apply (result: not highly flammable), no more testing is necessary.

Benthiavalicarb-isporpyl was classified as ‘not highly flammable’ in the EC Method A.10, hence no classification is required.

8.6.3 Conclusion on classification and labelling for flammable solids

Benthiavalicarb-isopropyl is not classified for flammability under CLP regulation.

8.7 Self-reactive substances

No specific data regarding self-reactive properties and none required.

8.7.1 Short summary and overall relevance of the provided information on self-reactive substances

Chemically, benthiavalicarb-isopropyl does not contain groups that are known to be self-reactive. Additionally, the BAM fall hammer test and the BAM friction test give information regarding the decomposition. In the BAM fall hammer test, no decomposition was observed while in the BAM friction test some decomposition was observed only through a black mark on the porcelain plate and pleg, without any strong exothermic reaction (no sign of ignition or explosion during the test).

8.7.2 Comparison with the CLP criteria

According to requirements of CLP regulation, the classification of a self-reactive substance or mixture shall be performed in accordance with test series A to H as described in Part II of the UN RTDG, Manual of Tests and Criteria. However, the classification procedures for self-reactive substances and mixtures do not need to be applied if there are no chemical groups present in the molecule associated with explosive or self-reactive properties (given in Tables A6.1 and A6.2 in Appendix 6 of the UN RTDG, Manual of Tests and Criteria).

Following its chemical structure and existing data, benthiavalicarb-isopropyl does not fall under the definition of a self-reactive substance and specific self-reactive substance test is not required.

8.7.3 Conclusion on classification and labelling for self-reactive substances

Benthiavalicarb-isopropyl is not classified as a self-reactive substance under CLP regulation.

8.8 Pyrophoric liquids

Hazard class is not applicable (benthiavalicarb-isopropyl is not a liquid)

8.9 Pyrophoric solids

No specific data regarding pyrophoric properties and none required.

8.9.1 Short summary and overall relevance of the provided information on pyrophoric solids

No specific data, derived in accordance with the recommended test method in CLP, has been provided. However, benthiavalicarb-isopropyl has been handled extensively in the air within all studies available in the dossier and there are no reports of self-ignition.

8.9.2 Comparison with the CLP criteria

According to requirements of CLP regulation, the classification procedure for pyrophoric solids does not need to apply when experience in manufacture or handling shows that the substance or mixture does not ignite spontaneously on coming into contact with air at normal temperatures (i.e. the substance is known to be stable at room temperature for prolonged periods of time (days)). During the course of the different studies realised for this dossier, benthiavalicarb-isopropyl was handled extensively in air and never ignited. Therefore, it does not meet the criteria for the classification of pyrophoric solid.

8.9.3 Conclusion on classification and labelling for pyrophoric solids

Benthiavalicarb-isopropyl is not classified as a pyrophoric solid under CLP regulation.

8.10 Self-heating substances

Table 11: Summary table of studies on self-heating substances

Method	Results	Remarks	Reference
EEC A.16	No relative self-ignition temperature from ambient temperature up to 179°C (which is approximately 10°C higher that the melting temperature).	KIF-230 technical grade Purity: 94.0% as KIF-230R-L	Tremain, 2001d Report Nr 131/452

8.10.1 Short summary and overall relevance of the provided information on self-heating substances

Due to polymorphism, benthiavalicarb-isopropyl has two melting temperatures: one at 153.1ºC and one at 169.5ºC (OECD 102, Takeuchi, 2000). Self-ignition temperature was investigated in a test following method EEC A.16: up until 179°C, approximately 10°C higher that the melting temperature, no relative self-ignition temperature was observed.

8.10.2 Comparison with the CLP criteria

Following CLP guidance (ECHA, 2017), EEC A.16 method is generally inappropriate for a reliable assessment, and the findings do not lead to a classification. However, the result in this case (EEC A16 method, Tremain, 2001d), i.e. no relative self-ignition temperature up to 10°C above the melting temperature, is sufficiently straightforward to conclude that benthiavalicarb-isopropyl will not self-ignited when under a solid form.

8.10.3 Conclusion on classification and labelling for self-heating substances

Benthiavalicarb-isopropyl is not classified for self-heating properties under CLP regulation.

8.11 Substances which in contact with water emit flammable gases

No specific data regarding the emission of flammable gases when a substance enters in contact with water are available.

8.11.1 Short summary and overall relevance of the provided information on substances which in contact with water emit flammable gases

No specific data, derived in accordance with the recommended test method in CLP, has been provided. However, benthiavalicarb-isopropyl has been in contact with water within many of the studies available in the dossier and there is no report of violent reaction and emission of gas.

8.11.2 Comparison with the CLP criteria

During the course of several studies conducted for this dossier (e.g.: studies on aquatic organisms), benthiavalicarb-isopropyl was in contact with water with no report of violent reaction and emission of gas.

According to requirements of CLP regulation, the classification procedure for this hazard class need not be applied if the chemical structure of the substance or mixture does not contain metals or metalloids, or experience in production or handling shows that the substance does not react with water or the substance is known to be soluble in water to form a stable mixture. According to the mentioned criteria, classification for this hazard class is not needed for benthiavalicarb-isopropyl.

8.11.3 Conclusion on classification and labelling for substances which in contact with water emit flammable gases

Benthiavalicarb-isopropyl is not classified for emission of flammable gas under CLP regulation.

8.12 Oxidising liquids

Hazard class is not applicable (benthiavalicarb-isopropyl is not a liquid).

8.13 Oxidising solids

Table 12: Summary table of studies on oxidising solids

Method	Results	Remarks	Reference
EEC A17	Non-oxidising	KIF-230 technical grade Purity: 94.0% as KIF-230R-L	Tremain, 2002 Report Nr 131/486

8.13.1 Short summary and overall relevance of the provided information on oxidising solids

Reference mixtures were prepared by mixing barium nitrate ($Ba(NO_3)_2$) and cellulose in various weight ratios (10 to 90%). Sample mixtures were prepared by mixing benthiavalicarb-isopropyl with cellulose in various weight ratios (10 to 90%). During the test, all sample mixtures with the different ratios burned. The three ratios giving the shortest burning time (260 seconds for the 10%/90% mixture, 289 seconds for the 20%/80% mixture and 285 seconds for the 40%/60% mixture) were then retested in six burning trials (shortest of the 6 trials: 256 seconds for the 10%/90% mixture, 288 seconds for the 20%/80% mixture and

277 seconds for the 40%/60% mixture). In comparison, the reference mixtures had burning times that were always shorter (except in the 80%/20% and 90%/10% mixtures which did not burned).

8.13.2 Comparison with the CLP criteria

If the 4:1 or 1:1 sample-to-cellulose by mass (corresponding to 80%/20% and 50%/50%) mixtures ignites or burns then the mean burning time of those mixtures should be compared to the mean burning time of 3:7 mixture by mass (30%/70%) of potassium bromate and cellulose or of 1:2 mixture by mass of calcium peroxide and cellulose. If the burning times of the substance (mixture) is equal or greater than the burning time of the reference mixture, then the criteria for classification as oxidising solid are not met.

In the case of EEC A.17, barium nitrate is used as a reference oxidiser instead of potassium bromate or calcium peroxide. Therefore, a conclusion on the need for classification under CLP cannot be made. However, results show that the burning times of benthiavalicarb-isopropyl in the mixtures 4:1 and 1:1 were longer than in 3:7 ammonium nitrate/cellulose. Furthermore, all (mean) burning times of the substance mixtures were longer than all (mean) burning times of the reference mixtures, clearly indicating that no classification is warranted under CLP.

8.13.3 Conclusion on classification and labelling for oxidising solids

Benthiavalicarb-isopropyl is not classified for oxidizing properties under CLP regulation.

8.14 Organic peroxides

Hazard class is not applicable (benthiavalicarb-isopropyl is not an organic peroxides).

8.15 Corrosive to metals

No specific data available regarding the corrosive properties to metals of benthiavalicarb-isopropyl.

8.15.1 Short summary and overall relevance of the provided information on the hazard class corrosive to metals

There is no specific study for this hazard class with benthiavalicarb isopropyl. However, some parameters of the substance can be used to waive/screen the necessity of exploring corrosive properties of benthiavalicarb-isopropyl.

Benthiavalicarb-isopropyl is solid with melting points of 153.1ºC and 169.5ºC (due to polymorphism), formulations containing the active substance are all wettable dispersible granules (no liquid form).

8.15.2 Comparison with the CLP criteria

Application of classification criteria in the UN-MTC, Section 37.4 excludes solids, while ‘liquids and solids that may become liquids (during transport)’, have to be considered for such a classification. Solids may become liquids by melting (due to an increase in temperature). Solids having a melting point lower than 55°C (which is the test temperature required in UN Test C.1) must then be taken into consideration. The other physical way to transform a solid into liquid is by dissolution in water or another solvent.

Therefore, based on the physical state of benthiavalicarb-isopropyl and the interpretation given in the CLP guidance (ECHA, 2017) for this hazard class, the active substance should not be considered for such a classification.

8.15.3 Conclusion on classification and labelling for corrosive to metals

Benthiavalicarb-isopropyl is not classified as corrosive to metals under CLP regulation.

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

The absorption, distribution, metabolism and excretion (ADME) in mammals of benthiavalicarb-isopropyl were investigated through two studies (Anonymous 1 and Anonymous 2). Summarised results are provided in Table 13.

Table 13: Summary table of toxicokinetic studies

Method	Results	Remarks	Reference
Absorption, distribution, metabolism and excretion following oral administration to the rat EPA OCSPP Guideline No 870.7845, OECD 417, EC B 36	**Rate and extent of absorption** Rapid (<48h); efficient (89-97%) at low dose, less efficient (41-54%) at high dose **Distribution** Widely distributed **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:** Extensive (low dose) to low (high dose) metabolization; major metabolite B11 (glucuronic acid conjugate of hydroxylated derivative); limited cleavage of the amide bond of the valyl-moiety	Test material: (^{14}C)-KIF-230R-L; purity: 99.5%	Anonymous 1, 2003, Report no. 535/55, DRAR Vol. 3 CA, B.6.1.1
Tissue levels following repeat dosing in the rat EPA OCSPP Guideline No 870.7845, OECD 417, EC B 32	**Distribution** Widely distributed **Metabolism** Extensive (low dose) to low (high dose) metabolization; major metabolite B11 (glucuronic acid conjugate of hydroxylated derivative); limited cleavage of the amide bond of the valyl-moiety **Potential for accumulation** Apparent accumulation after repeated administration, most probably due to recruitment of valine	Test material: (^{14}C)-KIF-230R-L; purity: 99.9%	Anonymous 2, 2003, Report no. 0535/093, DRAR Vol. 3 CA, B.6.1.1

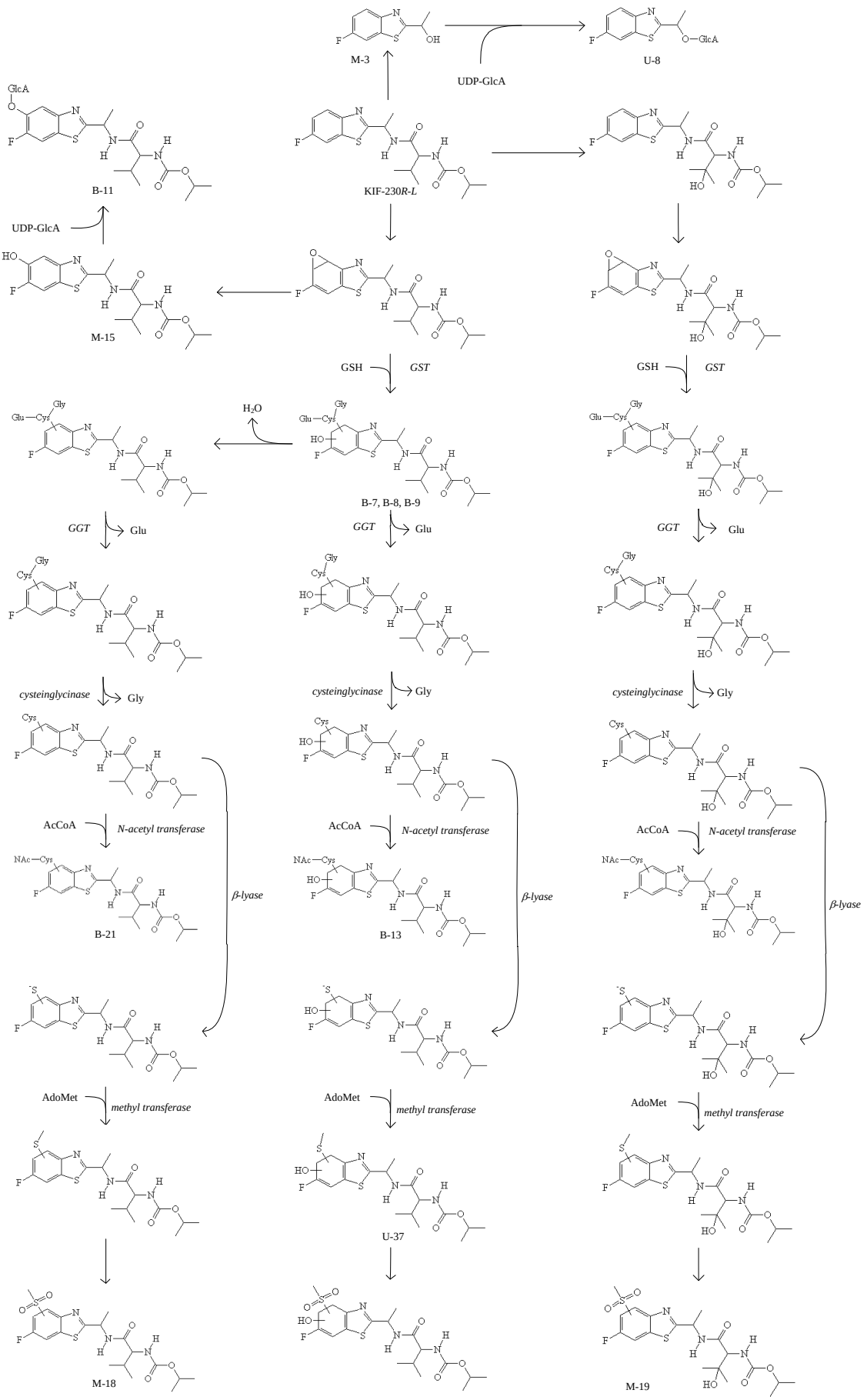
9.1 Short summary and overall relevance of the provided toxicokinetic information on the proposed classification(s)

Absorption, distribution, metabolism and excretion of benthiavalicarb-isopropyl was studied in rodents (Anonymous 1,2003). Two forms of KIF-230R-L labelled with ^{14}C at the benzene ring or valyl moiety

were administered to groups of two to 2 to 12 rats (Fischer CDF Crl:BR (F-344)) of each sex with a single dose of 5 or 400 mg/kg by oral gavage. The potential accumulation and tissue levels following repeated dosing was also studied in rats (Anonymous 2, 2003). During 7 or 14 days, 4 rats per sex received 5 mg/kg bw/day by oral gavage.

KIF-230R-L was extensively and rapidly absorbed (almost complete at the low dose, about 50% at the high dose) in both sexes. The absorption was slightly delayed at the high dose. The distribution was generally throughout the body, mainly in the gastrointestinal tract, bile duct and urinary bladder followed by liver and kidney. Rapid and quite extensive excretion was predominantly via the bile. The metabolism of KIF-230R-L was complex; the predominant routes of metabolism were by glutathione conjugation or by hydroxylation on the benzene or valyl moieties. Numerous metabolites have been isolated and co-chromatographed with authentic standards; the main metabolite was B11 upon analysis of urine and bile of bile-duct cannulated rats. Metabolites present in bile, urine and faeces of cannulated rats accounted for 43-60% of the administered dose. The parent substance was not present in urine or bile. After repeated administration of KIF-230R-L the distribution profile was similar to that obtained after a single administration. Kinetics data indicated delayed depuration in some tissues but as the absolute radioactivity in these tissues were not higher than those of the other tissues and were very low 14 days after administration and toxicological studies did not indicate that these tissues/organs were particularly targeted, it is concluded that the slow depuration is not of concern. Metabolites formed after repeated administrations were not quantitatively different from those formed after a single administration of the substance.

Figure 1 Proposed pathways for metabolism of benthiavalicarb-isopropyl in animals.



10 EVALUATION OF HEALTH HAZARDS

Acute toxicity

Benthiavalicarb-isopropyl (KIF-230) has a low acute toxicity after oral exposure (Anonymous 3 and 4, 1998), dermal exposure (Anonymous 5, 1998c), and after inhalation exposure (Anonymous 6, 2000a).

10.1 Acute toxicity - oral route

Table 14: Summary table of animal studies on acute oral toxicity

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels, duration of exposure	Value LD_{50}	Reference
Acute oral toxicity in rats, Compliant with test method B.1 of directive 92/69/EEC, GLP	5 rats/sex/dose Slc: Wistar, SPF	KIF-230, purity: 88.8% as KIF-230R-L	5,000mg/kg bw, single exposure gavage	>5,000 mg/kg bw (male and female)	Anonymous 3, 1998b Exp. No 4062, DRAR Vol. 3 CA, B.6.2.1
Acute oral toxicity in mice, Compliant with test method B.1 of directive 92/69/EEC; OECD 401, GLP	5 mice/sex/dose Slc: ICR (SPF)	KIF-230, purity: 88.8% as KIF-230R-L	5,000mg/kg bw, single exposure gavage	>5,000 mg/kg bw (male and female)	Anonymous 4,1998a report No.: 4061, DRAR Vol. 3 CA, B.6.2.1

No human data on acute oral toxicity is available.

10.1.1 Short summary and overall relevance of the provided information on acute oral toxicity

The oral acute toxicity of KIF-230 was tested on rats (Anonymous 3, 1998b) and mice (Anonymous 4, 1998a) by oral gavage of 5,000 mg/kg bw. Five individuals per sex and per dose were tested. In both tests, there was no mortality and no relevant finding in clinical signs, body weight and necropsy.

10.1.2 Comparison with the CLP criteria

The available LD_{50} were both above 5,000 mg a.s./kg b.w. which are above the CLP criteria for acute oral toxicity, the lowest classification, category 4, being when acute toxic endpoint is between 300 (excluded) and 2,000 mg a.s./kg bw (included). Therefore benthiavalicarb-isopropyl is not classified for acute oral toxicity.

10.1.3 Conclusion on classification and labelling for acute oral toxicity

Benthiavalicarb-isopropyl is not classified for acute oral toxicity under CLP regulation.

10.2 Acute toxicity - dermal route

Table 15: Summary table of animal studies on acute dermal toxicity

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels duration of exposure	Value LD_{50}	Reference
Acute dermal toxicity in rats Guidelines No. 82-1, EPA OCSPP& No 870.1200, OECD 402 GLP	5 rats/sex/dose Slc: Wistar (SPF)	KIF-230, purity: 88.8% as KIF-230R-L	2,000 mg/kg bw 0.0145-0199 g/cm² Dermal occlusive application 24h	>2,000 mg/kg bw (male and female)	Anonymous 5, 1998c, report No.: 4063, DRAR Vol.3 CA, B.6.2.2

No human data on acute dermal toxicity is available

10.2.1 Short summary and overall relevance of the provided information on acute dermal toxicity

Rats were exposed to KIF-230 in solid form (moistened with 1 mL water) at a dose level of 2,000 mg/kg bw and at a dose rate of about 0.0145-0199 g/cm², by dermal occlusive application for 24 hours (Anonymous 51998c). There was no mortality and no relevant finding in clinical signs and necropsy.

10.2.2 Comparison with the CLP criteria

The available LD_{50} was above 2,000 mg a.s./kg b.w. which is higher than the CLP criteria for acute dermal toxicity. Indeed, the lowest classification, category 4, is when the acute toxic endpoint is between 1,000 (excluded) and 2,000 mg a.s./kg bw (included). Therefore benthiavalicarb-isopropyl is not classified for acute dermal toxicity.

10.2.3 Conclusion on classification and labelling for acute dermal toxicity

Benthiavalicarb-isopropyl is not classified for acute dermal toxicity under CLP regulation.

10.3 Acute toxicity - inhalation route

Table 16: Summary table of animal studies on acute inhalation toxicity

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance, , form and particle size (MMAD)	Dose levels, duration of exposure	Value LC_{50}	Reference
Acute inhalation toxicity in rats Guidelines No. 81-3, EPA OCSPP & No 870.1300; OECD 403 GLP	5 rats/sex/dose Charles River Crl:CD® IGS BR	KIF-230, purity: 89.1%as KIF-230R-L Micronized dust aerosol MMAD= 3.9± 2.82 µm	Nominal: 19 mg/L Mean actual exposure concentration: 4.6±0.6 mg/L During 4.0h Inhalation rate: 7 l/h Mean pre-exposure bw: 263g (♂) and	>4.6 mg/L (male and female)	Anonymous 6, 2000a, report No.: WIL-156011, DRAR Vol. 3CA, B.6.2.3

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance, , form and particle size (MMAD)	Dose levels, duration of exposure	Value LC_{50}	Reference
			227g (♀)		

No human data on acute inhalation toxicity is available.

10.3.1 Short summary and overall relevance of the provided information on acute inhalation toxicity

5 rats/sex were exposed to a micronized dust aerosol of KIF-230 in a whole-body inhalation assay (Anonymous 6, 2000a), at a nominal concentration of 19 mg/L (nominal) resulting to a mean actual exposure concentration of 4.6 ± 0.6 mg/L (determined by gravimetry) during 4.0h. MMAD was equal to 3.9 ± 2.82 µm. About 51% of the particles were < 4.0 µm. One female and one male died on day 1. The clinical signs from the deceased rats were laboured respiration, rales, gasping, hypoactivity, clear lacrimation. The clinical signs of the survivors were also laboured respiration and rales, and in addition dried red material around nose/eyes/forelimbs, dried yellow material on urogenital area, decreased/mucoid faeces. Effects on body weight were observed between day 0 and 3 and day 0 and 7. Necropsy from the deceased rats showed dark red adrenals (in both sexes), dark patchy lungs (female) and gas-filled stomach (male), while in the survivors there were no relevant findings, except dark red/mottled lungs in one female.

10.3.2 Comparison with the CLP criteria

The available LC_{50} was above 4.6 ± 0.6 mg a.s./L, the actual mean measured concentration, as one female and one male over ten rats (20%) died during the test, on the first day. The lowest classification, category 4, for acute inhalation toxicity, is when the acute toxic endpoint, LC_{50}, is between 1.0 (excluded) and 5 mg a.s./L (included). Therefore, even though the actual mean exposure concentration only reached the upper limit value of the criteria, the data show that benthiavalicarb-isopropyl should not be classified for acute inhalation toxicity.

10.3.3 Conclusion on classification and labelling for acute inhalation toxicity

Benthiavalicarb-isopropyl is not classified for acute inhalation toxicity.

10.4 Skin corrosion/irritation

Table 17: Summary table of animal studies on skin corrosion/irritation

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels duration of exposure	Results -Observations and time point of onset -Mean scores/animal -Reversibility	Reference
Guidelines No. 81-5, EPA OCSPP & No 870.2500 GLP	6 male rabbits/ dose Crl: NZW	KIF-230, purity: 87.9% as KIF-230R-L moistened with 500 µL water	0.5 g/ 10 cm^2 4 hours	Average score for each animal (mean of 24, 48, 72 h observations): Score erythema: 0, 0, 0, 0, 0, 0 Score oedema: 0, 0, 0, 0, 0, 0	Anonymous 7, 1999, KCI Doc No. 198/993612/SE, DRAR Vol. 3 CA, B.6.2.4

No human data on skin corrosion/irritation is available

10.4.1 Short summary and overall relevance of the provided information on skin corrosion/irritation

Male rabbits were exposed to KIF-230 moistened with 500 µL water, in the amount of 0.5 g/ 10 cm² on back skin, by semi-occlusive application for 4 hours (Anonymous 7, 1999). The scores for erythema and oedema were both equal to zero at 24, 48 and 72 hours after application.

10.4.2 Comparison with the CLP criteria

To be classified for skin irritation under CLP, some positive lasting effect should be observed in one exposed animal which was not the case in the skin corrosion/irritation test performed with benthiavalicarb-isopropyl where no dermal effect was observed.

10.4.3 Conclusion on classification and labelling for skin corrosion/irritation

Benthiavalicarb-isopropyl is not classified for skin corrosion/irritation.

10.5 Serious eye damage/eye irritation

Table 18: Summary table of animal studies on serious eye damage/eye irritation

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels duration of exposure	Results - Observations and time point of onset - Mean scores/animal - Reversibility	Reference
Eye irritation study in the rabbit FIFRA Guidelines No. 81-5, EPA OCSPP & No 870.2400 GLP	6 male rabbits/ dose Crl: Kbl©BR	KIF-230, purity: 96% as KIF-230R-L	solid form, 0.061 g, corresponding to 0.1 mL of undiluted a.s. one application	Average score for each animal (mean of 24, 48, 72 h observations): Corneal opacity: 0, 0, 0, 0, 0, 0 Iritis: 0, 0, 0, 0, 0, 0 Conjunctival redness: 0.3, 1.6, 1.3, 0.6, 0.3, 0.6 Conjunctival chemosis: 0, 0, 0, 0, 0, 0 All signs were reversible within 4 days	Anonymous 8, 2000, KCI Doc No. 199/993939/SE, DRAR Vol. 3 CA, B.6.2.5

No human data on serious eye damage/eye irritation is available.

10.5.1 Short summary and overall relevance of the provided information on serious eye damage/eye irritation

Seven male rabbits were exposed to KIF-230 in solid form, by single instillation of 0.061 g, corresponding to 0.1 mL of the undiluted test substance into the everted lid of the left eye (Anonymous 8, 2000).

Screen study –rinsed eye:

One animal was treated in advance of the others. The treated eye was rinsed with distilled water 30 seconds after instillation lasting 30 seconds. Responses in rabbit were observed at 60 minutes, 24, 48 and 72 hours after exposure. Only conjunctiva redness score 1 was observed 1h and 24h after instillation. Ocular reactions had resolved by two days after instillation.

Main study – unrinsed eye:

All treated rabbits showed positive response for conjunctival redness with a score of 1 to 2 from one hour to 72 hours post instillation. Ocular reactions had resolved in all animals by either two or four days after instillation.

No cornea opacity, iridial inflammation or conjunctival chemosis was seen in any animal.

10.5.2 Comparison with the CLP criteria

The mean scores at 24, 48 and 72 hours after instillation, mean scores for corneal opacity or iris should be equal or above one, or conjunctival redness or oedema should be equal or above 2, in 2 of 3 (4/6) animals for the substance to be classified as eye irritant under criteria of CLP regulation. In this case, the highest score was 1.6 for conjunctival redness. Therefore benthiavalicarb-isopropyl should not be classified for eye irritation.

10.5.3 Conclusion on classification and labelling for serious eye damage/eye irritation

Benthiavalicarb-isopropyl is not classified as an eye irritant.

10.6 Respiratory sensitisation

No data available.

10.7 Skin sensitisation

Table 19: Summary table of animal studies on skin sensitisation

<table>
<tr><th>Method, guideline, deviations if any</th><th>Species, strain, sex, no/group</th><th>Test substance,</th><th>Dose levels duration of exposure</th><th>Results</th><th>Reference</th></tr>
<tr>
<td>Maximisation test
EPA OCSPP Guideline No 870.2600
GLP</td>
<td>20 female guinea pigs (Dunkin-Hartley) /test dose and 20 female guinea pigs /control group</td>
<td>KIF-230
(87.9% as KIF-230R-L; B.n.° G51-15-162)</td>
<td>Intradermal: 0.25% w/v KIF-230 in (FCA*) + Alembicol D, 3 pairs of injections.
Topical: 70% w/v KIF-230 in Alembicol D, 48 hours.
Challenge: 35 and 70% w/v in Alembicol D, 24 hours</td>
<td>Intradermal: slight irritations, comparable to effects in control.
Topical: no effect
Challenge:
<table>
<tr><td></td><td colspan="4">No. of sensitised animals</td></tr>
<tr><td></td><td colspan="2">Challenge with 35% benthiavalicarb</td><td colspan="2">Challenge with 70% benthiavalicarb</td></tr>
<tr><td></td><td>Control group</td><td>Tested group</td><td>Control group</td><td>Tested group</td></tr>
<tr><td colspan="5">challenge</td></tr>
<tr><td>24h</td><td>0/20</td><td>9/20</td><td>14/20</td><td>16/20</td></tr>
<tr><td>48h</td><td>0/20</td><td>10/20</td><td>7/20</td><td>15/20</td></tr>
</table>
</td>
<td>Anonymous 9, 2000a, KCI Doc No. 201/993857/SS, DRAR Vol. 3 CA, B.6.2.6</td>
</tr>
<tr>
<td>Buehler test
EPA OCSPP Guideline No 870.2600
GLP</td>
<td>20 female guinea pigs/ test dose, Dunkin-Hartley</td>
<td>KIF-230
(87.9% as KIF-230R-L; B.n.° G51-15-162)</td>
<td>Induction: 70% w/v in Alembicol D, 6 hours, at day 1, 8 and 15
Challenge: 40% w/v in Alembicol</td>
<td>Induction: sporadic slight dermal reaction, 3/20 animals
Challenge: No effect at 24 and 48h.</td>
<td>Anonymous 10, 2000b, KCI Doc No. 200/002387/SS, DRAR Vol. 3 CA, B.6.2.6</td>
</tr>
</table>

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels duration of exposure	Results	Reference
			D, 6 hours		
FCA = Freund's Complete Adjuvant					

No human data on skin sensitisation is available

10.7.1 Short summary and overall relevance of the provided information on skin sensitisation

Two skin sensitisation studies were conducted with guinea pigs: one Magnusson-Kligman maximisation test (Anonymous 9, 2000a) and one Buehler test (Anonymous 10, 2000b).

Three phases were conducted in the Magnusson-Kligman maximisation test:

- intradermal induction - on day 1- 20 female guinea pigs (Dunkin-Hartley) received three pairs of intradermal injections of respectively 100 µL of (i) 50% w:v Freund's Complete Adjuvant (FCA)/water emulsion, (ii) 0.25% w:v benthiavalicarb-isopropyl /Alembicol D, and (iii) 0.25% Benthiavalicarb in 50% w:v FCA/Alembicol D. 20 female control animals were given three pairs of intradermal injections of 100 µL with the concommittant blanks (FCA/water, Alembicol D, 50% w:v FCA/Alembicol D).

- topical induction - on day 7, 400 µL of 70% w:v benthiavalicarb-isopropyl in Alembicol D (tests) or Alembicol D (controls) was administered by the occlusive application during 48h.

- challenge - on day 22, 200 µL of 35% or 70% w:v benthiavalicarb-isopropyl in Alembicol D was applied on either an anterior or posterior flank for 24h.

In the first pretest (intradermal injection range-finding), benthiavalicarb-isopropyl was injected at 0.1, 0.25, 0.5 and 1.0% w:v in Alembicol D. Slight erythema and edema occurred at 0.25% mixture at 24h and 72h.

In the second pretest (topical induction range-finding), benthiavalicarb-isopropyl was applied at 10, 20, 50 and 70% w:v in Alembicol D. No irritation was observed up to and including 70% mixture at 24h and 48h.

The test facility concluded that a 70% w:v mixture was the maximum practical concentration that could be prepared which would give no rise to irritating effects during the challenge.

Additionally, 10 female guinea pigs were treated with hexyl cinnamic aldehyde (HCA, 10% v:v intradermal and topical induction, 50% and 100% v:v challenge).

After intradermal injection, necrosis was observed at all intradermal FCA-injection sites, while slight irritation was observed at the other injection site (0.25% test article in Alembicol D), in both control and test animal.

One day after percutaneous induction (70% test article in Alembicol D), no irritation was observed.

The animals treated with HCA (positive controls) exhibited 100% response after both 24h and 48h challenge times as expected.

The challenge with a 70% w:v benthiavalicarb-isopropyl at 48h elicited a skin response above the level observed in the controls, in more than 30% of the test animals.

The challenge with a 35% w:v benthiavalicarb-isopropyl at 24h and 48h elicited a skin response in 45 and 50% of animals, respectively, when no effects in any control animals were observed.

In the Buelher test, 20 female guinea pigs (Dunkin-Hartley) were subject to a topical induction test on day 1, 8 and 15, 500 µL of 40% w:v benthiavalicarb-isopropyl in Alembicol D was applied epidermally for 6h. On day 29 (challenge), 500 µL of 70% w:v benthiavalicarb-isopropyl in Alembicol D was applied for 6h. In the pretest (topical induction range-finding), benthiavalicarb-isopropyl was applied for 6h at 40, 50, 60 and 70% w:v in Alembicol D. Slight erythema and edema occurred in animals treated with 60% mixture and above at 24h and 72h. It was concluded that a 40% w:v mixture was the maximum practical concentration that could be prepared which would give no rise to irritating effects during the challenge. 24h after the 3 induction phases, sporadic incidences of slight to well-defined irritation was observed in the animals (induction 1: 1/20, induction 2: 3/20, induction 3: 1/20).

24h and 48h after challenge phase, no positive reaction was elicited, in neither treated nor control group.

The animals treated with HCA (positive controls) exhibited 90% and 100% response after respectively 24h and 48h challenge times as expected.

Additionally, 10 female guinea pigs were treated with Cinnamic aldehyde (HCA, 10% v:v topical induction, 50% and 100% v:v challenge).

10.7.2 Comparison with the CLP criteria

To be classified as a skin sensitizer under CLP regulation, for Category 1, when an adjuvant type test method for skin sensitisation is used, a response of at least 30% of the animals is considered as positive. Where data are not sufficient for sub-categorisation, skin sensitizer substance shall be classified as Category 1. Positive answers in ≥30% of animals were observed at the intradermal induction dose 0.25% of benthavalicarb-isopropyl in Guinea pig maximisation test (Anonymous 9, 2000a). Based on those results it is proposed to classified benthiavalicarb-isopropyl as a skin sensitizer category 1, without sub-categorisation (since dose ≤0.1% intradermal induction dose was not tested), with the hazard statement H317: “May cause an allergic skin reaction”.

10.7.3 Conclusion on classification and labelling for skin sensitisation

Benthiavalicarb-isopropyl is classified as skin sensitizer category 1, H317: “May cause an allergic skin reaction”. The corresponding pictogram is GHS07 with the signal word “Warning”.

10.8 Germ cell mutagenicity

Table 20: Summary table of mutagenicity/genotoxicity tests *in vitro*

Method, guideline, deviations if any	Test substance,	Relevant information about the study including rationale for dose selection (as applicable)	Observations	Reference
Bacterial assay for gene mutation OCSPP Test Guideline 870.5100 Acceptable	KIF-230 Lot: G51-15-162; 87.9% as KIF-230R-L	*S. typhimurium* (strains TA98, TA100, TA1535, TA1537) *E. coli* (strain WP2 uvrA) 8, 40, 200, 1,000 and 5,000 µg/plate 32, 80, 200, 500, 1,000, 2,000 and 5,000 µg/plate	Positive (strain TA98) +S9 mixture Positive result due the impurity I-6 Sensitivity demonstrated by positive control	Dawkes (1999), Report no. 535/44, Vol. 3 CA, B6.4.1/1
Bacterial assay for gene mutation OCSPP Test	KIF-230 Lot: G51-35-184; 91.9% as	*S. typhimurium* (strains TA98, TA100, TA1535, TA1537) *E. coli* (strain WP2 uvrA)	Negative ± S9 mixture Sensitivity demonstrated by positive	Mizuhashi (2001a), Report no. 5839, Vol. 3

Method, guideline, deviations if any	Test substance,	Relevant information about the study including rationale for dose selection (as applicable)	Observations	Reference
Guideline 870.5100 Acceptable	KIF-230R-L	39, 78, 156, 313, 625, 1,250, 2,500 and 5,000 µg/plate	controls	CA, B.6.4.1/2
Bacterial assay for gene mutation OCSPP Test Guideline 870.5100 Acceptable	KIF-230 Lot: G51-37-184; 95.8% as KIF-230R-L	*S. typhimurium* (strains TA98, TA100, TA1535, TA1537) *E. coli* (strain WP2 uvrA) 78, 156, 313, 625, 1,250, 2,500 and 5,000 µg/plate	Negative ± S9 mixture Sensitivity demonstrated by positive controls	Mizuhashi (2001b), Report no. 5840, Vol. 3 CA, B6.4.1/3
Bacterial assay for gene mutation OCSPP Test Guideline 870.5100 Acceptable	KIF-230 Lot: G51-36-184; 92.6% as KIF-230R-L	*S. typhimurium* (strains TA98, TA100, TA1535, TA1537) *E. coli* (strain WP2 uvrA) 39, 78, 156, 313, 626, 1,250, 2,500 and 5,000 µg/plate	Negative ± S9 mixture Sensitivity demonstrated by positive controls	Mizuhashi (2001c), Report no. 5918, Vol.3 CA, B.6.4.1/4
Bacterial assay for gene mutation OCSPP Test Guideline 870.5100 Acceptable	KIF-230 TG - lot no. G51-08-158; 88.6% as KIF-230R-L	*S. typhimurium* (strains TA98, TA100, TA1535, TA1537) *E. coli* (strain WP2 uvrA) 28, 45, 72, 116, 186, 298, 477, 763, 1,221, 1,953, 3,125 and 5,000 µg/plate	Positive (strain TA98) + S9 mixture Positive result due to the impurity I-6 Sensitivity demonstrated by positive controls	Mizuhashi (2001d), Report no. 5919, Vol. 3 CA, B.6.4.1/5
Bacterial assay for gene mutation OCSPP Test Guideline 870.5100 Acceptable	KIF-230 Lot: G51-47-190; 92.4% as KIF-230R-L	*S. typhimurium* (strain TA98) 313, 625, 1,250, 2,500 and 5,000 µg/ plate	Negative ± S9 mixture Sensitivity demonstrated by positive control	Mizuhashi (2002a), Report no. 6239, Vol.3 CA, B.6.4.1/6
Bacterial assay for gene mutation OCSPP Test Guideline 870.5100 Acceptable	KIF-230 Lot: G51-48-190; 94.8% as KIF-230R-L	*S. typhimurium* (strain TA98) 313, 625, 1,250, 2,500 and 5,000 µg/ plate	Negative ± S9 mixture Sensitivity demonstrated by positive control	Mizuhashi (2002b), Report no. 6240 Vol. 3 CA, B.6.4.1/7
Bacterial assay for gene mutation OCSPP Test Guideline 870.5100 Acceptable	KIF-230 Lot: G51-49-190; 92.7% as KIF-230R-L	*S. typhimurium* (strain TA98) 313, 625, 1,250, 2,500 and 5,000 µg/ plate	Negative ± S9 mixture Sensitivity demonstrated by positive control	Mizuhashi (2002c), Report no. 6241, Vol. 3 CA, B.6.4.1/8
Bacterial assay for gene mutation OCSPP Test Guideline 870.5100 Acceptable	KIF-230 Lot: G51-50-190; 91.5% as KIF-230R-L	*S. typhimurium* (strain TA98) 313, 625, 1,250, 2,500 and 5,000 µg/ plate	Negative ± S9 mixture Sensitivity demonstrated by positive control	Mizuhashi (2002d), Report no. 6242, Vol. 3 CA, B.5.4.1/9
Bacterial assay for gene mutation	KIF-230 Lot: G51-51-190;	*S. typhimurium* (strain TA98) 313, 625, 1,250, 2,500 and	Negative ± S9 mixture	Mizuhashi (2002e), Report no.

Method, guideline, deviations if any	Test substance,	Relevant information about the study including rationale for dose selection (as applicable)	Observations	Reference
OCSPP Test Guideline 870.5100 Acceptable	93.3% as KIF-230R-L	5,000 µg/ plate	Sensitivity demonstrated by positive control	6243, Vol. 3 CA, B.6.4.1/10
Bacterial assay for gene mutation OECD 471 Acceptable	KIF-230 TG - lot no. G51-56 ; 93.6% as KIF-230R-L	*S. typhimurium* (strains TA98, TA100, TA1535, TA1537) *E. coli* (strain WP2 uvrA) 16, 50, 158, 500, 1,581 and 5,000 µg/ plate 8, 20, 51, 128, 320, 800, 2,000 and 5,000 µg/plate	Negative ± S9 mixture Negative result confirmed in a repeat study Sensitivity demonstrated by positive controls	Ballantyne (2004a), Report no. 535/114, Vol. 3 CA, B.6.4.1/11
Bacterial assay for gene mutation OECD 471 Acceptable	KIF-230 TG - lot no. G51-56, 93.6% as KIF-230R-L	*S. typhimurium* (strains TA98, TA100, TA1535, TA1537) *E. coli* (WP2 uvrA) 16, 50, 158, 500, 1,581 and 5,000 µg/ plate 20, 51, 128, 320, 800, 2,000 and 5,000 µg/plate	Negative ± S9 mixture Negative result confirmed in a repeat study Sensitivity demonstrated by positive controls	Ballantyne (2004b), Report no. 535/115, Vol. 3 CA, B.6.4.1/12
Bacterial gene mutation assay OECD 471 Acceptable	KIF-230 Lot: G51-58; 94.6% as KIF-230R-L	*S. typhimurium* (strain TA98, TA100, TA1535, TA1537) *E. coli* (strain WP2 uvrA) 16, 50, 158, 500, 1,581 and 5,000 µg/ plate 8, 20, 51, 128, 320, 800, 2,000 and 5,000 µg/plate	Negative ± S9 mixture Negative result confirmed in a repeat study Sensitivity demonstrated by positive controls	Ballantyne (2004c), Report no. 535/116, Vol.3 CA, B.6.4.1/13
Bacterial reverse gene mutation OECD 471 Acceptable	KIF-230 Lot: G51-58; 94.6% as KIF-230R-L	*Salmonella typhimurium* (TA 1535, TA 1537, TA 98 and TA 100) *Escherichia coli* WP2 uvrA 16, 50, 158, 500, 1,581 and 5,000 µg/ plate 20, 51, 128, 320, 800, 2,000 and 5,000 µg/plate	Negative ± S9 mixture Negative result confirmed in a repeat study Sensitivity demonstrated by positive controls	Ballantyne (2004d), Report no. 535/117, Vol. 3 CA, B.6.4.1/14
Bacterial reverse gene mutation OECD 471 Acceptable	KIF-230 Lot: G51-59; 92.7% as KIF-230R-L	*Salmonella typhimurium* (TA 1535, TA 1537, TA 98 and TA 100) *Escherichia coli* WP2 uvrA 16, 50, 158, 500, 1,581 and 5,000 µg/ plate 8, 20, 51, 128, 320, 800, 2,000 and 5,000 µg/plate	Negative ± S9 mixture Negative result confirmed in a repeat study Sensitivity demonstrated by positive controls	Ballantyne (2004e), Report no. 535/118, Vol. 3 CA, B.6.4.1/15
Bacterial reverse gene mutation OECD 471 Acceptable	KIF-230 Lot: G51-59; 92.7% as KIF-230R-L	*Salmonella typhimurium* (TA 1535, TA 1537, TA 98 and TA 100) *Escherichia coli* WP2 uvrA 16, 50, 158, 500, 1,581 and 5,000 µg/ plate 20, 51, 128, 320, 800, 2,000 and 5,000 µg/plate	Negative ± S9 mixture Negative result confirmed in a repeat study Sensitivity demonstrated by positive controls	Ballantyne (2004f), Report no. 535/119, Vol. 3 CA, B.6.4.1/16
Clastogenicity in mammalian cells	KIF-230 Lot: G51-02-152;	Chinese hamster lung (CHL) cells 955, 1,910 and 3,820 µg/ml	Negative ± S9 mixture	Anonymous 11 (1998), Report no. 3391,

Method, guideline, deviations if any	Test substance,	Relevant information about the study including rationale for dose selection (as applicable)	Observations	Reference
OCSPP Test Guideline 870.5300 Acceptable	96.9% as KIF-230R-L		Sensitivity demonstrated by positive control	Vol.3 CA, B.6.4.1/17
Gene mutation in mammalian cells OCSPP Test Guideline 870.5300 Supportive (presence of white powdery test substance)	KIF-230 Lot: G51-15-162; 87.9% as KIF-230R-L	Mouse lymphoma cells 3.75, 7.5, 15, 30, 60 and 120 µg/ml 7.5, 15, 30, 60 and 120 µg/ml	Negative ± S9 mixture Sensitivity demonstrated by positive control	Anonymous 12 (1999a), Report no. 535/45, Vol. 3 CA, B.6.4.1/18
Unscheduled DNA synthesis Supportive	KIF-230 Lot: G51-15-162; 87.9% as KIF-230R-L	Rat hepatocytes 5, 16, 50, 158 and 500 µg/ml 16, 31, 63, 125, 250 and 500 µg/ml	Negative Sensitivity demonstrated by positive control	Anonymous 13 (1999b), Report no. 535/46, Vol. 3 CA, B.6.4.1/
Comet assay Not stated/ No EC protocol is available Acceptable	KIF-230 Lot: FL-3003; 93.4% as KIF-230R-L	Human lymphocytes 62, 104, 173, 288 and 480 µg/ml	Negative Sensitivity demonstrate by positive control	Anonymous 14 (2003), Report no. 7445, Vol. 3 CA, B.6.4.1/20

Table 21: Summary table of mutagenicity/genotoxicity tests in mammalian somatic or germ cells *in vivo*

Method, guideline, deviations if any	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
Mouse bone marrow micro-nucleus test method B.12 of directive 2000/32/EC Deviations but acceptable	KIF-230 Lot: G51-15-162; 87.9% as KIF-230R-L	Mouse (CD-1) 2,000 mg/kg dosed by oral gavage	Negative Sensitivity demonstrated by positive control	Anonymous 15 (2000), Report no. 535/47, Vol. 3. CA, B.6.4.2/1
Unscheduled DNA synthesis test method B.39 of directive 2000/32/EC Acceptable	KIF-230 Lot: G51-24-176; 92.3% as KIF-230R-L	Rat (Fischer CrJ: F344/Du) Hepatocytes 1,000 and 2,000 mg/kg dosed by oral gavage	Negative Sensitivity demonstrated by positive control	Anonymous 16 (2001e), Report no. 5336, Vol. 3 CA, B.6.4.2/2
Transgenic rodent mutation assay Methodology in line with open literature (Env. Mol. Mutagenesis 28: 363-375, 1996) Acceptable	KIF-230 Lot: G51-08-158; 88.6% as KIF-230R-L	Mouse (Muta™ mouse) hepatocytes 1,000 and 2,000 mg/kg dosed by oral gavage for 5 days	Negative Sensitivity demonstrated by positive control	Anonymous 17 (2000a), Report no. 4911., Vol.3 CA, B.6.4.2/3

No genotoxic activity was detected in somatic mammalian cells. Hence, it is not necessary to conduct a germ cell mutagenicity test.

10.8.1 Short summary and overall relevance of the provided information on germ cell mutagenicity

Several batches of benthiavalicarb-isopropyl were tested for their potency to induce mutagenic lesions in bacteria. Among the first set of batches (pilot batches), including numbers 15-162, 35-184, 36-184, 37-184 and 08-158, two of them proved to be positive, as illustrated by their potential to induce (frame-shift) mutations in *S. typhimurium* strain TA98. In subsequent analytical studies, it was demonstrated that the mutagenic potential in both batches 08-158 and 15-162 was caused by the presence of impurity KIF-230–I–6 (see confidential data and B.6.8.1.2.12). Additionally, batch 08-158 contained the genotoxic relevant impurity KIF-230–I–12 (see DRAR Volume 3 CA B.6.8.1.2.10).
The notifier provided a new five-batch analysis (batches numbers 47-190, 48-190, 49-190, 50-190 and 51-190), which was claimed to correspond with the impurity profile of the commercially manufactured active substance.
The genotoxicity studies on this new set of batches, which were conducted only in bacterial strain TA98, both in the presence and in the absence of S9, demonstrated that the active substance was indeed 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.

Other *in vitro* (UDS, chromosome aberration, mammalian gene mutation) or *in vivo* (UDS, bone marrow micronucleus, a mammalian gene mutation in transgenic mouse) genotoxicity tests with the technical active substance were negative.
A slight increase of polyploid cell incidence was detected in the *in vitro* chromosome-aberration assay, in the absence of exogenous 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 *in vitro* single cell gel assay (Comet-assay on lymphocytes), and the analysis of 8-OH DNA-adducts in liver cells (2-week feeding study in rats and mouse, see B.6.8.2.3), offered additional evidence that benthiavalicarb-isopropyl is not genotoxic both *in vivo* and *in vitro*.

10.8.2 Comparison with the CLP criteria

Classification for genotoxicity/mutagenicity is based on results of the *in vitro* and *in vivo* tests. It was demonstrated that the positive results in 2/16 bacterial reverse mutation (‘Ames’) assays may be attributable to the impurities I-6 and I-12, which were not present in the profile of the commercial manufactured active substance (it was only found in the test substance). The KIF-230 batch (G51-08-158) that was used for the long-term carcinogenicity studies was tested for mutagenicity in the Muta™Mouse assay by gavage at doses up to 2,000 mg/kg bw once daily for 5 days (DRAR Volume 3 CA 6.4.2-03) and found negative. Since this negative gene mutation test has been carried out *in vivo* using the relevant route of administration and in the test species that showed a clear increase in the incidence of liver and thyroid tumours, there is no reason to believe that the presence of the impurities, that tested only positive in *Salmonella thyphimurium* strain TA98 with S9, would have had any influence on the production of the tumours. Benthiavalicarb-isopropyl was not mutagenic in a valid *in vivo* somatic cell mutagenicity/genotoxicity tests in mammals and so according to the guidance on the application of the CLP criteria no classification is warranted.

10.8.3 Conclusion on classification and labelling for germ cell mutagenicity

Benthiavalicarb-isopropyl is not classified as genotoxic/ mutagenic under the CLP regulation.

10.9 Carcinogenicity

The long-term toxicity and carcinogenicity of benthiavalicarb-isopropyl were investigated in mice and rats (Anonymous 18, 2001a and Anonymous 20, 2001b). The results are summarized in Table 22. Seventeen mechanistic studies (Anonymous 22, McMahon, 2018a-e; Anonymous 25 and 26, 2001c-d; Anonymous 27-32, 2001a-b, 2002a-c, 2003; Anonymous 33, 2015) were also submitted in order to investigate the mode of action of the tumours observed in the long-term studies. Results are summarized in Table 23. Both, long term studies and mechanistic studies are then further discussed in section 10.9.1, however for more information; please refer to DRAR Volume 3 CA, section B.6.5 Long-term toxicity and carcinogenicity (for Anonymous 22, McMahon, 2018a-e; Anonymous 25 and 26, 2001c-d; Anonymous 27-32, 2001a-b, 2002a-b, 2003) and section B.6.9.3. Endocrine disrupting properties (for Anonymous 32, 2002c and Anonymous 33, 2015). Unless stated otherwise, all reported effects in Table 22 have been found to be statistically significant.

Table 22: Summary table of animal studies on long-term toxicity and carcinogenicity

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
2-year chronic toxicity / oncogenicity study in rats - OCSPP Guideline No 870.4300 - OECD 453(2008) Acceptable Rats - F344/DuCrj (Fischer, SPF) 80 animals/sex/group	KIF-230, batch G51-08-158, purity: 88.8-89.1% as KIF-230R-L 0; 50; 200; 5,000; 10,000 ppm - M: 0, 2.5; 9.9, 249.6, 518.3 mg/kg bw/day - F: 0, 3.2, 12.5, 318.2, 649.4 mg/kg bw/day - 104 weeks (5-6 weeks at the start of dosing)	NOAEL: M: 9.9 mg/kg bw/day; F: 12.5 mg/kg bw/day LOAEL: M: 250 mg/kg bw/day; F: 318 mg/kg bw/day – In this table only neoplastic lesions are described. Numerous non-neoplastic lesions and effects were observed at the two highest doses tested. Please refer to Table 28 of section 10.12 (STOT RE) for summary. • Increase in the incidence of hepatocellular adenoma (14.0%) observed at 10,000 ppm (518.3 mg/kg bw/d) in males at termination but these tumours were within the historical control range of the test laboratory (0.0-18.0%). • Increase in the incidence of uterus adenocarcinoma at 5,000 (318.2 mg/kg bw/d) and 10,000 ppm (649.4 mg/kg bw/d) (22.0% and 20.0%, respectively) and was above maximal historical control value (8%). The increase after 78 weeks of treatment was not statistically significant.	Anonymous 18, 2001a., DRAR Report no. 3822, Vol.3 CA, B.6.5/1
Historical control data on the findings observed in the former studies: Chronic/Carcinogenic study in rats with KIF-230 Technical	-	Historical control data are submitted from the testing laboratory (BioSafety Research Centre for Foods, Drugs and Pesticides, "An-Pyo Centre") for F344/DuCrj rats that were used in long-term carcinogenicity studies performed in the period 1996 to 2005. The historical control database used covers 15 studies and 750 animals from the control groups. In male rats the spontaneous tumours incidence for hepatocellular adenoma ranged from 0.0 to 18.0% and in females from 0.0 to 8.0%. In female rats the spontaneous incidence of uterine adenocarcinoma ranged from 0.0 to 8.0%.	Anonymous 19 2017, DRAR Historical control Studies No.: 3822, Vol. 3 CA, B.6.5/5
2-years oncogenicity study in mice EPA OCSPP Guideline No 870.4200, OECD Test Guideline 451 Acceptable Mice, B6C3F1 70 animals/sex/group	KIF-230, batch G51-08-158, purity: 88.8-89.1% as KIF-230R-L 0; 20; 100; 2,500; 5,000 ppm - M: 0, 2.7, 13.7, 358, 731 mg/kg bw/day - F: 0, 3.7,	NOAEL: M: 13.7 mg/kg bw/day, F: 18.6 mg/kg bw/day LOAEL: M: 358 / mg/kg bw/day, F: 459 mg/kg bw/day In this table only neoplastic lesion are described. Numerous non neoplastic lesions and effect were observed at the two highest tested doses. Please refer to Table 28 of section 10.12 (STOT RE) for summary. • Increase in the incidence of hepatocellular adenoma at 2,500 and 5,000 ppm (86.0% and 94.0%, respectively), and hepatocellular carcinoma at 2,500 and 5,000 ppm (70.0% and 86.0%, respectively) in males after 104 weeks of treatment. Also, a statistically significant increase in the incidence of	Anonymous 20, 2001b. DRAR Report no. 3823, Vol.3 CA, 6.5/2

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
	18.6, 459, 928 mg/kg bw/day - 104 weeks (5-6 weeks at the start of dosing)	hepatocellular adenoma in males at 5,000 ppm after 78 weeks (10/10) and 52 weeks of treatment (7/10). • Increase in the incidence of hepatocellular adenoma at 2,500 and 5,000 ppm (40.0% and 46.0%, respectively) in females after 104 weeks of treatment. Not statistically significant increase in the incidence of hepatocellular carcinoma at 2,500 and 5,000 ppm (14.0% and 12.0%, respectively) in females. These incidences are still within the historical control range of hepatocellular carcinoma in females of the test laboratory (2.0% to 16.0%). • Increase in the incidence of hepatoblastoma at 2,500 and 5,000 ppm (24.0% and 18.0%, respectively) in males after 104 weeks of treatment. • Increase in the incidence of thyroid follicular cell adenoma at 5,000 ppm (18.0%) and a not statistically significant increase at 2,500 ppm (8.0%) after 104 weeks of treatment.	
Historical control data on the findings observed in the former studies: Oncogenicity study in mice with benthiavalicarb-isopropyl	-	Historical control data are submitted from the testing laboratory (BioSafety Research Centre for Foods, Drugs and Pesticides, "An-Pyo Centre") for B6C3F1 mice that were used in long-term carcinogenicity studies performed in the period 1996 to 2005. The historical control database covers 14 long-term carcinogenicity studies with 705 animals from the control groups. Hepatocellular adenoma: in males from 16.0 to 56.0% and in females from 6.0 to 26.0%. Hepatocellular carcinoma: in males from 10.0 to 40.0% and in females from 2.0 to 16.0%. Follicular cell adenoma: in males from 0.0 to 6.0% and in females from 0.0 to 5.5%. Hepatoblastoma: in males from 0.0 to 2.0% and in females from 0.0 to 0.0%.	Anonymos 21 2018, DRAR Historical control Studies No 3823 (001-209), Vol.3 CA, 6.5/4

One study with hepatocytes from three individual male human donors is available as part of mechanistic studies investigating the relevance to human of the hepatocellular and thyroid follicular cell toxicity found in mice (McMahon, 2018d). Please refer to Table 23 and section 10.9.1 for more information regarding this study.

Table 23: Summary table of other studies relevant for long-term toxicity and carcinogenicity

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
In vivo study: Evaluation of the KIF-230 TGAI hepatocellular and thyroid follicular cell toxicity No guideline Acceptable Mouse C57BL/6N Male, 15/dose	KIF-230R-L, purity: 99.0% 0, 500 and 5,000 ppm 7 days: 80 and 740 mg a.s./kg bw/day 28 days: 77 and 660 mg a.s./kg bw/day 7 and 28-days Positive control:	**Gene expression:** • Cyp2b10 mRNA: 450- and 1,900-fold increase at 500 and 5,000 ppm, respectively. • Cyp3a11 mRNA: 1.2- and 6.6-fold increase at 500 and 5,000 ppm, respectively. • Cyp1a1 and Cyp1a2 mRNA: less than 1.4 increase at 500 and 5,000 ppm. **Enzyme activity:** • PROD: 31- and 65-fold increase at 500 and 5,000 ppm, respectively. • BROD: 28- and 150-fold increase at 500 and 5,000 ppm, respectively.	Anonymous 22 2018a, DRAR Study No. CXR1882, Vol. 3 CA, B.6.5.1

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
	phenobarbital sodium salt (PB) at 500 ppm 7 days: 87 mg PB/kg bw/day 28 days: 79 mg PB/kg bw/day	• EROD: 0.9- and 4.6-fold increase at 500 and 5,000 ppm, respectively. • T4-UDPGT: 0.3- and 1.3-fold increase at 500 and 5,000 ppm, respectively. • BQ: 0.5- and 3.2-fold increase at 500 and 5,000 ppm, respectively. **Plasma hormone levels :** • Total T4: 0.9- and 0.7-fold increase at 5,000 ppm after 7 and 28 days respectively. • Total T3: No change at 500 and 5,000 ppm after 7 and 28 days. • TSH: tendency of increased TSH plasma levels after 7 days. This tendency of increase could not be demonstrated at 28 days despite increased Tshb expression in the pituitary (see further). **Gene expression in the pituitary glands:** • Tshb (thyroid stimulating hormone beta) mRNA: 3.8-fold increase at 5,000 ppm after 28 days of treatment. • Trhr (thyrotropin-releasing hormone receptor) mRNA: 1.3-fold increase at 5,000 ppm after 28 days of treatment. **Cell proliferation:** • Hepatocellular proliferation: 3.6-fold increase at 5,000ppm after 7 days of treatment. • Thyroid follicular cell proliferation: 32 and 51% increase at 500 and 5,000 ppm, respectively, after 28 days of treatment.	
In vitro study KIF-230 mechanism of action in cultured wild-type mouse hepatocytes No guideline Acceptable Male C57BL/6 mouse hepatocytes	KIF-230R-L, purity: 99% 0, 3 µM, 10 µM, 30 µM, and 100 µM, Positive control PB: 100 µM and 1 mM Epidermal growth factor (EGF): 25 ng/ml. cultured with KIF-230R-L and phenobarbital (PB) and Epidermal Growth Factor (EGF) 96 hours + 72 hours in the presence of BrdU for evaluation of cell proliferation	**Gene expression:** • Cyb2b10 mRNA: 44% decrease at 100 µM (cytotoxicity), no increase at other concentration levels. • Cyp3a11 mRNA: 1.5-fold increase at 30 µM, no increase at other concentration levels. • Cyp1a1 mRNA: No increase at any concentration level. • Cyp1a2 mRNA: 1.5-fold increase at 100 µM (cytotoxicity), no increase at other concentration levels. **Enzyme activity:** • BROD: 0.88-, 2.0-, and 1.6-fold increase at 3, 10, and 30 µM, respectively. No significant increase at 100 µM due to cytotoxicity. • PROD: 1.4-, 2.5-, and 2.1-fold increase at 3, 10, and 30 µM, respectively. No significant increase at 100 µM due to cytotoxicity • BQ: About 1-fold increase at 10 and 30 µM. No significant increase at 100 µM due to cytotoxicity EROD: No statistically significant change **Cell proliferation:** Hepatocellular proliferation: 33, 51 and 54% at 10 µM, 30 µM and 100 µM, respectively.	McMahon 2018b, DRAR Study No. 180071-1/45, Vol. 3 CA, B.6.5.1
In vitro study KIF-230 mechanism	KIF-230R-L, purity: 99%	**Gene expression:** • Cyb2b10 mRNA: No increase.	McMahon 2018c,

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
of action in cultured mouse (CAR-/-/PXR-/-) hepatocytes No guideline Acceptable Hepatocyte from CAR/PXR knock-out mice (KO-mice), male	0, 3 µM, 10 µM, 30 µM, and 100 µM Positive control: PB:100 µM and 1 mM EGF: 25 ng/ml. 96 hours + 72 hours in the presence of BrdU for evaluation of cell proliferation	• Cyp3a11 mRNA: No increase. • Cyp1a1 mRNA: 1.1-fold increase at 100 µM. • Cyp1a2 mRNA: marginal increase, 0.4 to 0.6-fold at 3, 10 and 30µM and 2.8-fold increase at 100 µM. **Enzyme activity:** • PROD and BROD: No increase. • BQ: 50% decrease at 30 µM. No change at other concentrations. • EROD: 40% decrease at 10 µM and 1.9-fold increase at 100 µM. **Cell proliferation:** Hepatocellular proliferation: No increase.	DRAR Study No. 180073-1/45, Vol. 3 CA, B.6.5.1
In vitro study KIF-230 mechanism of action in cryopreserved human hepatocytes No guideline Acceptable Human hepatocytes, 3 donors	KIF-230R-L, purity: 99% 0, 3 µM, 10 µM, 30 µM, and 100 µM Positive control: PB: 100 µM and 1 mM EGF:25 ng/ml. 96 hours + 72 hours in the presence of BrdU for evaluation of cell proliferation	**Gene expression:** • CYP2B6 mRNA: 1.0- to 1.2-fold, 1.4- to 2.4-fold, and 1.0- to 5.5-fold increase at 10, 30, and 100 µM, respectively. • CYP3A4 mRNA: 1.4- to 3.6-fold, 3.4- to 5.1-fold, 3.6- to 6.7-fold, and 3.8- to 5.9-fold increase at 3, 10, 30, and 100 µM, respectively. • CYP1A1 mRNA: 0.3- to 0.5-fold, and 0.6- to 0.8-fold increase at 30 and 100 µM. respectively. • CYP1A2 mRNA: 0.6- and 0.7-fold increase in one donor at 30 and 100 µM, respectively. **Cell proliferation**: Hepatocellular proliferation: No increase.	McMahon, 2018d, DRAR Study No. 180073 - 1/68, Vol. 3 CA, B.6.5.1
In vitro study Investigation into the potential for KIF-230 to inhibit Thyroid Peroxidase (TPO) activity *in vitro* No guideline Acceptable Female Yorkshire pig thyroid microsomes	KIF-230R-L, purity: 99% Positive control: 6-propyl-2-thiouracil (PTU) 9 concentrations: from 0.01 to 100 µM	TPO (thyroid peroxidase) inhibition (guaiacol oxidation): No effect up to 100 µM.	McMahon 2018e, DRAR Study No. 180073 - 1/68, Vol. 3 CA, B.6.5.1
A two-stage hepato-carcinogenicity study in rats No guideline Acceptable Rat, F344/DuCrj Fischer- SPF 12 males/groups	KIF-230 TGAI, purity: 88.8-89.1% as KIF-230R-L Initiation study, 2 wks Saline: 0.9% DENA: 200 mg/kg i.p. (single dose) Promotion study, 6 wks KIF-230: 0; 10,000 ppm (from wk 2 to	**Mortality and clinical signs**: None **Food consumption and body weight**: 8% decrease in the group "DENA + a.s." compared to the group "saline + a.s." over the 8 weeks. Body weight gain was 10% lower in the group "DENA + a.s." compared to the group "saline + a.s." over the 8 weeks. **Liver weight and gross pathology**: Enlarged liver and increased liver weight (8%) in the group "DENA + a.s." compared to the group "saline + a.s.".	Anonymous 23, 2000a, DRAR Report n°4905 (001-260)

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
	8 via diet) 610.3mg a.s./kg bw/day PB: 0.05% (from wk 2 to 8 via diet) At wk 3 after i.p. injection, a ⅔ partial hepatectomy (PH) was performed on the animals of all groups, in order to induce mitosis	**Cellular findings:** *Saline + a.s.:* Increased incidence of hepatocellular hypertrophy Marginal and not statistically significantly increased incidence of mitosis.) *DENA + a.s.:* Increased incidence of hepatocellular hypertrophy Increased incidence of mitosis Increased incidence of acidophilic cell foci Increased incidence of clear-, mixed- and vacuolated cell foci	
A two-stage hepato-carcinogenicity initiator study in rat. No guideline Acceptable Rat, F344/DuCrj Fischer- SPF 12 males/groups	KIF-230 TGAI, purity: 88.8-89.1% as KIF-230R-L Initiation study, 2 weeks DENA: 200 mg/kg i.p. KIF-230: 2,000 mg/kg bw (Single dose) Promotion study, 6 wks PB: 0.05% (from wk 2 to 10 via diet) DGA3: 300 mg/kg bw i.p. (single dose at week 3) 2/3 hepatectomized (PH)	**Mortality and clinical signs**: None **Food consumption and body weight**: No effect on food consumption in a.s. group over the 8 weeks. No effect on body weight and body weight gain in a.s. group. **Liver weight and gross pathology**: Absolute and relative liver weight statistically significantly increased when compared to DENA group (9%). **Cellular findings**: Lower incidence for mitosis, clear- and eosinophilic foci in the a.s. group when compared to DENA. Fatty change, hypertrophy and necrosis at comparable level in a.s. group and DENA group.	Anonymous 24, 2000b, DRAR Report n°4906 (001-261)
Induction of drug metabolic enzyme and proliferation of hepatocytes in rats No guideline Acceptable Rat, F344/DuCrj Fischer- SPF 8 rats/sex/dose	KIF-230 TGAI, purity: 88.8-89.1% as KIF-230R-L 0, 10 or 1,000 mg/kg bw/day 7 days by oral gavage	**Mortality and clinical signs**: None **Body weight and body weight gain:** • Body weight gain: 43% increase in males and 100% in females at 1,000 mg/kg bw/day. **Gross pathology and histopathology**: Enlarged liver in males at 1,000 mg/kg bw/day. 11% increase in males and 10% increase in females of relative liver weight at 1,000 mg/kg bw. No histopathological findings. **Enzyme induction:** • Total CYP450: 18% increase in males at 1,000 mg/kg bw/day. • CYP1A1/CYP1A2: 1.6-fold increase in males at 1,000 mg/kg bw/day. • CYP2B1/CYP2B2: 1.6-fold increase in males at 1000 mg/kg bw/day.	Anonymous 25, 2001c, DRAR Report n°4900 (001-259)

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
		• CYP3A2: 1.0-fold increase in males and 1.3-fold increase in females at 1000 mg/kg bw/day. • CYP2E1 and CYP4A1: No relevant change. **Cell proliferation**: Hepatocellular proliferation: 62% and 58% at 10 and 1,000 mg/kg bw/day in males, respectively.	
Induction of drug metabolic enzyme and proliferation of hepatocytes in mice No guideline Acceptable Mouse, Slc:B6C3F1 (C57BL/6 x C3H®(SPF) 8 mice/sex/dose	KIF-230 TGAI, purity: 88.8-89.1% as KIF-230R-L 0, 10 or 1,000 mg/kg bw/day 7 days by oral gavage	**Mortality and clinical signs**: None **Body weight and body weight gain**: No relevant findings. **Gross pathology and histopathology**: Hepatocyte hypertrophy in males and females at 1,000 mg/kg bw/day. 20% and 24% increase in relative liver weight at 1,000 mg/kg bw/day in males and females, respectively. **Enzyme induction:** • Total P-450: 71% increase and 92% increase at 1,000 mg/kg bw/day in males and females, respectively. • Cyp1a1/Cyp1a2: 1.5-fold and 63% increase at 1,000 mg/kg bw/day in males and females, respectively. • Cyp2b1/Cyp2b2: 1.8-fold and 5.5-fold increase at 1,000 mg/kg bw/day in males and females, respectively. • Cyp3a2: 1.0-fold and 1.7-fold increase at 1,000 mg/kg bw/day in mlaes and females, respectively. • Cyp2e1 and Cyp4a1: No relevant change. **Cell proliferation:** Hepatocellular proliferation: No increase.	Anonymous 26, 2001d, DRAR Report n°4899 (001-258)
Oxidative DNA damage in the liver of rats No Guideline Acceptable Rat, F344/DuCrj Fischer- SPF 5 rats/sex/dose	KIF-230 TGAI, purity: 88.8-89.1% as KIF-230R-L 0, 200 and 10,000 ppm M: 17.4 and 797.5 mg a.s./kg bw/d F: 17.1 and 914.5 mg a.s./kg bw/d 2 weeks via diet	Hepatic 8-OHdG remained unaffected after 2 weeks of treatment up to 10,000 ppm.	Anonymous 27, 2001a, DRAR Report n°5433 (001-284)
Oxidative DNA damage in liver of mice No Guideline Acceptable 5 mice/sex/dose Slc:B6C3F1(C57BL/6 x C3H®(SPF)	KIF-230 TGAI, purity: 88.8-89.1% as KIF-230R-L 0, 100 and 5,000 ppm M: 19.4 and 1031.2 mg a.s./kg bw/d F: 26.1 and 1203.7 mg a.s./kg bw/d	Hepatic 8-OHdG remained unaffected after 2 weeks of treatment up to 5,000ppm.	Anonymous 28, 2001b, DRAR Report n°5434 (001-285)

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
	2 weeks via diet		
In vitro study Two-stage transformation assay on Balb/c 3T3 cells Test method B.21 of directive 88/302/EEC Pre-incubated Balb/c 3T3 cells	KIF-230 TGAI, purity: 88.8-89.1% as KIF-230R-L Initiation assay KIF-230: 10.4, 17.3, 28.8, 48.0 and 80.0 µg/ml (72 hours incubation) TPA: 0.1 µg/ml (promotor, 11 days incubation) Promotion assay KIF-230: 0, 3, 6, 9, 12 and 15 µg/ml (11 days incubation) 3-methylcholanthrene: 0.2 µg/ml (initiator, 72 hours incubation)	**Main test:** No focal transformation when the a.s. was tested as an initiator. **Promotor test**: Increase in incidence of foci: 0.8, 0.5, and 0.3 mean number of foci/ dish at 3, 6, and 9 µg/L, respectively, against 0.1 mean number of foci/ dishes in control.	Nakajima, 2000b, DRAR Report n°4909 (001-262)
Effect on thyroid hormones in male rats No guideline Acceptable, supplementary information Rat, F344/DuCjr-Fischer SPF 10 males/dose	KIF-230 TGAI, purity: 88.6-89.1% as KIF-230R-L 0, 200 and 10,000 ppm 13.3 and 661.4 mg a.s./kg bw/d 14 days via the diet Levels of TSH, T3, T4 and T4 UDP-GT were measured.	**Mortality and clinical signs:** No relevant findings. **Body weight and body weight gain**: No relevant findings. **Gross pathology and histopathology:** Enlarged livers. No increase in thyroid size. 24% and 22% increase in absolute and relative liver weight at 10,000 ppm, respectively **Enzyme activity**: •T4 UDP-GT: 16% increase at 10,000 ppm after 14 days of treatment. **Serum hormone levels:** • Total T4: 15% and 18% decrease at 10,000 ppm after 7 and 14 days of treatment, respectively. • TSH and total T3: Unaffected.	Anonymous 29, 2002a, DRAR Report n°5903 (001-323),
Effect on thyroid hormones in male mice No guideline Acceptable, supplementary information	KIF-230 TGAI, purity: 88.6-89.1% as KIF-230R-L 0, 100 and 5,000 ppm 17.0 and 855.0 mg a.s./kg bw/d	**Mortality and clinical signs:** No relevant findings. **Body weight and body weight gain:** No relevant findings. **Gross pathology and histopathology**: Dark and enlarged livers at 5,000 ppm.	Anonymous 30, 2002b, DRAR Report n°5904 (001-324)

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
Mouse, Slc: B6C3F1, C57BL/6xC3H- SPF 6 males/dose/sampling time	14 days via the diet Levels of TSH, T3, T4 and T4 UDP-GT were measured.	No increase in thyroid size. 62% and 53% increase in absolute and relative liver weight after 14 days of treatment, respectively. **Enzyme activity:** • T4 UDP-GT: 65% increase at 5,000 ppm after 14 days of treatment. **Serum hormone levels:** Total T4: 29% and 27% decrease at 5,000 ppm after 7 and 14 days of treatment, respectively. • TSH and T3: Unaffected.	
Effect on serum TSH of male mice No guideline Acceptable, supplementary information Mouse Slc: B6C3F1, C57BL/6xC3H- SPF 12 males /dose/sampling time	KIF-230 TGAI, purity: 88.6-89.1% as KIF-230R-L 0, 100 and 5,000 ppm 15.7 and 809.8 mg a.s./kg bw/d via the diet for 2, 4, 8 and 16 weeks Serum TSH concentration was measured via radio-immunoassay.	**Mortality and clinical signs**: No relevant findings. **Body weight and body weight gain:** 20% decrease in body weight gain over the 16 weeks of treatment. **Serum hormone levels:** TSH: 14% increase at 5,000 ppm after 16 weeks of treatment.	Anonymous 31, 2003, DRAR Report n°6655 (001-386)
Oncogenetic mechanism of uterine cancer No guideline Acceptable Rat, F344/DuCjr-Fischer SPF 10 females/dose	KIF-230 TGAI, purity: 88.6-89.1% as KIF-230R-L 0; 200 and 10,000 ppm 11.9 and 593.9 mg a.s./kg bw/d 56 days feeding study Aromatase activity was measured in liver, uterus and ovaries. Serum concentrations of oestradiol, progesterone and luteinizing hormone (LH) were measured in serum at pre-dosing and at weeks 2, 4, 6 and 8 of dosing.	NOAEL= 11.6 mg/kg bw/d LOAEL= 576.2 mg/kg bw/d (increase in liver size/weight, increase in liver aromatase) **Mortality and clinical signs**: No relevant findings. **Body weight and body weight gain:** No relevant findings. **Gross necropsy and organ weight**: Dark and enlarged livers. 31% and 29% increase in absolute and relative liver weight at 10,000 ppm after 8 weeks of treatment, respectively. No effect on uterus and ovary size and weight. **Enzyme activity:** Aromatase: 36% increase in liver, no increase in ovary and uterus at 10,000 ppm after 8 weeks of treatment. **Serum hormone levels:** No significant change at any dose and sampling time.	Anonymous 32, 2002c, DRAR Report n°5914(001-325)
Uterotrophic bioassay in the ovariectomised	KIF-230 TGAI, purity: 97% as	**Mortality and clinical signs**: No relevant findings.	Anonymous 33, 2015.

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
rat OECD No. 440, US EPA Test Guideline OPPTS 890.1600 Acceptable Rat, Sprague-Dawley Crl:CD®(SD) IGS BR 6 females/dose	KIF-230R-L 0, 10, 100 or 1000 mg/kg bw/d Positive control 17α-ethynylestradiol 14 days	**Body weight and food consumption:** No relevant findings. **Organ weights:** No effect on uterine and vaginal weight. **Histopathology:** No effect on uterus and vaginal tissues. **Cell proliferation**: Uterine tissue: No increase. Vaginal tissue: No increase. There was no evidence of any estrogenic effect.	DRAR Report n° 41401234

10.9.1 Short summary and overall relevance of the provided information on carcinogenicity

In both long-term studies with mice and rats, all neoplastic effects were observed at doses at or above the maximum tolerable dose (MTD). The MTD is the dose inducing slight toxic effects/able to elicit signs of minimal toxicity, such as - but not exclusively - less than 10% decrease of body weight gain. The animal's normal lifespan should not be significantly altered due to effects other than the one studied, in this case, carcinogenicity (OECD 2000, 2012, 2015, ISGC 1986). It is of note that the spacing between the two highest doses and the other lower doses used in the long-term toxicity studies with mice and rats was too large and not the most appropriate. For rats: 50 and 200 ppm for the two low doses and 5,000 and 10,000 ppm for the two high doses. For mice: 20 and 100 ppm for the two low doses and 2,500 and 5,000 ppm for the two high doses

In the two-year toxicity study with mice (Anonymous 20, 2001b), a statistically significant increase in mortality was seen in males at a dose level 5,000 ppm. Body weight gain calculated over the treatment period of 104 weeks was statistically significantly decreased in males by 26% and 30% at 2,500 and 5,000 ppm respectively.

From the histopathological examination of the tissues after 104 weeks of treatment statistically significant changes were observed in bone marrow, stomach, liver, thyroid, ovaries, uterus and adrenals.

In the bone marrow, there was an increase in megacaryocytes at 5,000 ppm in males. Forestomach ulcers, lymphocytic infiltration and squamous cell hyperplasia were observed at 2,500 and 5,000 ppm in males.

Increased incidences in hepatocellular adenoma were observed at 2,500 and 5,000 ppm in males and females, hepatocellular carcinoma and hepatoblastoma at 2,500 and 5,000 ppm in males, hepatocytic hypertrophy at 2,500 and 5,000 ppm in males and females, intermediate fatty change and foci of cellular alteration at 2,500 and 5,000 ppm in males and females, anisonucleosis at 2,500 and 5,000 ppm in males and 5,000 ppm in females, necrosis at 2,500 and 5,000 ppm in males and 5,000 ppm in females, single-cell necrosis at 2,500 and 5,000 ppm in males and 5,000 ppm in females, lymphocytic infiltration, multinucleated hepatocytes, accumulation of macrophages, bile duct proliferation, extramedullary hematopoiesis and fibrosis at 2,500 ppm in males.

Increased incidences of follicular cell hyperplasia were observed at 2,500 and 5,000 ppm in males and females and follicular cell adenoma at 5,000 ppm in males. Ovarian atrophy was reported at 2,500 and 5,000 ppm and uterine angiectasis at 5,000 ppm in females. In the adrenals, cortical hypertrophy was observed at 2,500 and 5,000 ppm in males and females.

Because of the adverse effects seen at 2,500 and 5,000 ppm, the MTD for treatment of 104 weeks with KIF-230 in the mouse should be set at 2,500 ppm.

In the two-year toxicity study with rats (Anonymous 18, 2001a), effects in body weight and body weight gain were noted with statistical significance in both males and females throughout the study but without consistent or long-lasting effects.

From the histopathological examination of the tissues after treatment for 104 weeks statistically significant changes were observed in the pancreas, liver and kidneys.

Atrophy of the exocrine pancreas was observed at 10,000 ppm in males and females.

Increased incidences of hepatocellular adenoma were observed at 10,000 ppm in males, fatty change at 5,000 and 10,000 ppm in females, spongiosis hepatis at 5,000 and 10,000 ppm in males, hepatocytic hypertrophy at 10,000 ppm in males and at 5,000 and 10,000 ppm in females. Glomerulosclerosis of the kidneys was observed at 5,000 and 10,000 ppm in females, calculus at 5,000 and 10,000 ppm in males and females, chronic nephropathy at 5,000 and 10,000 ppm in males, brown pigment deposition at 5,000 and 10,000 ppm in females, dilated tubules at 5,000 ppm and 10,000 ppm in males, hyaline droplets at 5,000 and 10,000 ppm in males and at 10,000 ppm in females, lymphocytic infiltration at 5,000 and 10,000 ppm in females, fibrosis and transitional cell hyperplasia at 10,000 ppm in males. Uterine adenocarcinoma was observed in females at 5,000 and 10,000 ppm. Because of the adverse effects seen at 5,000 and 10,000 ppm, the MTD for treatment of 104 weeks with KIF-230 in the rat should be set at 5,000 ppm.

Hepatocellular adenoma and carcinoma

In the male F344 rat, a statistically significant increased incidence of hepatocellular adenoma (14%) has been observed at the high dose level (10,000 ppm) only after 104 weeks of treatment. Although there is a positive trend, this tumour incidence is still within the historical control range (0.0-18.0%) of male F344 rats of the test laboratory recorded between 1996 and 2005. In the male B6C3F1 mouse, a statistically significant increased incidence was observed of hepatocellular adenoma (86% and 94% at 2,500 ppm and 5,000 ppm, respectively), and hepatocellular carcinoma (70% and 86% at 2,500 and 5,000 ppm, respectively) after 104 weeks of treatment. (Anonymous 18 and 20, 2001a-b). Based on four mechanistic toxicology studies *in vitro* and *in vivo* in the mouse (Anonymous 22, McMahon, 2018a-d), it can be concluded that the hepatocellular tumours produced by KIF-230 in male and female mice are based on a mode of action which operates through CAR activation. The key events, i.e. altered gene expression, hepatocellular proliferation, clonal expansion leading to altered foci and hepatocellular adenomas/ carcinomas, and associative events, i.e. Cyp2b10 and Cyp3a11 enzyme induction, increase in relative liver weight and liver hypertrophy, that is typical for this mode of action in the mouse have been demonstrated to be present. The concordance of dose-response relationships, the temporal association, the strength, the consistency and specificity of association with the tumour response, the biological plausibility, the absence of alternative modes of action and the species specificity of these key events have been proven (Martens 2018a). Therefore, KIF-230 can be considered as a compound acting through a CAR-mediated mode of action, similar to that of phenobarbital. As a consequence, KIF-230 is not expected to increase the risk of liver tumour development in humans.

Hepatoblastoma

In the male B6C3F1 mouse, a statistically significant increase in the incidence of hepatoblastoma was observed at 2,500 and 5,000 ppm (24% and 18%, respectively) with no dose-response relationship at these dose levels (Anonymous 20, 2001b). These incidences are higher than the historical control range of the test laboratory (0.0-2.0% for males and 0.0-0.0% for females) for the period from 1996 to 2005. In terms of the relationship of the hepatoblastomas in the B6C3F1 mouse and those appearing in the human population, there are several fundamental differences between the biology and development of the neoplasms in the two species.

Hepatoblastomas in humans generally arise in children under the age of five and are extremely rare in juveniles and adults and unknown in old age. The tumour shows a strong association with inherited syndromes such as Familial Adenomatous Polyposis and Beckwith–Wiedemann syndrome and other congenital anomalies and a considerably weaker association with occupational exposure to metals, petroleum products, and paints or pigments. It occurs in the absence of other liver pathologies, either neoplastic or non-neoplastic and is thought to derive de novo from mutated hepatoblasts retained in the liver during development.

There is clear evidence that mouse hepatoblastomas can be chemically-induced and that male B6C3F1 mice are considerably more sensitive to their induction than are female B6C3F1 mice. It is also clear that they only arise during the later stages of the lifespan of the mouse and that they are an end-of-life neoplasm even when chemically-induced. There is also considerable support for the hypothesis that murine hepatoblastomas arise out of, and share similar mutational spectra to, hepatocellular carcinomas and adenomas appearing in the same mouse livers and that de novo evolution from hepatoblasts is extremely unlikely.

There are however some morphological and molecular similarities between hepatoblastomas in B6C3F1 mice and those occurring in man. Similar mutations and unusual protein distributions, such as those affecting β-catenin and other proteins related to the Wnt pathway, are seen in hepatoblastoma from both species.

Nonetheless, considering the divergent evolution, biology and age of onset differences between the murine and human hepatoblastoma and the almost unique appearance of chemically-induced hepatoblastomas in the B6C3F1 mouse strain, chemically-induced murine hepatoblastomas should not be considered relevant to human hazard characterisation as it appears to be primarily an artefact of the use of the B6C3F1 mouse. There is no evidence that other mouse strains, except the Crj:BDF1 mouse, can develop these neoplasms under the same conditions (Martens 2018b; Foster and Provan 2018a-b).

Thyroid follicular cell adenoma

In the male mouse, a statistically significantly increased incidence of thyroid follicular cell adenoma of 18% was observed at 5,000 ppm. (Anonymous 20, 2001b). From the data of the standard toxicology and mechanistic toxicology studies *in vitro* and *in vivo* (Anonymous 22, McMahon, 2018a-e), it can be concluded that the thyroid follicular cell tumours produced by KIF-230 in male mice are based on a mode of action which operates through CAR activation. The key events, i.e. CAR activation leading to increased activity of T4 UDP-GT, increased production of TSH by the pituitary, thyroid follicular cell proliferation and thyroid follicular cell adenomas, that are typical for this mode of action in the mouse have been demonstrated to be present. The concordance of dose-response relationships, the temporal association, the strength, the consistency and specificity of association with the tumour response, the biological plausibility, the absence of alternative modes of action (e.g. inhibition of thyroid peroxidase) and the species specificity of these key events have been proven (Martens 2018c). Therefore, KIF-230 can be considered as a compound acting through a CAR-mediated mode of action, similar to that of phenobarbital, which is considered not to be relevant to humans. As a consequence, KIF-230 is not expected to increase the risk of thyroid follicular cell tumour development in humans.

Uterine adenocarcinoma

In the female F344 rat a statistically significant increase in the incidence of uterus adenocarcinoma was seen at 5,000 ppm and 10,000 ppm (22% and 20%, respectively) with no dose-response relationship at these dose levels. (Anonymous 18, 2001a). These incidences are higher than the historical control range of the test laboratory in the period from 1996 to 2005 (0.0-8.0%). Although the available data on KIF-230 in the F344 rat is not sufficient to demonstrate with certainty a mode of action, it has been established that mutagenicity, oxidative stress (Anonymous 27 and 28, 2001a-b), uterine cytotoxicity and inflammation, uterine pre-neoplastic lesions, direct estrogen activity and hormonal changes such as estrogen metabolism and E2/P4-ratio (Anonymous 32 2002c, Anonymous 33 2015), at least in early lifetime rats, can be excluded as possible causes for endometrial cancer. Additionally, as already stated before, these tumours were only observed at 5,000 and 10,000 ppm, dose levels where severe adverse effects were observed in liver, and kidney indicating that the MTD was reached or exceeded.

10.9.2 Comparison with the CLP criteria

Comparison with criteria for Category 1A classification: In accordance with the criteria in the CLP regulation, classification for carcinogenicity Category 1A is reserved for substances known to have carcinogenic potential in humans. In the absence of human data, category 1A is not triggered.

Comparison with criteria for Category 1B classification: In accordance with the criteria in the CLP regulation, classification for carcinogenicity Category 1B is reserved for substances that are presumed to be carcinogenic in humans, and is largely based on data from animal studies where there is sufficient evidence to demonstrate animal carcinogenicity (presumed human carcinogen).

To assess the strength of evidence and to conclude whether benthiavalicarb-isopropyl triggers Cat. 1B, Cat. 2 or no classification, the Guidance on the Application of the CLP Criteria (version 5.0, July 2017) in section 3.6.2.2.2. establishes certain important factors which may be taken into consideration when assessing the overall level of concern. These factors are displayed in Table 24 below.

Table 24: Compilation of factors to be taken into consideration in the hazard assessment

Species and strain	Tumour type and background incidence	Multi-site responses	Progression of lesions to malignancy	Reduced tumour latency	Responses in single or both sexes	Confounding effect by excessive toxicity?	Route of exposure	MoA and relevance to humans
F344/DuCrj Fisher	Hepatocellular adenoma (14% incidence in males) HC: 0-18%	No	No	No After 104 weeks	Males	Yes MTD reached at 5,000 ppm	Oral 5,000 ppm 10,000 ppm	CAR activation, not relevant to humans (in analogy to the findings in the mouse and high incidence (48%) in hepatocellular hypertrophy at 10,000 ppm).
F344/DuCrj Fisher	Uterus adenocarcinoma HC: 0-8%	No	Not applicable	No After 78 weeks (not statistically significant) and 104 weeks	Females	Yes MTD reached at 5,000 ppm	Oral 5,000 ppm 10,000 ppm	Unknown but not: mutagenicity, oxidative stress, cytotoxicity, inflammation, pre-neoplastic lesions, direct estrogen activity and hormonal changes (e.g. estrogen metabolism, E2/P4-ratio)
B6C3F1 mice	Hepatocellular adenoma HC: 16-56% in males, 6-26% in females	Yes	Yes	No After 52 weeks for males After 78 weeks for females	Males and females	Yes MTD reached at 2,500ppm	Oral 2,500 ppm 5,000 ppm	CAR activation, not relevant to humans

Species and strain	Tumour type and background incidence	Multi-site responses	Progression of lesions to malignancy	Reduced tumour latency	Responses in single or both sexes	Confounding effect by excessive toxicity?	Route of exposure	MoA and relevance to humans
B6C3F1 mice	Hepatocellular carcinoma HC: 10-40% in males	Yes	Not applicable	No After 104 weeks	Males	Yes MTD reached at 2,500 ppm	Oral 2,500 ppm 5,000 ppm	CAR activation, not relevant to humans
B6C3F1 mice	Hepatoblastoma HC: not available	Yes	Not applicable	No After 104 weeks	Males	Yes MTD reached at 2,500 ppm	Oral 2,500 ppm 5,000 ppm	Tumour type biologically different from the counterpart in humans and specific to the B6C3F1 mouse where it is associated with hepatocellular tumours of which the MOA is CAR activation. Not relevant to humans.
B6C3F1 mice	Thyroid follicular cell adenomas HC: 0-6% in males	Yes	No	No After 104 weeks	Males	Yes MTD reached at 5,000 ppm	Oral 5000ppm	CAR activation leading to increased biliary excretion of thyroid hormones. Not relevant to humans.

Based on the fact that a mode of action has been established for the hepatocellular tumours and thyroid tumours that are not relevant to man, thus, these tumours should not be taken into account for carcinogenicity classification. No mode of action was established for the production of hepatoblastomas in the B6C3F1 mouse but, since the biological nature of these mouse tumours is very different from the hepatoblastomas in humans, and such type of tumours is considered specific to this strain of mice, these tumors should not be considered as relevant to man. No mode of action has been established for the production of uterine adenocarcinoma, although all possible causes for endometrial cancer in humans have been explored and excluded.

Comparison with criteria for Category 2 classification: In accordance with the criteria in the CLP regulation, classification for carcinogenicity Category 2 is reserved for substances where there is evidence obtained from human and/or animal studies but which is not sufficiently convincing to place the substance in Category 1.

Based on the effects seen in the long term studies, i.e., uterine tumors incidence in the rat, benthiavalicarb-isopropyl is considered as a carcinogen towards rats and should be classified according to Regulation (EC) No 1272/2008 as Carc. 2 (H351): Suspected of causing cancer.

10.9.3 Conclusion on classification and labelling for carcinogenicity

It is proposed that KIF-230 (benthiavalicarb-isopropyl) should be classified as a category 2 carcinogen based on the uterine adenocarcinoma incidence observed in rats at or beyond the MTD.

10.10 Reproductive toxicity

One multigenerational study was conducted with benthiavalicarb-isopropyl in mice. Results are summarised in Table 25.

Two teratogenicity studies were realised with the active substance, one in rats and one in rabbits. The results are summarised in Table 26: of Section 10.10.4.

10.10.1 Adverse effects on sexual function and fertility

Table 25: Summary table of animal studies on adverse effects on sexual function and fertility

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
2-generation reproduction study in CD rats EPA OPPTS 870.3800; OECD 416 Rat, CD (Sprague-Dawley origin) F0: 25 animals/sex/group F1: 22 ± 1 animals/sex/group	**Parent** KIF-230 (TGAI), , purity: 88.8-89.1% as KIF-230R-L 0, 100, 1,000 and 10,000 ppm F0: Males: 0, 6.9, 68.5 and 702.4 mg/kg bw/d Females: 0, 6.8 to 15.5, 67.3 to 167.7 and 708.3 to 1,672.9 mg/kg bw/day F1: Males: 0, 10.0, 99.7 and 1057.8 mg/kg bw/d Females: 0, 6.5 to 14.3, 67.2 to 146.7 and 702.5 to 1456.1 mg/kg bw/d. F0, F1: 10 weeks	**Parent** NOAEL: M: 10 mg/kg bw/d F: 106 mg/kg bw/d LOAEL: M: 99.7 mg/kg bw/d F: 1,114.6 mg/kg bw/d **Body weight:** **F0:** increased body weight in females at 1,000 ppm (6% at day 70) during premating but not at 10,000 ppm. Increased body weight gain during premating at 100 ppm (9%) and 1,000 ppm (14%). Food consumption and efficiency was also slightly increased during part of the premating and lactation periods at 1,000 ppm. **F1:** Decrease body weight in females at 10,000 ppm (9% at 77 days) and of body weight gain (10%) during premating, part of gestation (but not at the end of gestation) at the same dose and during lactation period at all doses but without dose-effect relationship (6, 7 and 6% at 100, 1,000 and 10,000 ppm at the end of lactation period). Mean food efficiency during premating period was slightly decrease in males and females at 10,000 ppm. **Organ weight:** **F0:** relative liver weight was increased in males at 1,000 ppm (6%) and both absolute and relative liver weight were increased in males and females at 10,000 ppm (absolute: 22 & 25%; relative: 24 & 30%). Increased adrenals weight in males at 10,000 ppm (absolute: 12%; relative: 9%). Thymus weight was decreased in females at 10,000 ppm (absolute: 24%; relative: 21%). **F1:** liver weight was increased in males and females at 10,000 ppm (absolute: 23 & 20%; relative: 24 & 36%). **Histopathology:** F0: Hepatocyte hypertrophy was noted in males and females at 10,000 ppm. F1: Hepatocyte hypertrophy was noted in males and females at 10,000 ppm and lymphocyte infiltration in males at 10,000 ppm.	Anonymous 34, 1999, DRAR Report no. 3820,
	Pup development KIF-230 (TGAI) 0, 100, 1,000,	**Pup development** NOAEL: 67.2 mg/kg bw/d LOAEL: 702.5 mg/kg bw/day	

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
	10,000 ppm F1: Males: 0, 10.0, 99.7 and 1057.8 mg/kg bw/d Females: 0, 6.5 to 14.3, 67.2 to 146.7 and 702.5 to 1456.1 mg/kg bw/d.	**Organ weight:** **F1:** Absolute and relative liver weights were increased in males at 10,000 ppm (absolute: 8%; relative: 19%) while only relative liver weight was increased in females at 10,000 ppm (16%). Decrease of thymus weight in males and females at 10,000 ppm (absolute: 18 & 18%; relative:12 & 6%). Spleen weight was decreased in males and females at 10,000 ppm (absolute: 22 & 20%; relative: 13 & 11%). **F2:** Liver weight was increased at 10,000 ppm (absolute: 4 & 8%; relative: 16 & 13%). %). Decrease of thymus weight in males and females at 10,000 ppm (absolute: 16 & 15%; relative:4 & 16%). Spleen weight was decreased in males and females at 10,000 ppm (absolute: 23 & 16%; relative: 13 & 11%).	
	Reproduction KIF-230 (TGAI) 0, 100, 1000, 10000 ppm F0: Males: 0, 6.9, 68.5 and 702.4 mg/kg bw/d Females: 0, 6.8 to 15.5, 67.3 to 167.7 and 708.3 to 1,672.9 mg/kg bw/day F1: Males: 0, 10.0, 99.7 and 1057.8 mg/kg bw/d Females: 0, 6.5 to 14.3, 67.2 to 146.7 and 702.5 to 1456.1 mg/kg bw/d.	**Reproduction** NOAEL: 67.2 mg/kg bw/d LOAEL: / **Reproductive function and performance:** **F0:** Mating, fertility, oestrus cyclicity, or sperm number, activity and morphology were unaffected. **F1:** Number of sperm were reduced at 100 ppm (38%) and 10,000 ppm (22%) but not at 1,000 ppm. Mating, fertility, oestrus cyclicity, or sperm activity and morphology were unaffected in all groups.	

10.10.2 Short summary and overall relevance of the provided information on adverse effects on sexual function and fertility

During a two-generation reproduction toxicity study, benthiavalicarb-isopropyl was continuously administered to groups of 25 Sprague-Dawley rats per sex and per dose in the diet at dose levels of 0, 100, 1,000 and 10,000 ppm (mean achieved dose of 0, 6.9, 68.5 and 702 mg/kg bw/day in the F0 males and 0, 6.8, 67.3 and 708 mg/kg/day in the F0 females during gestation; mean achieved dose of 0, 10.0, 99.7 and 1058 mg/kg/day in the F1 males and 0, 6.5, 67.2 and 703 mg/kg/day in the F1 females during gestation). F0 and F1 parents were dosed for at least 10 weeks before they were mated to produce F1 and F2 litters, respectively. The F1 pups were weaned at 22 days post-natum and selected randomly to establish new groups of 22 ± 1 pups per sex as parents for the F2 generation. No treatment-related adverse effects were observed in parent animals on mortality, clinical signs, body weight, body weight gain, food consumption or gestation index. Changes were observed in the liver of the males in the 1,000 and 10,000 ppm groups and the females

of the 10,000 ppmgroup including slight hypertrophy and increased and/or relative organ weight. The enlarged liver was observed in one F0 and one F1 female at 10,000 ppm. No treatment-related effects were observed on fertility and reproductive performance. The only treatment-related effects observed among the offspring of the F1 and F2 generations included increased absolute and/or relative liver weights and decreased absolute and relative weights of thymus and spleen in the 10,000 ppm group. The NOAEL for the study was 10.0 mg/kg/day in males and 67.2 mg/kg/day in females.

10.10.3 Comparison with the CLP criteria

No human information is available on the effects of benthiavalicarb-isopropyl on the reproductive system. A reliable 2-generation study in rats showed that benthiavalicarb-isopropyl has no treatment-related adverse effects on sexual function and fertility. Consequently, classification is not warranted.

10.10.4 Adverse effects on development

Table 26: Summary table of animal studies on adverse effects on development

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
Teratogenicity study in rats EPA OPPTS 870.3700 (1998) Acceptable Rat, Srj:CD (SD) (Sprague-Dawley origin) 25 pregnant females/dose	- KIF-230 TGAI, , purity: 88.8-89.1% as KIF-230R-L - 0, 10, 100, 1,000 mg a.s./kg bw/day From gestation day 7 to 19 inclusive	**Dam** NOAEL: 10 mg a.s./kg bw/day LOAEL: 100 mg a.s./kg bw/day Organ weight: liver weight was increased at 1,000 mg/kg bw/day (absolute: 12%; relative: 11%). Increased adrenal weight at 100 mg/kg bw/day (absolute: 12%; relative: 8%). Gross pathology: enlarged liver was observed in 2 dams at 100 mg/kg bw/day and in 6 dams at 1,000 mg/kg bw/d. Caesarean section data: number of corpora luteum, implantations, live foetuses, sex ratios, foetal weights or placental weights remained unchanged at all doses. **Foetus** NOAEL:100 mg/kg bw/day LOAEL: 1,000 mg/kg bw/day **Development:** at 1,000 mg/kg bw/day, 32/176 foetuses from 11/24 litters were found with thymic remnant in the neck and 13/175 foetuses from 9/24 were found with splitting of the rib cartilage, both these findings were not statistically significant and within historical control of the testing laboratory. **Caesarean section data:** number of corpora luteum, implantations, live foetuses, sex ratios, foetal weights or placental weights remained unchanged at all doses	Anonymous 35, 2000a. DRAR Report no. 4541, Vol.3 CA, B.6.6.3
Historical control data on the findings observed in former studies: Teratogenicity study in rats	-	Historical control data are submitted from the testing laboratory (BioSafety Research Centre for Foods, Drugs and Pesticides, "An-Pyo Centre") for Srj:CD (SD) (Sprague-Dawley) that were used in the teratogenicity studies. Over 799 fetuses in 112 litters, thymic remnant in the neck ranged from 5.2 to 25.4% with an average of 12.76%. In studies performed during the 1999 year, over 223 fetuses in 30 litters observed, splitting of the rib cartilage ranged from 6.4 to 8.3% with an average of 7.4%.	Anonymous 35, 2000a. DRAR Report no. 4541, Vol.3 CA, B.6.6.3
Embryo-foetal	KIF-230	**Dam**	Anonymous

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
toxicity study in rat OECD 414 Acceptable Rat, CD (Sprague-Dawley origin) 22 pregnant females/dose	TGAI, , purity: 93.6% as KIF-230R-L - 0, 10, 100, 1000 mg a.s./kg bw/day From gestation day 5 to 19 inclusive	NOAEL: 10 mg a.s./kg bw/day LOAEL: 100 mg a.s./kg bw/day Organ weight: relative liver weight was increased at 1,000 mg/kg bw/day (6%). Adrenals weight was increased at 100 mg/kg bw/day (absolute: 14%; relative: 16%) and 1,000 mg/kg bw/d (absolute: 29%; relative: 16%). **Foetus** NOAEL: 100 mg/kg bw/day LOAEL: 1,000 mg/kg/day **Development:** Very slight incidence of ribs/costal cartilage variations at the top dose level in 9/l44 foetuses from 5/21 litters.	36, 2004. DRAR Report KCI 283/042632, Vol. 3 CA, B.6.6.3
Teratogenicity in rabbits EPA 1998, Method B.31 (Annex to Regulation (EC) 440/2008) Rabbit, New Zealand White 22 pregnant females/dose	KIF-230 TGAI, , purity: 87.5-87.9% as KIF-230R-L - 0, 10, 20, 40 mg a.s./kg bw/day From gestation day 6 to 28	**Dam** NOAEL: 20 mg a.s./kg bw/day LOAEL: 40 mg a.s./kg bw/day Body weight: on group mean no effect was observed in body weight, body weight gain and food consumption. However, one animal hardly took food in the latter half of the gestation period and became malnourished. Organ weight: relative liver weight was increased at 40 mg/kg bw/day (11%). Gestation: two animals aborted at 40 mg/kg bw/d, on days 25 and 28. One of the two was the animal with low food consumption. Caesarean section data: numbers of corpora lutea, implantation sites, live or dead foetuses, or resorptions; as well as sex ratio, live foetus weight or placental weight remained unaffected. **Foetus:** NOAEL: 20 mg/kg/day LOAEL: 40 mg/kg/day **Development:** 12/155 nano foetuses from 2/19 litters were recorded at 40 mg/kg bw/day. Incomplete ossification of the hindlimb talus in 14/155 was evidenced with a slightly higher incidence at the top dose level. Nanofetuses was defined as fetuses with less than 60% of the mean fetal weight in the control group by the study author.	Anonymous 37, 2000b. DRAR Report No. 4762, Vol. 3 CA, B.6.6.3

10.10.5 Short summary and overall relevance of the provided information on adverse effects on development

Teratogenicity study with rats (Anonymous 35, 2000a; Anonymous 36, 2004)

In a first developmental toxicity study (Anonymous 35, 2000a) benthiavalicarb-isopropyl was administered by oral gavage to groups of 25 presumed pregnant Sprague-Dawley rats at dose levels of 0, 10, 100 and 1,000 mg a.s./kg bw/day between day 7 and 19 of gestation. All dams were euthanized on day 20 of gestation, their foetuses removed by caesarean section and examined. There were no effects of the treatment on survival, clinical signs, body weights, body weight gains or food consumption. Increased absolute and

relative adrenal weight was noted at 100 and 1,000 mg a.s./kg bw/day. Additionally, an increase of absolute and relative liver weight was observed at 1,000 mg a.s./kg bw/day. There were incidences of an enlarged liver. At 1,000 mg a.s./kg bw/day, there were possible treatment-related visceral and skeletal malformations in the foetuses which were however not statistically significant and within the historical control range of the laboratory performing the test (cf. Table 26). The NOAEL for the study was 10 mg a.s./kg bw/day for maternal toxicity and 100 mg a.s./kg bw/day for developmental toxicity.

In a second developmental toxicity study (Anonymous 36, 2004), benthiavalicarb-isopropyl was administered by oral gavage to groups of 25 presumed pregnant Sprague-Dawley rats at dose levels of 0, 10, 100 and 1,000 mg a.s./kg bw/day between day 5 and 19 of gestation. All dams were euthanized on day 20 of gestation, their foetuses removed by caesarean section and examined. There was no effect of the treatment on survival, clinical signs, body weights, body weight gains or food consumption. Absolute and relative adrenals weights were increased at 100 and 1,000 mg a.s./kg body weight/day. Relative liver weight was also increased at 1,000 mg/kg body weight/day. There was a slightly higher incidence of ribs/costal cartilage variations at the top dose level. Due to this finding, the NOAEL for developmental toxicity is set at 100 mg a.s./kg body weight/day. For maternal toxicity, the NOAEL is also set at 10 mg a.s./kg bw/day based on elevated adrenal weights at 100 mg a.s./kg bw/day and above.

Teratoginicity study with rabbits (Anonymous 37, 2000b)

In a developmental toxicity study, benthiavalicarb-isopropyl was administered via oral gavage to groups of 22 presumed pregnant New Zealand White rabbits at dose levels of 0, 10, 20 and 40 mg/kg/day between day 6 and 28 of gestation. All dams were sacrificed on day 29 of gestation; their foetuses were removed by caesarean section and examined. At 40 mg/kg body weight/day, relative liver weight was increased. Additionally, two dams aborted at 40 mg/kg body weight/day, but the cause could not be elucidated at necropsy. One of the two dams hardly took food in the latter half of the gestation period and became malnourished, which probably resulted in abortion. A higher number of nano-foetuses (defined as fetuses with less than 60% of the mean fetal weight in the control group by the study author) was recorded at 40 mg/kg body weight/day. However, 10 of the 12 nanofetuses in that dose group were present in one litter which indicates that this increase in incidence is due to the condition of one single dam and not related to treatment. An increase in the incidence of delayed talus ossification was also observed at 40 mg a.s./kg bw/day, although the incidence rate was low. This finding was judged as an incidental change and was not considered to be an effect of the administration of the test substance, considering that ossification was fully normal at other parts. The NOAEL of the study was 20 mg a.s./kg bw/day for maternal and developmental toxicity.

10.10.6 Comparison with the CLP criteria

According to the results of submitted studies, no irreversible effects such as structural malformations, foetal embryo/lethality, and significant postnatal functional deficiencies were observed. The effects observed were minor developmental changes and were not statistically significant or dose-dependent and they could be associated with maternal toxicity. Consequently, the classification of benthiavalicarb-isopropyl for developmental adverse effects is not warranted.

10.10.7 Adverse effects on or via lactation

Summary of animal studies on effects on or via lactation

Clinical signs, body weight and food consumption were observed during lactation periods in the two-generation study in rat (Anonymous 34, 1999). No substance-related effect was observed. Please refer to Table 25.

Summary of human data on effects on or via lactation

No data available.

Summary of other studies relevant for effects on or via lactation

No data available.

10.10.8 Short summary and overall relevance of the provided information on effects on or via lactation

Clinical signs, body weight and food consumption were observed during lactation periods in the two-generation study in rat (Anonymous 34, 1999). No substance-related effect was observed. Please refer to Table 25: of Section 10.10.2 for more information.

10.10.9 Comparison with the CLP criteria

Effects on or via lactation are allocated to a separate single category. It is recognised that for many substances there is no information on the potential to cause adverse effects on the offspring via lactation. However, substances which are absorbed by women and have been shown to interfere with lactation, or which may be present (including metabolites) in breast milk in amounts sufficient to cause concern for the health of a breastfed child, shall be classified and labelled to indicate this property hazardous to breastfed babies. This classification can be assigned on the:

(a) human evidence indicating a hazard to babies during the lactation period; and/or

(b) results of one or two generation studies in animals which provide clear evidence of adverse effect in the offspring due to transfer in the milk or adverse effect on the quality of the milk; and/or

(c) absorption, metabolism, distribution and excretion studies that indicate the likelihood that the substance is present in potentially toxic levels in breast milk.

There were no effects observed in the available data to warrant classification of benthiavalicarb-isopropyl, for effects on or via lactation according to the above mentionned criteria.

10.10.10 Conclusion on classification and labelling for reproductive toxicity

Benthiavalicarb-isopropyl is not classified for reproductive toxicity.

10.11 Specific target organ toxicity-single exposure

Table 27: Summary table of animal studies on STOT SE

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, route of exposure, dose levels, duration of exposure	Results	Reference
Acute oral toxicity in rats Compliant with test method B.1 of directive 92/69/EEC, 5 rats/sex/dose, Slc: Wistar, SPF	KIF-230, purity: 88.8% as KIF-230R-L 5,000 mg a.s./kg bw, gavage, one time	No relevant effect	Anonymous 3, 1998b, DRAR Exp. No 4062, Vol. 3 CA, B.6.2.1

Acute oral toxicity in mice Compliant with test method B.1 of directive 92/69/EEC; OECD 401 Deviations: Nb of rats + no positive control + no HC 5 mice/sex/dose, Slc: ICR (SPF)	KIF-230, purity: 88.8% as KIF-230R-L 5,000 mg a.s./kg bw, gavage, one time	No relevant effect	Anonymous 4, 1998a, DRAR report No.: 4061, Vol. 3 CA, B.6.2.1
Acute dermal toxicity study in rats Guidelines No. 82-1, EPA OCSPP & No 870.1200, OECD 402 5 rats/sex, Slc:Wistar (SPF)	KIF-230, purity: 88.8% as KIF-230R-L 2,000 mg a.s./kg bw dose rate: 0.0145-0199 g/cm²	Body weight: 1/5 females showed a slightly impaired body weight gain on day 8.	Anonymous 5, 1998c, DRAR report No.: 4063, Vol. 3 CA, B.6.2.2
Acute inhalation study of KIF-230 (TGAI) in albino rats Guideline No. 81-3, EPA OCSPP & No 870.1300; OECD 403 5 rats/sex, Charles River Crl:CD® IGS BR	KIF-230, purity: 89.1% as KIF-230R-L Dust aerosol Nominal: 19 mg/L Mean actual exposure concentration: 4.6±0.6 mg a.s./L MMAD = 3.9± 2.82 µm	Mortality: 1/5 males and 1/5 females died on day 1 Clinical signs: Decedents: laboured respiration, rales, gasping, hypoactivity, clear lacrimation. Survivors: laboured respiration, rales, dried red material around nose/eyes/forelimbs, dried yellow material on urogenital area, decreased/mucoid faeces Body weight: bw loss (<10%) on d0-3 or reduced bw gain on d0-7 Necropsy: Decedents: dark red adrenals (males and females, dark patchy lungs (females) and gas-filled stomach (males) Survivors: no relevant findings, except dark red/mottled lungs in one female.	Anonymous 6, 2000a, DRAR report No.: WIL-156011, Vol. 3, B.6.2.3.
Acute oral neurotoxicity study in rats OPPTS Guideline 870.6200 OECD 424 5 rats/sex/dose, Sprague Dawley Crl:CD® (SD)IGS BR	KIF-230, purity: 92.3% as KIF-230R-L 2,000 mg a.s./kg bw, single oral gavage	NOAEL= 2,000 mg/kg bw/day LOAEL > 2,000 mg/kg bw/day Functional Observational Battery (FOB): A statistically significant decreased motor activity was observed in the treated males when compared to control animals on day 1 of treatment. The value (1184) was below the historical data range (2047-3902) of the perfomring laboratory (Springborn laboratories, Inc.), but the study control value (2047) was also at the lower end. The decrease of motor activity in males at day 1 was not observed at later stages and was concluded as not toxicologically relevant.. There was no statisticaly significant difference for females between control and treated group.	Anonymous 38 and 39, 2001 and 2002 - amended final report-, DRAR Report no. 3404.12, Vol. 3CA, B.6.7

10.11.1 Short summary and overall relevance of the provided information on specific target organ toxicity – single exposure

In all of the acute studies but one, no relevant findings or effects were observed. In the acute inhalation study in albino rats, dark red adrenals were observed in the two deceased animals as the relevant effects but not considered as a "severe" effect. The two other effects observed in the lungs and stomach are most probably due to the inhalation process than to direct substance toxicity. For more details on the studies protocols and results, please refer to DRAR Volume 3 CA, B.6.2.1, B.6.2.2, B.6.2.3 and B.6.7

10.11.2 Comparison with the CLP criteria

In order to be classified as a substance targeting a specific organ after a single exposure, the significant non-lethal toxic effect should be observable on a specific organ at a certain level. Depending on the level of toxic effect, a substance can either be in category 1 (guidance value for classification: ≤ 300 mg a.s./kg bw) or category 2 (guidance value for classification: ≤ 2000 mg a.s./kg bw and >300 mg/kg bw). According to the available acute toxicity studies, benthiavalicarb-isopropyl does not have a significant toxic effect on any specific organ and should therefore not be classified for this hazard class.

No signs were observed to be regarded for classification for STOT SE 3 according to CLP Regulation (respiratory tract irritation and narcotic effects)

10.11.3 Conclusion on classification and labelling for STOT SE

Benthiavalicarb-isopropyl is not classified for specific target organ toxicity after single exposure.

10.12 Specific target organ toxicity-repeated exposure

The sub-chronic toxicity of benthiavalicarb-isopropyl was investigated in mice, rats and dogs. The results are summarized in Table 28 and below in section 10.12.1. For more detailed information on the sub-chronic toxicity studies, please refer to DRAR Volume 3 CA, B.6: Toxicology and Metabolism, section B.6.3: Short-term toxicity.

The long-term toxicity of benthiavalicarb-isopropyl was investigated in mice and rats. The results are summarised in Table 28 and below in section 10.12.1 and Table 22 of section 10.9 of the present document. For more detailed information on the long-term toxicity studies, please refer to DRAR Volume 3 CA, B.6: Toxicology and Metabolism, section B.6.5 Long-term toxicity and carcinogenicity.

In this section, three 90-days studies on rats, mice and dogs and a one-year study in dogs are presented. Also, a cross-reference is made to the short-term dermal toxicity with repeated exposure in rats and to two long-term toxicity and carcinogenicity studies with rats and mice. One range-finding study in a dog is also presented as supportive information. Unless stated otherwise, all reported effects in Table 28 are statistically significant.

Table 28: Summary table of animal studies on STOT RE

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, route of exposure, dose levels, duration of exposure	Results	Reference
28-days oral toxicity in dog - range-finding study	KIF-230, purity: 87.7% as KIF-230R-L Oral,	NOAEL: 300 mg a.s./kg bw/day LOAEL: 1,000 mg a.s./kg bw/day **Organ weight**: increased absolute and relative liver weight without dose-dependency in males at 100 mg/kg bw/day (absolute: 18%; relative: 17%) and 1,000 mg/kg bw/day (absolute: 16%;	Anonymous 40, 1998, DRAR Report no. 3390, Vol. 3 CA.

Not compliant with test method B.7. of Directive 96/54/EEC additional information Beagle dogs 2 dogs/sex/dose	0, 100, 300, 1000 mg a.s./kg bw/day 28 days	relative: 11%) and in females at 300 mg/kg bw/day (absolute: 14%; relative: 13%) and 1,000 mg/kg bw/day (absolute: 36%; relative: 45%). No statistical analysis was performed because of the low number of animals per group. **Gross pathology and histopathology**: liver enlargement in both males and females with panlobular hepatocyte hypertrophy at 1,000 mg/kg bw/day. One female with unilateral kidney atrophy (fibrous scars) in the same dose group.	B.6.3.1/1
28-days dermal toxicity in rat FIFRA Guideline No. 81-3, EPA OCSPP Guideline No 870.1300; OECD 403 Acceptable Rat, Crl:CD®(SD)IGS BR 10 rats/sex/dose	KIF-230, purity: 87.9% as KIF-230R-L Dermal 0, 100, 300, 1000 mg a.s./kg bw/day 28 days	NOAEL: 300 mg a.s./kg bw/day LOAEL: 1,000 mg a.s./kg bw/day **Clinical chemistry**: increase in albumin levels (4%) in males at and increase in globulin levels (10%) in females but with unaffected A/G-ratios at 1,000 mg/kg bw/day. Increase in inorganic phosphorus (23%) in females at 1,000 mg/kg bw/day. Increase in sorbitol dehydrogenase activities (38%) in males at 1,000 mg/kg bw/day. Dose-related decreases of AST (between 17 and 22%) and ALT (between 19 and 21%) activities in males without significant pathological meaning. **Organ weight**: dose related decrease in thymus weight (22, 18 and 13% at 100, 300 and 1,000 mg/kg bw/day respectively). **Gross pathology and histopathology**: marginal liver cell necrosis was observed at 1,000 mg/kg bw/day in males. Marginal increased incidence of squamous hyperplasia in females at 1,000 mg/kg bw/day (9/10 vs 5/10 in control).	Anonymous41, 2000b, DRAR Report No.: WIL-156012, Vol. 3 CA 6.3.3
sub-chronic oral neurotoxicity, OECD 424 Rat, Sprague-Dawley Crl:CD® (SD)IGS BR	KIF-230, purity: 92.6% as KIF-230R-L Oral, 0, 200, 2000, 20,000 ppm M: 0, 17.7, 174.1, 1853.7 mg a.s./kg bw/day F: 0, 19.3, 185.7, 1845.8 mg a.s./kg bw/day	NOAEL: M: 174.1 mg a.s./kg/day F: 1845.8mg a.s./kg/day LOAEL: M: 1853.7 mg a.s./kg/day F: >1845.8 mg/kg/day **Body weight:** Decreased body weight gain at the top dose of 20,000 ppm in males (18% at the end of the study). Food efficiency was also decreased (20%). **FOB:** slight decrease of motor activity (low level) detected in males at 20,000 ppm (25%).	Anonymous 42, 2002, Report no. KCI 207/022387, Vol. 3 CA, B.6.7
90-days oral toxicity in mice Test method B.26 of directive	KIF-230, purity: 87.7% as KIF-230R-L Oral, 0; 50; 200;	NOAEL: M: 33.0 mg a.s./kg bw/day F: 45.2 mg a.s./kg bw/day LOAEL: M: 1293 mg a.s./kg bw/day F: 1620 mg/kg bw/day **Body weight**: decrease in body weight gain in males by 32% at	Anonymous 43, 1998a, DRAR Report no. 3385, Vol. 3 CA 6.3.2/1

2001/59/EC Acceptable Mice, B6C3F1, SPF 10 mice/sex/dose	7,000 and 20,000 ppm M: 0, 8.4, 33.0, 1293, 4031 mg a.s./kg bw/day F: 0, 11.3, 45.2, 1620, 4946 mg a.s./kg bw/day 90 days	7,000 ppm and by 43% at 20,000 ppm over the entire treatment period of 13 weeks. **Haematology**: slight macrocytic anaemia in males and females at 7,000 and 20,000 ppm without increase in reticulocyte ratio. Thrombocytosis in the males at 7,000 ppm and above. **Organ weight**: increase in liver weight at 7,000 ppm (absolute: 63 and 51 %; relative: 87 and 59% in males and females, respectively) and at 20,000 ppm (absolute: 97 and 96%; relative: 136 and 109% in males and females, respectively). Decrease in ovary weight at 20,000 ppm (absolute: 29%; relative: 18%). Decrease in absolute kidney weight at 7,000 ppm in males (10%) and above in both males and females (22 & 8%). **Gross necropsy**: patches on stomach and liver, as well as black and enlarged livers and brown thyroid glands at 7,000 and 20,000 ppm in males and females. **Histopathology**: anisonucleosis in liver at dose levels from 7,000 ppm and above in males, fatty change at 20,000 ppm in males, hepatocytic hypertrophy from 7,000 ppm and above in males and females, multinucleated giant cells at 20,000 ppm in males, necrosis from 7,000 ppm and above in males and females; bile duct proliferation at 20,000 ppm in males and females. In the ovaries, there was a decrease in corpora lutea at a dose level of 20,000 ppm in females. **Enzymatic induction** in the hepatocytes in both sexes at 7,000 ppm and above, increased and/or dilated rough endoplasmic reticulum.	
90-days oral toxicity in rats EPA OCSPP Guideline No 870.3100 Acceptable Rat, F344/DuCrj (Fisher) 10 rats/sex/dose	KIF-230, purity: 87.7% as KIF-230R-L Oral 0; 50; 200; 5,000 and 20,000 ppm M: 0, 3.5, 14.1, 353, 1444 mg a.s./kg/day F: 0, 3.9, 15.3, 379, 1552 mg a.s./kg/day 90 days	NOAEL: M: 14.1 mg a.s./kg bw/day F: 15.3 mg a.s./kg bw/day LOAEL: M: 353 mg a.s./kg bw/day F: 379 mg a.s./kg bw/day **Haematology**: decrease of red blood cell parameters at 5,000 ppm and above in both sexes. **Blood chemistry**: increase of calcium level in males at 5,000 ppm (3%) and at 20,000 ppm in males (4%) and females (6%). Increase of total cholesterol at 5,000 ppm in males (16%) and females (44%) and at 20,000 ppm (30 in males and 94% in females). Increase of free cholesterol in females at 5,000 ppm (36%) and at 20,000 ppm in males (27%) and females (100%). Increase of phospholipids in females at 5,000 ppm (21%) and at 20,000 ppm in both males (14%) and females (51%). Total protein increased in males at 5,000 ppm (4%) and in both sexes at 20,000 ppm (7% in males and 10% in females). Increase of α2-globulin in both sexes at 5,000 ppm (10%) and 20,000 ppm (17% in males and 25% in females), of α1-globulin at 20,000 ppm in both sexes (7% in males and 18% in females) and of β-globulin at top dose in females (10%). The A/G ratio was decreased in females at 5,000 and 20,000 ppm (~10%). Increased γ-GT activity at 5,000 ppm in males (167%) and females (307%) and at 20,000 ppm also in both sexes (416% in males and 573% in females). **Organ weight**: liver weight was increased at 5,000 ppm (absolute: 19 and 29%; relative: 21 and 23%, in males and females, respectively) and 20,000 ppm (absolute: 27 and 50%; relative: 34 & 45%, in males and females, respectively). Absolute adrenals weight was increased at 5,000 ppm in males (14%) and females	Anonymous 44, 1998b, DRAR Report no. 3386, Vol. 3 CA 6.3.2/2

<table>
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<td></td>
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<td>(12%) and at 20,000 ppm (19% in males and 14% in females) as well as relative adrenal weight in males at 20,000 ppm (21%). Absolute kidney weight was increased in females at 5,000 ppm (8%) and 20,000 ppm (7%).

Gross necropsy: livers were blackish and enlarged in the top-dose animals in both sexes.

Histopathology: Hepatocytic hypertrophy was observed at 20,000 ppm in males and females. Mineralisation was observed at 20,000 ppm in females.</td>
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<tr>
<td>90-days oral toxicity in dogs

EPA OCSPP Guideline No 870.3150; corresponding to the OECD 409

Acceptable

Beagle dogs

4 dogs/dose/sex</td>
<td>KIF-230, purity: 88.8% as KIF-230R-L

Oral

0, 40, 200, 1,000 mg a.s./kg bw/day

90 days</td>
<td>NOAEL: 40 mg a.s./kg bw/day

LOAEL: 200 mg a.s./kg bw/day

Haematology: slight but significant decreases of red blood cell parameters at 1,000 mg a.s./kg bw/din both sexes and in females at 200 ppm for haematocrit and haemoglobin. Platelets were higher in both sexes at top dose.
<table>
<tr><th>Dose (mg/kg bw/d)</th><th></th><th>0</th><th></th><th>40</th><th></th><th>200</th><th></th><th>1000</th><th></th></tr>
<tr><td></td><td>week</td><td>M</td><td>F</td><td>M</td><td>F</td><td>M</td><td>F</td><td>M</td><td>F</td></tr>
<tr><td>HCT</td><td>6</td><td>44.6</td><td>49.9</td><td>41.0</td><td>43.8</td><td>44.3</td><td>39.9*</td><td>38.8</td><td>40.8*</td></tr>
<tr><td></td><td>13</td><td>44.8</td><td>51.1</td><td>41.2</td><td>43.8*</td><td>43.2</td><td>42.3**</td><td>34.3*</td><td>38.2**</td></tr>
<tr><td>Hb</td><td>6</td><td>14.4</td><td>16.0</td><td>13.1</td><td>14.2</td><td>14.1</td><td>12.9*</td><td>11.9</td><td>12.5*</td></tr>
<tr><td></td><td>13</td><td>14.3</td><td>16.6</td><td>13.4</td><td>14.2*</td><td>14.0</td><td>13.5**</td><td>10.8*</td><td>11.7**</td></tr>
<tr><td>RBC</td><td>6</td><td>6.46</td><td>7.16</td><td>6.05</td><td>6.52</td><td>6.55</td><td>5.93</td><td>5.30</td><td>5.51*</td></tr>
<tr><td></td><td>13</td><td>6.52</td><td>7.39</td><td>6.08</td><td>6.51</td><td>6.33</td><td>6.24</td><td>4.85**</td><td>5.18**</td></tr>
<tr><td>MCV</td><td>6</td><td>69</td><td>70</td><td>68</td><td>67</td><td>67</td><td>67</td><td>73*</td><td>74*</td></tr>
<tr><td></td><td>13</td><td>68.7</td><td>69.1</td><td>67.6</td><td>67.5</td><td>67.9</td><td>67.9</td><td>70.9</td><td>74.2*</td></tr>
<tr><td>MCHC</td><td>6</td><td>32</td><td>32</td><td>32</td><td>32</td><td>31</td><td>32</td><td>30.6**</td><td>30.7**</td></tr>
<tr><td></td><td>13</td><td>31.9</td><td>32.5</td><td>32.4</td><td>32.4</td><td>32.5</td><td>31.9</td><td>31.5</td><td>30.6**</td></tr>
<tr><td>PLT</td><td>6</td><td>325</td><td>312</td><td>381</td><td>352</td><td>322</td><td>350</td><td>569*</td><td>567**</td></tr>
<tr><td></td><td>13</td><td>312</td><td>302</td><td>390</td><td>383</td><td>380</td><td>404</td><td>613**</td><td>637**</td></tr>
<tr><td>Ret.</td><td>6</td><td>6</td><td>7</td><td>5</td><td>9</td><td>4</td><td>7</td><td>5</td><td>5</td></tr>
<tr><td></td><td>13</td><td>11</td><td>6</td><td>5</td><td>10</td><td>7</td><td>8</td><td>25*</td><td>25↑**</td></tr>
</table>
Statistically significant modification, Dunnett's t-test *p<0.05, **p<0.01, n=4

Blood chemistry: at top dose, increased of total bilirubin in males (125%) and females (120%), of ALP (107% in males and 171% in females) and gamma-GTP activities (93% in males and 72% in females) and decrease of total protein (10%) at 200 ppm in females and at 1,000 ppm in males (18%) and females (10%). Calcium was also decrease in both sexes at top dose (7%) The A/G ratio was decreased in females at 200 mg a.s./kg bw/d (27%) and at 1,000 mg a.s./kg bw/d (26%). Albumin level decreased in females at 40, 200 and 1,000 mg a.s./kg bw/d (respectively: 10, 21 and 24%) and in males at 1,000 mg a.S./kg bw/day (26%).

Organ weight: increased relative liver weight in females at 200 mg/kg (43%) and increased liver weight at 1,000 mg a.s./kg bw/d (absolute: 60 and 58%; relative: 75 and 70%, in males and females, respectively).

Gross necropsy and histopathology: large liver at the top dose. Deposition of pigment and hepatocytic hypertrophy were observed at 1,000 mg a.s./kg bw in males and females</td>
<td>Anonymous 45, 1999,

DRAR Report no. 3812, Vol. 3 CA 6.3.2/3</td>
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<td>Dog 1 year

US EPA FIFRA Pesticide Assessment Guidelines, Section 83-1, 1984 (OCSPP</td>
<td>KIF-230, purity: 87.5 – 87.9% as KIF-230R-L

Oral

0, 4, 40, 400 mg a.s./kg</td>
<td>NOAEL: 40 mg a.s./kg bw/day

LOAEL: 400 mg a.s./kg bw/day

Blood chemistry: while some parameters were statistically significantly different from the control during the test, at termination, no significant difference was noted for any of these parameters at all doses.

Organ weight: increased absolute liver weight at 400 mg a.s./kg</td>
<td>Anonymous 46 2001,

DRAR Report no. 4551, CA 6.3.2/6</td>
</tr>
</table>

<table>
<tr>
<td>870.4100), OECD Test Guideline 452

Beagle dogs

4 dogs/dose/sex</td>
<td>bw/day

1 year</td>
<td>bw/day (21% and 28% in males and females, respectively) and increased relative liver weight in female at top dose (18%).

Gross pathology and histopathology: no significant effect. Only increase in the incidence of pituitary cysts (slight) was noted in females without a clear dose-response relationship.</td>
<td></td>
</tr>
<tr>
<td>2-years chronic toxicity / oncogenicity study in rats

EPA OCSPP Guideline No 870.4300; OECD Test Guideline 453 adopted in 08 September 2008.

Rat, F344/DuCrj (Fischer, SPF)

80 animals/sex/group</td>
<td>KIF-230, purity: 88.8-89.1% as KIF-230R-L

0, 50, 200, 5,000, 10,000 ppm

M: 0, 2.5; 9.9, 249.6, 518.3 mg a.s./kg bw/day

F: 0, 3.2, 12.5, 318.2, 649.4 mg a.s./kg bw/day

2 years</td>
<td>NOAEL: M: 9.9 mg/kg bw/day; F: 12.5 mg/kg bw/day

LOAEL: M: 250 mg/kg bw/day; F: 318 mg/kg bw/day

Body weight: slight but statistically significant decrease of body weight in females at 10,000 ppm (4%) and of body weight gain over the whole period of the study (7%).

Haematology: slight but statistically significant decrease in blood parameters, except platelet which increased (between 6 to 19%) at the two top doses in both sexes.
<table>
<tr><th colspan="2">Dose (ppm)</th><th colspan="2">200</th><th colspan="2">5000</th><th colspan="2">10000</th></tr>
<tr><th></th><th></th><th>♂</th><th>♀</th><th>♂</th><th>♀</th><th>♂</th><th>♀</th></tr>
<tr><td>Hct</td><td>week 26</td><td></td><td></td><td>-</td><td>↓4%**</td><td>-</td><td>↓4%**</td></tr>
<tr><td></td><td>week 78</td><td></td><td></td><td></td><td></td><td>-</td><td>↓4%**</td></tr>
<tr><td></td><td>week 104</td><td></td><td></td><td>-</td><td>↓2%**</td><td>↓6%*</td><td>↓4%**</td></tr>
<tr><td>Hb</td><td>week 26</td><td></td><td></td><td>-</td><td>↓4%**</td><td>↓3%*</td><td>↓4%**</td></tr>
<tr><td></td><td>week 52</td><td></td><td></td><td>-</td><td>↓3%*</td><td>-</td><td>↓4%**</td></tr>
<tr><td></td><td>week 78</td><td></td><td></td><td></td><td></td><td></td><td>↓5%**</td></tr>
<tr><td></td><td>week 104</td><td></td><td></td><td>-</td><td>↓2%*</td><td>↓6%*</td><td>↓4%**</td></tr>
<tr><td>RBC</td><td>week 26</td><td></td><td></td><td>-</td><td>↓2%*</td><td>-</td><td>↓2%*</td></tr>
<tr><td>MCV</td><td>week 52</td><td>-</td><td>↓2%*</td><td>-</td><td>↓4%**</td><td>-</td><td>↓5%**</td></tr>
<tr><td></td><td>week 78</td><td></td><td></td><td>-</td><td>↓4%**</td><td>-</td><td>↓5%**</td></tr>
<tr><td></td><td>week 104</td><td></td><td></td><td>↓4%**</td><td>↓2%**</td><td>↓4%**</td><td>↓3%**</td></tr>
<tr><td>MCH</td><td>week 26</td><td></td><td></td><td>-</td><td>↓2%*</td><td>-</td><td>↓2%**</td></tr>
<tr><td></td><td>week 52</td><td></td><td></td><td>-</td><td>↓5%**</td><td>-</td><td>↓7%**</td></tr>
<tr><td></td><td>week 78</td><td></td><td></td><td>-</td><td>↓5%**</td><td>-</td><td>↓6%**</td></tr>
<tr><td></td><td>week 104</td><td></td><td></td><td>↓5%**</td><td>↓2%**</td><td>↓5%**</td><td>↓3%**</td></tr>
<tr><td>Plt</td><td>week 26</td><td></td><td></td><td>↑20%**</td><td>↑18%*</td><td>↑17%**</td><td>↑10%**</td></tr>
<tr><td></td><td>week 52</td><td></td><td></td><td>↑5%*</td><td>↑8%*</td><td>↑7%*</td><td>-</td></tr>
<tr><td></td><td>week 78</td><td></td><td></td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td></td><td>week 104</td><td></td><td></td><td>↑14%**</td><td>↑6%**</td><td>↑19%**</td><td>↑8%**</td></tr>
<tr><td>reticulocyte</td><td>week 26</td><td></td><td></td><td>↑78%*</td><td>-</td><td>↑56**</td><td>-</td></tr>
<tr><td>WBC</td><td>week 104</td><td></td><td></td><td></td><td></td><td>↑33%**</td><td>↑11%**</td></tr>
</table>
Only statistically significant increase/decrease compared to control are presented. No stat. significant difference in 50ppm group compared to control.
* Significantly different from the control: p <0.05; ** Significantly different from the control: p <0.01

Blood chemistry: at termination, there was an increase of total cholesterol in females at 5,000 ppm (67%) and 10,000 ppm (72%), of free cholesterol at 5,000 ppm (70%) and 10,000 ppm (83%), of phospholipid at 5,000 ppm (43%) and 10,000 ppm (47%), of total protein at 5,000 ppm (6%) and 10,000 ppm (8%), of γ-GT activity at 5,000 ppm (167%) and 10,000 ppm (217%). There was a decrease of total bilirubin at the same doses (50%), of AST (44% at 5,000 ppm and 39% at 10,000 ppm) and of ALT (41% at 5,000 ppm and 40% at 10,000 ppm). In males, only γ-GT activity was increased at termination at 5,000 ppm (31%) and 10,000ppm (164%).

Organ weight: liver weight was increased at all sacrifice times in the 5,000 ppm group (at termination, absolute: 22 and 16%; relative: 21 and 19%; in males and females, respectively) and in the 10,000 ppm group also in both sexes (at termination, absolute: 29 and 24%; relative: 33 and 29%; in males and females,</td>
<td>Anonymous 18, 2001a.,

DRAR Report no. 3822, Vol.3 CA, B.6.5/1</td>
</tr>
</table>

		respectively). Kidney weight was also increased at 5,000 ppm (at termination, absolute: 10 & 5%; relative: 7 & 8%; in males and females, respectively) and 10,000 ppm (at termination, absolute: 16 & 9%; relative: 18 & 15%; in males and females, respectively). In addition, adrenals weight was also increased in males at 5,000 ppm (absolute and relative: 20% at termination) while only relative adrenals weight was increased in female at 200 and 5,000 ppm (7 and 14%, respectively); at top dose, absolute and relative adrenals weights were increased (absolute: 16 and 10%; relative: 20 and 14%, in males and females, respectively). Spleen weight was reduced in females at 5,000 ppm and 10,000 ppm (~20-25%) while relative heart weight (6%) and relative brain weight (4%) were increased at 10,000 ppm in females. **Gross pathology**: liver enlargement was observed in both sexes in the interim sacrifices (wk 26: 10 males and 9 females at 10,000 ppm, wk 52: 5 males at 5,000 ppm, 9 males and 9 females at 10,000ppm, wk 78: 5 males and 4 females at 5,000ppm, 8 males and 9 females at 10,000ppm, no enlarged liver in control at any time point) but not at termination in the 5,000 and 10,000 ppm groups. However, white and brown patches were observed in males at 5,000 ppm (brown: 36 at 5,000ppm against 12 in control; white: 16 at 5,000 ppm against 5 in control) and 10,000ppm (brown: 34 at 10,000ppm; white: 24 at 10,000ppm) and red patches in females were observed in the 5,000 (13 at 5,000ppm against 5 in control) and 10,000 ppm (19 at 10,000ppm)at termination. Granular kidney surface was evidenced in both sexes at 10,000 ppm at termination (9 in males and 3 in females at 10,000 ppm against 0 in control). Black patches were also observed in the Harderian gland either in males (8 at 10,000ppm against 0 in control) or in females (28 at 5,000 ppm and 41 at 10,000 ppm against 0 in control). Tail nodules were detected at the two top doses in males as well as. Non neoplastic histopathology: hepatocytic hypertrophy was recorded at 10,000 ppm in males (24/44 against 1/38 in control) and at 5,000 (7/46 against 1/40 in control) and 10,000 ppm (25/45) in females. Fatty degeneration was observed infemales (39/42 at 5,000 ppm, 36/45 at 10,000 ppm against 21/40 in control) as well as focal changes, in association with spongiosis hepatis in males (39/46 at 5,000 ppm, 42/44 at 10,000 ppm against 19/38 in control). Glomerulosclerosis of the kidneys was observed in females at 5,000 (20/42 against 6/40 in control) and 10,000 ppm (26/45), calculus at 5,000 and 10,000 ppm in males (10/46 at 5,000 ppm, 12/44 at 10,000 ppm against 0/38 in control) and females (17/42 at 5,000 ppm, 25/45 at 10,000 ppm against 8/40 in control), chronic nephropathy in males at 5,000 (23/46 against 6/38 in control) and 10,000 ppm (26/44) , brown pigment deposition in females at 5,000 (19/42 agains 2/40 in control) and 10,000 ppm (19/45) , dilated tubules in males at 5,000 ppm (26/46 against 10/38 in control) and 10,000 ppm (33/44) , hyaline droplets in males at 5,000 (37/46 against 17/38 in control) and 10,000 ppm (32/44) and at 10,000 ppm in females (19/45 against 9/40 in control), lymphocytic infiltration in females at 5,000 and 10,000 ppm (18/42 at 5,000 ppm, 23/45 at 10,000 ppm against 9/40 in control) , fibrosis in males (5 at 10,000 ppm against 0 in control) and transitional cell hyperplasia in males (10 at 10,000 ppm against 1 in control) at 10,000 ppm. Atrophy of the exocrine pancreas was also observed at 10,000 ppm in males (22/44 against 11/38 in control) and females (15/45 against 3/40 in control) as well as Harderian gland dilatation in males at 10,000 ppm (13/44	

<table>
<tr><td></td><td></td><td>against 2/38 in control) and females at 5,000 ppm (40/42 against 0/40 in control) and 10,000 ppm (45/45).

N.B.: for neoplastic histopathology please refer to section 10.9 of the present document..</td><td></td></tr>
<tr><td>2-years oncogenicity study in mice

EPA OCSPP Guideline No 870.4200, OECD Test Guideline 451
Mice, B6C3F1
70 animals/sex/group</td><td>KIF-230, purity: 88.8-89.1% as KIF-230R-L

0, 20, 100, 2,500, 5,000 ppm

M: 0, 2.7, 13.7, 358, 731 mg/kg/day
F: 0, 3.7, 18.6, 459, 928 mg/kg/day
2 years</td><td>NOAEL: M: 13.7 mg/kg bw/day; F: 18.6 mg/kg bw/day
LOAEL: M: 358 / mg/kg bw/day; F: 459 mg/kg bw/day
Body weight: body weight gain calculated over the treatment period of 104 weeks was statistically significantly decreased in males by 26% and 30% at 2,500 and 5,000 ppm respectively.
Haematology: An increase of platelet counts in both males and females was observed at 2500 ppm (wk 52: increase of 13% in males; wk 104: 19% increase in males and 17% in females) and 5,000ppm (wk 52: increase of 25% in males and 16% in females; wk 72: increase of 13% in males and 27% in females; wk 104: 20% in males and females). At termination, slight increases in males of: haematocrit at 5,000 ppm (9%) and haemoglobin content at 2,500 ppm (5%) and 5,000 ppm (8%) and of RBC count at 5,000 ppm (12%). There was a slight decreases in the males of MCV at 2,500 ppm (2%) and at 5,000 ppm (3%) and of MCH at 5,000 ppm (3%). However, those changes in males were not coherent with those from earlier sampling times. Statistical significant decreases (males) or increases (females) of WBC at all doses on week 104 were not considered meaningful in the absence of both a proper dose-related response and confirmative modifications in the differential leukocyte counts.
<table>
<tr><td>Week 104</td><td colspan="2">WBC</td></tr>
<tr><td>Dose (ppm)</td><td>M</td><td>F</td></tr>
<tr><td>20</td><td>- 31%**</td><td>+131%*</td></tr>
<tr><td>100</td><td>- 45%**</td><td>- 23%*</td></tr>
<tr><td>2500</td><td>- 35%**</td><td>- 8%</td></tr>
<tr><td>5000</td><td>- 25%*</td><td>+ 54**</td></tr>
<tr><td colspan="3">Significant difference from control group; *: $p \leq 0.05$ **: $p \leq 0.01$</td></tr>
</table>
Organ weight: liver weights were highly significantly increased at all sacrifice times at 2,500 ppm (at termination, absolute: 113 and 67%; relative: 140 and 61%; in males and females, respectively) and 5,000 ppm (at termination, absolute: 174 and 77%; relative: 218 and 73%; in males and females, respectively). Absolute and relative adrenals weights were increased in males at termination at 2,500 ppm (absolute: 20%; relative: 31%) and 5,000ppm (absolute: 20%; relative: 38%). In females, absolute and relative ovary weights were decreased at termination (absolute: 11%; relative: 33%).
Gross pathology: similar effects were observed in 2,500 and 5,000 ppm. Enlarged livers (wk 52: 5 and 10 in males and 8 and 10 in females at 2,500 and 5,000 ppm, respectively against 0 in control; wk: 78: 6 and 8 in males and 9 and 10 in females at 2,500 and 5,000 ppm, respectively against 0 in control; wk 104: 13 and 27 in females at 2,500 and 5,000 ppm against 7 in control) and brown zones (wk 104: in males, 26 at 2,500 ppm and 20 at 5,000ppm against 6 in control and in females 25 at 2,500 ppm and</td><td>Anonymous 20, 2001b.
DRAR Report no. 3823, Vol.3 CA, 6.5/2</td></tr>
</table>

		24 at 5,000 ppm against 0 in control) were observed in males and females. White zones on the stomach of males were statistically increased at 2,500 ppm (31 against 19 in control) but not at 5,000 ppm (18). Liver nodules were observed in males and females (wk 78: 10 at 5,000 ppm in males against 4 in control; week 104: in males, 34 at 2,500 ppm and 28 at 5,000 ppm against 22 in control) and in females, 27 at 2,500 ppm and 30 at 5,000 ppm against 7 in control) and white zones were observed at top dose in males at week 78 (8 at 5,000 ppm agains 3 in control) but not at termination while in females white zones were observed to be statistically signicifantly increase at 5,000ppm only at termination (23 against 6 in control). In addition, at the top dose: enlarged lymph node (12 at 5,000 ppm against 4 in control) and Harderian gland nodules (6 at 5,000 ppm against 0 in control) were observed in females and red zones on the liver and thymus atrophy (not confirmed by histopathology) were observed in males. **Non neoplastic histopathology**: The following statistically significant observations were made: hepatocytic hypertrophy in males (30/35 at 2,500 ppm and 20/28 at 5,000 ppm agains 0/41 in control) and females (40/41 at 2,500 ppm and 42/43 at 5,000 ppm aganst 0/41 in control), intermediate fatty change in males (30/35 at 2,500 and 20/28 at 5,000 ppm against 0/41 in control) and females (37/41 at 2,500 ppm and 33/43 at 5,000 ppm against 0/41 in control), foci of cellular alteration in males (35/35 at 2,500 and 28/28 at 5,000 ppm against 20/41 in control) and in females (36/41 at 2,500 ppm and 34/43 at 5,000 ppm against 9/41 in control), anisonucleosis in males (11/35 at 2,500 and 13/28 at 5,000 ppm against 1/41 in control) and in females (12/43 at 5,000 ppm against 2/41 in control), necrosis in males (15/35 at 2,500 and 22/28 at 5,000 ppm against 2/41 in control) and at 5,000 ppm in females (10/43 against 1/41 in control), single cell necrosis in males (33/35 at 2,500 and 28/28 at 5,000 ppm against 1/41 in control) and at 5,000 ppm in females (6/43 against 0/41 in control), lymphocytic infiltration and in females (22/35 at 2,500 ppm and 17/28 at 5,000 ppm against 12/41 in control), multinucleated hepatocytes in males (8/35 at 2,500 ppm and 4/28 at 5,000 ppm against 0/41 in control), accumulation of macrophages in males (28/35 at 2,500 ppm and 28/28 at 5,000 ppm against 4/41 in control), bile duct proliferation in males (5/35 at 2,500 ppm and 12/28 at 5,000 ppm agains 0/41 in control), extramedullary hematopoiesis in males (8/35 at 2,500 and 14/28 at 5,000 ppm against 2/41 in control) and fibrosis at 2,500 ppm in males (5/35 against 0/41). Forestomach ulcers (13/35 at 2,500 ppm and 16/28 at 5,000 ppm against 6/41 in control), lymphocytic infiltration (22/35 at 2,500 ppm and 17/28 at 5,000 ppm against 12/41 in control) and squamous cell hyperplasia (29/35 at 2,500 ppm and 19/28 at 5,000 ppm against 18/41 in control) were observed at 2,500 and 5,000 ppm in the males Ovaries atrophy was evidenced at 2,500 (22/41 against 4/41in control) and 5,000 ppm (30/43). Uterus angiectatis was observed at 5,000 ppm (6/43 against 0/41 in control). Thyroid follicular cell hyperplasia was observed in males (12/35 at 2,500 ppm and 27/28 at 5,000 ppm against 2/41 in control) and females (20/41 at 2,500 and 26/43 at 5,000 ppm against 5/41 in control), as well as dilated follicles in males (12/35 at 2,500 ppm and 17/28 at 5,000 ppm against 2/41 in control) at the same doses	

		and in females only at 5,000 ppm (10/43 against 1/41 in control). Increase in megacaryocytes in bone marrow at 5,000 ppm in the males (8/28 against 3/41 in control). Adrenal hypertrophy in males (13/35 at 2,500 and 20/28 at 5,000 ppm against 0/41 in control)and females (38/41 at 2,500 ppm and 42/43 at 5,000 ppm against 1/41 in control). N.B.: for neoplastic histopathology please refer to section 10.9 of the present document.	

10.12.1 Short summary and overall relevance of the provided information on specific target organ toxicity – repeated exposure

28-days dermal toxicity study in rats (Anonymous 41 2000b)

Groups of 10 rats/sex/dose (Crl:CD®(SD)IGS BR) were dermally exposed to benthiavalicarb-isopropyl at dose level of 0; 10; 300 and 1,000 mg/kg body weight for 28 days. The only toxicological findings considered possibly substance-related in the rat following dermal exposure for 28 days at the top dose of 1,000 mg/kg/day were increased sorbitol dehydrogenase activity and marginal liver cell necrosis. Squamous hyperplasia was observed as a local histopathological finding. However, the reported histopathological findings and the toxicological significance of the clinical chemistry findings remain unclear. The NOAEL was set at 300 mg/kg/day.

Subchronic toxicity study in rat (Anonymous 42, 2002)

In a sub-chronic neurotoxicity study benthiavalicarb-isopropyl was administered to groups of 10 CD rats per sex and dose in the diet at doses of 0, 200, 2,000 and 20,000 ppm (mean achieved dose of 0, 17.7, 174.1 and 1,853.7 mg/kg/day in males and 0, 19.3, 185.7 and 1,845.8 mg/kg/day in females) for 4 weeks. No treatment-related effects on mortality, clinical signs, food consumption, brain weight, gross necropsy or neuropathological parameters were observed. Although a slight effect on motor activity was noted in males at 20,000 ppm, it was not considered to be a sign of neurotoxicity. In the males of the 20,000 ppm group, decreased body weight gains were observed during the first week and up until the end of the study. **The NOAEL for this study is 174.1 mg/kg/day in males and 185.7 mg/kg/day in females.**

90 days toxicity study in the mouse (Anonymous 43, 1998a)

Benthiavalicarb-isopropyl was administered to groups of 10 mice (B6C3F1) per sex and dose at the concentrations of 0, 50, 200, 7,000 and 20,000 ppm in the diet (mean achieved dose of 0, 8.4, 33.0, 1,293 and 4,031 mg/kg body weight/day in males and 0, 11.3, 45.2, 1,620 and 4,946 mg/kg/day in females).

Body weight gain calculated over the entire treatment period of 13 weeks was statistically significantly decreased in males by 32% and 43% at 7,000 and 20,000 ppm respectively. Food consumption increased sporadically in males and females at 20,000 ppm and increased slightly in the males of the 7,000 mg/kg group. Food efficiency decreased in the males of the 7,000 and 20,000 ppm groups and the females of the 20,000 ppmgroup. Some effects on haematology were observed at 7,000 and 20,000 ppm in males and females. Increased absolute and relative liver weights were noted in both sexes at 7,000 and 20,000 ppm, as well as decreased absolute kidney weight at 7,000 ppm for males and both sexes at 20,000 ppm. Decrease of ovary weight at 20,000 ppm was also recorded.

Gross lesions observed included enlarged liver and black-coloured liver. Histopathological effects noted in the liver of males and females included necrosis, bile duct hyperplasia and hepatocellular hypertrophy; fatty

change, anisonucleosis and formation of multinucleated giant cells were observed in males only. Additional findings included brown-coloured thyroid in all males of the 20,000 ppm group. In the ovaries, there was a decrease in corpora lutea at a dose level of 20,000 ppm in females.

No treatment-related effects were observed in males and females of the 50 and 200 ppm groups. The NOAEL of 33.0 mg/kg/day for males and 45.2 mg/kg/day for females is based on decreased body weight, body weight gain and food efficiency in males; increased absolute and relative liver weight, enlarged liver, black-coloured liver and histopathological liver effects (necrosis, hypertrophy, bile duct proliferation) at 7,000 ppm.

Based on these observations, MTD for treatment of mice for 13 weeks should be set at 7,000 ppm.

90 days toxicity study in the rat (Anonymous 44, 1998b)

Benthiavalicarb-isopropyl was administered to groups of 10 rats (F344/DuCrj, Fisher) per sex and dose, at concentrations of 0, 50, 200, 5,000 and 20,000 ppm in the diet (mean achieved dose of 0, 3.5, 14.1, 353 and 1,444 in males and 0, 3.9, 15.3, 379 and 1,552 mg/kg/day in females) for 13 weeks.

Absolute and relative liver weights increased in males and females at 5,000 and 20,000 ppm, as well as absolute adrenals weight and absolute the kidney weight in females. Black and enlarged livers were observed in both sexes at 20,000 ppm. Mineralisation in kidney at 20,000 ppm in females was also recorded. Hepatocyte hypertrophy was observed in both sexes at 5,000 and 20,000 ppm. Related to liver toxicity a dose-dependent increase of clinical chemistry parameters was observed, including total cholesterol and GGT in both sexes at 5,000 and 20,000 ppm, free cholesterol and phospholipids in the males of the 20,000 ppm group and the females of the 5,000 and 20,000 ppm groups and total protein in the males of the 5,000 and 20,000 ppm groups and females of the 20,000 ppm group.

The NOAEL is 14.1 mg/kg/day for males and 15.3 mg/kg/day for females based on hepatocyte hypertrophy in both sexes and increases in absolute and relative liver weights and total cholesterol and GGT in both sexes, increases of free cholesterol and phospholipids in the females and total protein in the males at a dose level of 5,000 ppm.

At the high dose of 20,000 ppm, only relatively mild effects were observed in the liver and the kidney. Therefore, the MTD for a treatment of 13 weeks in the rat can be considered to be greater than 20,000 ppm

Sub-chronic and chronic toxicity in the dog (Anonymous 40 1998, Anonymous 45 1999, Anonymous 46 2001)

In a dog range-finding test, doses of 0, 100, 300 and 1,000 mg/kg/day were given in gelatine capsules daily, 7 days per week, for 4 weeks to groups of two dogs per sex and dose. The only findings possibly related to the treatment were increased liver weight and hepatocyte hypertrophy in males and females at 1,000 mg/kg/day. The NOAEL was 300 mg/kg/day.

In a 13-weeks toxicity study, benthiavalicarb-isopropyl was administered daily in gelatine capsules to groups of 4 beagle dogs per sex and dose at dose levels of 0, 40, 200 and 1,000 mg/kg/day for 13 weeks. At 200 mg/kg/day, a decrease in haematocrit, haemoglobin and serum albumin was observed in females. At 1,000 mg/kg/day, the concentrations of serum total bilirubin, gamma-glutamyl transferase and alkaline phosphatase increased, while the concentration of serum albumin decreased in both sexes. Additionally, increased relative liver weights and diffuse lobular hepatocyte hypertrophy were observed in the males and females at 200 mg/kg/day. Decreased absolute and relative thymus weights were also noted at 200 mg/kg/day. Hemosiderin pigment deposits were observed in the spleen of males at 200 mg/kg/day, but the lesion was less severe than at 1000 mg/kg/day. The NOAEL for the study was 40 mg/kg/day for both males and females.

Based on these observations, the MTD for a treatment of 13 weeks in the dog can be considered to be greater than 1,000 mg/kg bw.

In a 52-weeks toxicity study, benthiavalicarb-isopropyl was administered in gelatine capsules to groups of 4 beagle dogs per sex and dose at dose levels of 0, 4, 40 and 400 mg/kg/day for 52 weeks. Decreased serum albumin levels and albumin/globulin levels were observed in females at 400 mg/kg/day. Levels of serum-free fatty acids were higher than in the controls in males at 400 mg/kg/day. Increased absolute and relative liver weights were observed in both sexes at 400 mg/kg/day. From the histopathological examination, only increase in the incidence of pituitary cysts (slight) was noted in females without a clear dose-response relationship. The NOAEL for the study was 40 mg/kg/day for both males and females.

Based on the observations, the MTD for a treatment of 52 weeks in the dog can be considered to be greater than 400 mg/kg bw.

Long-term toxicity study in rats and mice

Please refer to section 10.9 of the present document for the summaries about long term toxicity studies in rats and mice.

Table 29: Extrapolation of equivalent effective dose for toxicity studies of greater or lesser duration than 90 days [if adequate, otherwise please delete]

Study reference	Effective dose (mg/kg/d)	Length of exposure	Extrapolated effective dose when extrapolated to 90-day exposure	Classification supported by the study
Rat, dermal Anonymous 41, 2000b, Report no. WIL-156012, Vol.3 CA 6.3.3/1	> 1,000 mg/kg bw/day	28 days	>3,000 mg/kg bw/d	No (Cat 1: effects above 30 mg/kg bw/day. Cat 2: Effect above 300 mg/kg bw/day)
Rat, oral – neurotoxicity Anonymous 42, 2002, Report no. KCI 207/022387, Vol. 3 CA, B.6.7	1853.8 mg/kg/day	28 days	>5,561 mg/kg bw/d	No (Cat 1: effects above 30 mg/kg bw/day. Cat 2: Effect above 300 mg/kg bw/day)
Mouse, oral Anonymous 43, 1998a, Report no. 3385, Vol. 3 CA 6.3.2/1	Interpolation: between 33 mg/kg bw/day and 1293 mg/kg bw/day: 630 mg/kg bw/day. Additionally, in the two years LOAEL is at 358 mg/kg bw/day	90 days	Not applicable	No (Cat 1: effects above 10 mg/kg bw/day. Cat 2: effect expected above 100 mg/kg bw/day)
Rat, oral Anonymous 44, 1998b, Report no. 3386, Vol. 3 CA 6.3.2/2	Interpolation: between 14.1 mg/kg bw/day and 353 mg/kg bw/day: 169.5 mg/kg bw/day. Additionally, in the two years LOAEL is at 249.6 mg/kg bw/day	90 days	Not applicable	No (Cat 1: effects above 10 mg/kg bw/day. Cat 2: effect expected above 100 mg/kg bw/day)
Dog, oral Anonymous 45, 1999,	1,000 mg/kg bw/day	90 days	Not applicable	No GV for dog

Study reference	Effective dose (mg/kg/d)	Length of exposure	Extrapolated effective dose when extrapolated to 90-day exposure	Classification supported by the study
Report no. 3812, Vol. 3 CA 6.3.2/3				
Dog, oral Anonymous 46, 2001, Report no. 4551, CA 6.3.2/6	> 400 mg/kg bw/day	1 year	Not applicable	No GV for dog
Rat, oral Anonymous 18, 2001a., Report no. 3822, Vol.3 CA, B.6.5/1	249.6 mg/kg bw/day	2 years	31.2 mg/kg bw/d	No (Cat 1: effects above 2.5 mg/kg bw/day. Cat 2: effect expected above 25 mg/kg bw/day)
Mouse, oral Anonymous 20, 2001b. Report no. 3823, Vol.3 CA, 6.5/2	358 mg/kg bw/day	2 years	44.75 mg/kg bw/d	No (Cat 1: effects above 2.5 mg/kg bw/day. Cat 2: effect expected above 25 mg/kg bw/day)

10.12.2 Comparison with the CLP criteria

In order to be classified as a substance targeting a specific organ after repeated exposure, the significant non-lethal toxic effect should be observable on a specific organ (either category 1 or 2 depending on the level of toxic effect and test) at a certain level. In the case of benthiavalicarb-isopropyl, while severe effects have been observed mainly in the liver, they were only seen at doses sufficiently above the guidance values given by CLP Regulation.

10.12.3 Conclusion on classification and labelling for STOT RE

Benthiavalicarb-isopropyl is not classified for specific target organ toxicity after repeated exposure.

10.13 Aspiration hazard

Hazard class is not applicable.

11 EVALUATION OF ENVIRONMENTAL HAZARDS

Benthiavalicarb-isopropyl is a fungicide active substance considered under Directive 91/414/EEC (subsequently Regulation 1107/2009) for representative use as a treatment of aerial parts downward spraying. Available studies on environmental fate and ecotoxicology have been considered and summarised in the original Draft Renewal Assessment Report, 2018 (DRAR, Volume 3, Annex B8 and Annex B9) and the renewal of approval dossier.

The key information pertinent to determining the environmental hazard classification for Benthiavalicarb-isopropyl is presented below.

11.1 Rapid degradability of organic substances

Table 30: Summary of relevant information on rapid degradability

Method	Results	Remarks	Reference
EC Method C4, OECD TG 301B	CO2 evolution was found to be 2-3% of the theoretical maximum value after 28 days incubation of KIF-230R-L. KIF-230 is not readily biodegradable	Ready biodegradability Inoculum: sewage plant effluent The study is considered acceptable	DRAR Vol. 3CA, B.8.2.2.1/01 Bealing, 1998,
OECD Test Guideline No. 309	In the 11 µg/l dose, degradation was rapid after a lag phase of 36 days with a T1/2 of 13.9 days. DT50 and 90 on the whole study period were respectively 49.9 and 82.2 days (HS). Major metabolites were: KIF-230-M8, KIF-230-M5 and KIF-230-M4. In the 108 µg/l dose, degradation was slow after a lag phase of 37 days with a T1/2 of 65.7days. DT50 and 90 on the whole study period were respectively 103 and 256 days (HS). Major metabolite was: KIF-230-M5.	Water aerobic Pelagic pond system (pH 8.28) under aerobic conditions for 62 days at 23°C The study is considered acceptable	DRAR Vol. 3CA, B.8.2.2.2/01 Feldmann S, 2015 Doc. no.: 150011
BBA Guidelines for PPP (Part IV, 5-1) (Dec. 1990); SETAC Pesticides, Section 8.2 (March 1995) and EPA, subdivision N, Section 162-4 (Oct. 1982).	In the Millstream Pond water, benthiavalicarb-isopropyl degraded rapidly reaching 10.2% after 30 days and 5.1% at last sampling time (100 days). DT50 dissipation from water, sediment and system were respectively: 3.69 days (DFOP), 25.7 days (SFO) and 18.2 days (SFO). DegT50 water and sediment were respectively: 17.2 and 21.7 days (SFO). Major metabolites were: KIF-230-M3, KIF-230-M5 and KIF-230-M4. In the Emperor Lake water, benthiavalicarb-isopropyl also degraded rapidly reaching 3.3% after 59 days. DT50 dissipation from water, sediment and system were respectively: 7.71 days, 16.5 days (SFO) and 15.1 days (SFO). DegT50 water and sediment were respectively: 25.7 and 9.63 days (SFO). Major metabolites were: KIF-230-M3, KIF-230-M5 and KIF-230-M4.	Water/sediment Pond water/sediment system (pH 8.2) and a lake water/sediment system (pH 6.8) under aerobic conditions for 100 days at 20°C The study is considered acceptable	DRAR Vol. 3CA, B.8.2.2.3/01 Goodyear A, 2000
SETAC Pesticides, Section 1.1 (March 1995); EPA, Subdivision N, Section 162-1 (Oct. 1982); MAFF: 59 NohSan No. 4200 (Jan. 1985). OECD No 307 (April 2002)	KIF-230 decreased rapidly from 93 - 96% of the applied amount at day 0 to 1 - 2% of the applied radioactivity at 120 days. DT50 in sandy loam, silt loam and clay loam were respectively 16.4, 11.1 and 10.6 days (SFO). The corresponding DT90 were 57.6, 36.7 and 35.4 days.	Soil aerobic Sandy loam (pH 5.1, 1.3% organic carbon), silt loam (pH 6.7, 3.0% OC), clay loam (pH 7.7, 4.0% OC) for 120 days in the dark at 20°C and 45% of the maximum water holding capacity. The study is considered acceptable	DRAR Vol. 3CA, B.8.1.1.2/01 Purser D and Goodyear A, 2001.
EPA Subdivision N, Section 161-3 (Oct. 1982); SETAC Pesticides, Section 2 (March	The half-lives in the dark control and light exposed samples were 12.4 and 20.4 days, respectively. These results indicate soil photolysis is not a significant route of degradation for the active substance. Major metabolites: KIF-230-M-1 and KIF-230-M-	Photolysis Silt loam soil (pH 7.4, 5.0% organic carbon) for 30 days at 25°C and 29 - 38% moisture. 12 hours irradiation,	DRAR Vol. 3CA, B.8.1.1.3/01 Lewis CJ, 2001

Method	Results	Remarks	Reference
1995)	5	xenon lamp with no wavelength < 290 nm. The study is considered acceptable	
OECD Test Guideline No. 307	KIF-230-M-5 decreased steadily in the sandy loam and silt loam soils with 22 and 25% of the initial applied concentrations after 120 days. In the loam soil the concentration declined rapidly to 6% of the applied amount over a period of 37 days. DT50 in silt loam, loamy sand and loam were respectively 42.8, 26.2 and 2.13 days (DFOP). The corresponding DT90 were 1480, 178 and 24.2 days.	KIF-230-M-5 in soil Silt loam (pH 5.71, 1.42% organic carbon), loamy sand (pH 4.92, 0.92% OC), loam (pH 7.20, 1.98% OC) for up to 120 days in the dark at 20°C and with default field capacity The study is considered acceptable	DRAR Vol. 3CA, B.8.1.1.4.1.2/01 Voelkel W, 2015
SETAC Pesticides, Section 1.1 (March 1995). Complies with OECD No 307 (April 2002)	KIF-230-M-4 decreased from 79 - 86% to 13 - 40% of the applied amount in the first 6 hours. Then it decreased very slowly to 4 - 7% of the applied amount at study termination. DT50 in silt loam, sandy loam and clay loam were respectively 0.06, 0.08 and 0.18 days (DFOP). The corresponding DT90 were 33.7, 82.0 and 64.3 days.	KIF-230-M-4 in soil Silt loam (pH 6.7, 4.5% organic carbon), sandy loam (pH 5.5, 1.3% OC), clay loam (pH 8.0, 2.7% OC) for 90 days in the dark at 20°C and 45% water holding capacity The study is considered acceptable	DRAR Vol. 3CA, B.8.1.1.4.1.2/02 Wright DR, 2001
SETAC Pesticides, Section 1.1 (March 1995). Complies with OECD No 307 (April 2002)	KIF-230-M-3 decreased from 88 - 90% of applied amount at day 0 to 4.9 - 8.4% at the end of the study period DT50 in silt loam was 7.34 (SFO), in sandy loam it was 6.93 (SFO) and in clay loam it was 2.34 days for trigger (FOMC) and 5.55 days for modelling (SFO). The corresponding DT90 were 24.4, 23.0, 19.8 for triggering and 18.4 days for modelling	KIF-230-M-3 in soil Silt loam (pH 6.7, 4.5% organic carbon), sandy loam (pH 5.5, 1.4% OC), clay loam (pH 8.0, 2.7% OC) for 30 days in the dark at 20°C and 45% water holding capacity The study is considered acceptable	DRAR Vol. 3CA, B.8.1.1.4.1.2/03 Wright DR, 2001
SETAC Pesticides, Section 1.1 (March 1995). Complies with OECD No 307 (April 2002)	KIF-230-M-1 decreased quickly in silt loam from 80% of applied amount at day 0 to 5.6% at 30 days. Decrease was a slower in clay loam, passing from 81% applied amount at day 0 to 9.2% at 60 days. In sandy loam, decrease was very slow, passing from 89% of applied amount at day 0 to 19% at 120 days. DT50 in silt loam, sandy loam and clay loam were respectively 3.83, 12.7 and 7.42 days (DFOP). The corresponding DT90 were 15.5, 249 and 67.6 days.	KIF-230-M-1 in soil Silt loam (pH 6.7, 4.5% organic carbon), sandy loam (pH 5.5, 1.4% OC), clay loam (pH 8.0, 2.7% OC) for 30 days in the dark at 20°C and 45% water holding capacity The study is considered acceptable	DRAR Vol. 3CA, B.8.1.1.4.1.2/04 Wright DR, 2001
OECD Test Guideline No. 307	KIF-230-M-8 decreased rapidly to 2 - 4% of the applied amount after 14 days in the silt loam and loam soils. In the loamy sand soil, the concentration decreased more slowly and represented 8% of the applied amount after 28 days. DT50 in silt loam, loamy sand and loam were respectively 2.87, 7.44 and 1.85 days (SFO). The	KIF-230-M-8 in soil Silt loam (pH 5.8, 1.38% organic carbon), loamy sand (pH 5.4, 1.16% OC), loam (pH 7.2, 1.98% OC) for 28 days in the dark at 21°C and 14.8 - 31.9% moisture.	DRAR Vol. 3CA, B.8.1.1.4.1.2/05 Voelkel W, 2015 Doc. no.: 1150126

Method	Results	Remarks	Reference
	corresponding DT90 were 9.53, 24.7 and 6.14 days.	The study is considered acceptable	
Testing Method C.7 (Directive 92/69/EEC). EPA Subdivision N, Section 161-1 (October 1982); MAFF: 59 NohSan No. 4200 (January 1985) and OECD no. 111 (May 1981).	KIF-230 was considered hydrolytically stable. DT50 > 1 year at 25°C. No major hydrolysis products.	KIF-230 was studied at 25°C and 50°C in sterile aqueous buffer solutions at pH 4, pH 5, pH 7 and pH 9. The study is considered acceptable	DRAR Vol. 3CA, B.8.2.1.1/01 Yeomans P and Swales S, 2000
SETAC Pesticides, Section 10 (March 1995); EPA Pesticide Guidelines, Subdivision N, Section 161-2 (October 1982)	Photolytic DT50 = 16.2 days at pH 5, 543 days at pH 7 and 191 days at pH 9. Many minor photolytic degradation products at pH 5, all ≤ 5% AR.	KIF-230 under intermittent artificial light for 12 h/day, for 30 days at 25°C in sterile aqueous buffered solutions at pH 5, pH 7 and pH 9 The study is considered acceptable	DRAR Vol. 3CA, B.8.2.1.2/01 Lewis C, 2001
EPA OPPTS 835.5270 - (January 1998)	Photolytic DT50 = 795 days (SFO) No photolytic degradation products	KIF-230 in synthetic humic water under natural sunlight for 16 days The study is considered acceptable	DRAR Vol. 3CA, B.8.2.1.3/01 Habeeb SB, 2016 Doc. No.: 160001

11.1.1 Ready biodegradability

The ready biodegradability of KIF-230R-L was investigated using sewage plant effluent as the biological inoculum. The test system was shown to be viable based on the acceptable degradation of sodium benzoate. KIF-230R-L was demonstrated not to inhibit the biological degradation benzoate. CO2 evolution after 28 days incubation of KIF-230R-L was found to be 2-3% of the theoretical maximum value.. KIF-230R-L is not readily biodegradable under the conditions of the test.

11.1.2 BOD_5/COD

No data submitted.

11.1.3 Hydrolysis

The hydrolysis of benthiavalicarb-isopropyl was studied at 25°C and 50°C in sterile aqueous buffer solutions at pH 4, pH 5, pH 7 and pH 9. The nominal concentration of benthiavalicarb-isopropyl was 4 µg a.s./ml. Acetonitrile was used as co-solvent (0.9%-v/v). Total recovery of radioactivity was in the range of 96 to 107%.

Benthiavalicarb-isopropyl was considered hydrolytically stable. The half-life is assumed to be more than one year at 25°C. No major hydrolysis products were detected.

11.1.4 Other convincing scientific evidence

No data available.

11.1.4.1 Field investigations and monitoring data (if relevant for C&L)

No data available.

11.1.4.2 Inherent and enhanced ready biodegradability tests

No test was performed on inherent and enhanced ready biodegradability, however, there are sufficient available studies to describe the degradation behaviour of benthiavalicarb-isopropyl in the environment.

11.1.4.3 Water, water-sediment and soil degradation data (including simulation studies)

Aquatic simulation tests

Two studies are available: one aerobic mineralisation in surface water study (Feldmann S, 2015) and one water/sediment study (Goodyear A, 2000).

Aerobic mineralisation in surface water

The degradation and metabolism of benthiavalicarb-isopropyl were studied in a pelagic pond system (pH 8.28) under aerobic conditions for 62 days at 23°C. The test material was applied at a low dose of 11 µg/l and a high dose of 108 µg/l.

In the low dose system, degradation of benthiavalicarb-isopropyl was rapid after the ended lag phase (36 days) with a t½ value of 13.9 days (Hockey Stick). In the case of the pond system treated with the high dose, degradation after the ended lag phase (37 days) was much slower with a t½ value of 65.7days (Hockey Stick). CO2 and other volatile organic compounds did not exceed 1% of the applied radioactivity at any dose.

In both test systems, 1-(6-fluoro-2,3-benzothiazol-2-yl)ethanamine (KIF-230-M-5) comprised circa 19 - 25% of the applied radioactivity at the end of the study. In the low dose test system 1-(6-fluoro-2,3-benzo-thiazol-2-yl)ethanone (KIF-230-M-4) comprised circa 24% of the applied radioactivity, N-[1-(6-fluoro-2,3-benzothiazol-2-yl)ethyl]ethanamide (KIF-230-M-8) comprised circa 10% of the applied radioactivity and 1-(6-fluoro-2,3-benzothiazol-2-yl)ethanol (KIF-230-M-3) comprised circa 5% of the applied radioactivity at the end of the study.

Water/sediment study

The degradation and metabolism of benthiavalicarb-isopropyl was studied (Goodyear 2000) in a pond water/sediment system (pH 8.2) and a lake water/sediment system (pH 6.8) under aerobic conditions for 100 days at 20°C. The test material used was [Bz-U-14C]-labelled benthiavalicarb-isopropyl.

In both systems, the disappearance of benthiavalicarb-isopropyl from water was rapid with DT50 values of 3.69 (DFOP) and 7.71 (SFO) days. The decline of benthiavalicarb-isopropyl from the aqueous phase was accompanied by a corresponding increase in residues in the sediment which represented 82 and 94% of the applied radioactivity after 100 days incubation.

The main metabolites detected in the sediments were 1-(6-fluoro-1,3-benzothiazol-2-yl)ethanamine (KIF-230-M-5) at circa 12% of applied radioactivity, 1-(6-fluoro-1,3-benzothiazol-2-yl)ethanone (KIF-230-M-4) at circa 23% of applied radioactivity and 1-(6-fluoro-1,3-benzothiazol-2-yl)ethanol (KIF-230-M-3) at circa 26% of applied radioactivity. 6-fluoro-2-hydroxy-1,3-benzothiazole was a minor degradation product (5% of the applied radioactivity). The degradation profile of benthiavalicarb-isopropyl was similar for aerobic soil and aerobic water/sediment systems, indicating that degradation in sediment was the result of microbial degradation. Volatile substances (CO2 and other organic volatile compounds) did not exceed 4% of the applied radioactivity. In the water layer of both test systems, 1-(6-fluoro-1,3-benzothiazol-2-yl)ethanamine comprised < 3% of applied radioactivity, 1-(6-fluoro-1,3-benzothiazol-2-yl) ethanone comprised < 0.5% of applied radioactivity and 1-(6-fluoro-1,3-benzothiazol-2-yl) ethanol comprised ≤ 6% of applied radioactivity.

Route of degradation in aerobic soil

The degradation of [Val-2-^{14}C]- and [Bz-U-^{14}C]-labelled benthiavalicarb-isopropyl was studied (Purser D and Goodyear A, 2001) in a sandy loam soil (pH 7.0, 2.5% organic carbon) for 365 days under aerobic conditions in the dark at 20°C and 27% moisture. Both labelled test materials were applied at a rate of 2 mg/kg soil.

The concentration of the parent compound decreased from 96 - 97% of the applied amount at day 0, to 2% at day 120 and to 0.3 - 0.4% after 365 days. The half-lives of [Val-2-^{14}C]- and [Bz-U-^{14}C]-labelled benthiavalicarb-isopropyl in soil were 16.1 - 21.9 days and 53.0 - 72.7 days.

The half-lives of [Val-2-^{14}C]- and [Bz-U-^{14}C]-labelled benthiavalicarb-isopropyl in soil were 16.1 - 21.9 days and 53.0 - 72.7 days (SFO).

The major degradation products detected were 6-fluoro-2-hydroxy-1,3-benzothiazole (KIF-230-M-1), 1-(6-fluoro-1,3-benzothioazol-2-yl)ethanone (KIF-230-M-4) and 1-(6-fluoro-1,3-benzo-thiazol-2-yl)ethanamine (KIF-230-M-5) with a maximum concentration of 10, 8 and 12% of the applied amount, observed on the 120th, 30th and 30th day of incubation, respectively. The corresponding concentrations at the end of the study period were 3, 0.7 and 1% of the applied amount, respectively. Non-extractable radioactivity increased from 2% of the applied amount at day 0 to 27 - 62%of the applied amount at the end of the study period. At study termination, evolved $^{14}CO_2$ and organic volatiles were 20 - 54% and < 0.1% of the applied amount, respectively.

In the second degradation in aerobic soil (Ikeda M, Usami S, Mizutani H and Yagi A, 2005), the degradation and metabolism of [Val-2-^{14}C]- and [Bz-U-^{14}C]-labelled benthiavalicarb-isopropyl were studied in two Japanese soils (Ushiku and Kakegawa) for 56 days in a closed system in darkness at 30°C and 55% of maximum water holding capacity following application of 0.75 mg a.s./kg dry soil.

The DT_{50} values for degradation of parent material, based on first-order reaction kinetics, were respectively 6.9 and 4.2 days in Ushiku soil and respectively 2.8 and 3.4 days in Kakegawa soil (SFO).

Where [Bz-U-^{14}C]-labelled benthiavalicarb-isopropyl was applied to soil, the major degradation product detected was 1-(6-fluoro-1,3-benzothiazol-2-yl)ethanamine (KIF-230-M-5 with 20% of applied radioactivity). Other significant metabolites were 1-(6-fluoro-1,3-benzothiazol-2-yl)ethanone (KIF-230-M-4 with 9% of applied radioactivity) and 1-(6-fluoro-1,3-benzothiazol-2-yl)ethanol (KIF-230-M-3 with max 4% of applied radioactivity). The final soil residue was 6-fluoro-2-hydroxy-1,3-benzothiazole (KIF-230-M-1 with 6% of the applied radioactivity). These metabolites were not found where [Val-2-^{14}C]-labelled benthiavalicarb-isopropyl was applied to soil. In the case of [Val-2-^{14}C]-labelled benthiavalicarb-isopropyl a higher CO_2 production occurred indicating that mineralisation is the major degradation route of the valine moiety in soil. Non-extractable radioactivity increased to *ca*. 55% of the applied amount of [Bz-U-^{14}C]-labelled benthiavalicarb-isopropyl and to *ca*. 36% of the applied amount of [Val-2-^{14}C]-labelled benthiavalicarb-isopropyl at day 56. On the basis of public literature data, it was indicated that bound benzothiazole metabolites degrade slowly in soil.

Soil photolysis study

The photolytic degradation of [Bz-U-^{14}C]-labelled benthiavalicarb-isopropyl was studied (Lewis CJ, 2001) on a silt loam soil (pH 7.4, 5.0% organic carbon) from the United Kingdom at 2 mg a.s./kg soil for 30 days at

25°C and 29 - 38% moisture. [Bz-U-^{14}C]-labelled benthiavalicarb-isopropyl was applied on the soil surface. The treated samples were irradiated for 12 hours per day using a xenon lamp filtered to cut off wavelengths below 290 nm.

The half-lives of [Bz-U-^{14}C]-labelled benthiavalicarb-isopropyl in the dark control and light-exposed samples were 12.4 and 20.4 days (SFO), respectively. These results indicate that soil photolysis does not contribute to the dissipation of benthiavalicarb-isopropyl in soil.

In the dark control samples, the concentration of the parent compound decreased from 95% at day 0 to 23% of the applied amount at test termination. The major degradation products identified were 6-fluoro-2-hydroxy-1,3-benzothiazole (KIF-230-M-1 with max 16.2% of applied radioactivity) and 1-(6-fluoro-1,3-benzothiazol-2-yl)ethan-amine (KIF-230-M-5 with max 11.4% of applied radioactivity). At study termination, the evolved CO_2 and volatile organic compounds in the dark samples amounted to 1.8% and 0.2% of the applied amount, respectively. Non-extractable residues in the dark control samples amounted to 25% of the applied amount.

In the light-exposed samples, the concentration of the parent compound decreased from 95% at day 0 to 41% of the applied amount at test termination. The major degradation products were also 6-fluoro-2-hydroxy-1,3-benzothiazole (KIF-230-M-1) and 1-(6-fluoro-1,3-benzothiazol-2-yl)ethanamine (KIF-230-M-5) with maximum concentrations of 12 and 5% of the applied amount, respectively, observed on the 30th day of incubation. In the light exposed samples the evolved CO_2 and volatile organic compounds amounted to 1.5 and 0.5% of the applied amount, respectively. Non-extractable residues remaining after reflux extraction amounted to 19% of the applied amount at the end of the study

Rate degradation in aerobic soil

In Purser and Goodyear (2001), the degradation rate of radiolabelled benthiavalicarb-isopropyl was tested in parallel to the route of degradation. It was studied in a sandy loam, silt loam and clay loam soil (pH 5.1 - 7.7, 1.3 - 4.0% organic carbon) from the United Kingdom for 120 days under aerobic conditions in the dark at 20°C and 45% of the maximum water holding capacity at a rate of 2 mg a.s./kg soil.

The concentration of the parent compound decreased rapidly from 93 - 96% of the applied amount at day 0 to 1 - 2% of the applied radioactivity at the end of the study period. The half-lives (DT_{50}) for benthiavalicarb-isopropyl were 16.4, 11.1 and 10.2 days in sandy loam, silt loam and clay loam soil, respectively. The principal metabolite KIF-230-M-5 appeared to be moderately persistent in soil with DT_{50} values ranging from 15.6 to 66.2 days. These values are only indicative.

The major degradation products were 1-(6-fluoro-1,3-benzothiazol-2-yl)ethanamine (KIF-230-M-5 with max 27% of the applied radioactivity) in the sandy loam soil on the 58th day of incubation, 1-(6-fluoro-1,3-benzothiazol-2-yl)ethanone (KIF-230-M-4 with max 9.8% of the applied radioactivity) in the silt loam soil on the 28th day of incubation, 1-(6-fluoro-1,3-benzothiazol-2-yl)ethanol (KIF-230-M-3 with max 12% of the applied radioactivity) observed in the silt loam soil on the 28th day of incubation and 6-fluoro-2-hydroxy-1,3-benzothiazol (KIF-230-M-1 with max 28% of the applied radioactivity) in the sandy loam soil on the last day of incubation. Non-extractable ^{14}C-residues increased to 23 - 58% of the applied radioactivity at the end of the incubation period. At study termination, evolved CO_2 amounted to 4 - 12% of the applied radioactivity. No other volatile degradation products were detected.

Aerobic degradation of KIF-230-M-5

The degradation of non-labelled 1-(6-fluoro-1,3-benzothiazol-2-yl)ethanamine (KIF-230-M-5) was studied in silt loam, loamy sand and loam soils (pH 4.9 - 7.2, 0.9 - 2.0% organic carbon) from Germany for up to120

days under aerobic conditions in the dark at 20°C and with moisture contents around the corresponding default field capacity at a rate of 1 mg/kg dry soil.

Since CO_2 and other organic volatiles were not recovered in this study, the mass balance was not completed. On day 0 the concentrations in the silt loam, sandy loam and loam soil were 0.735, 1.015 and 1.039 mg/kg soil, respectively. In the sandy loam and silt loam soils, the concentrations decreased steadily to 22 and 25% of the corresponding initial concentrations after 120 days of incubation. In the loam soil, the concentration declined rapidly to 6% of the applied amount over a period of 37 days.

The calculated DT_{50} and DT_{90} values for KIF-230-M-5 in the silt loam, sandy loam and loam soils were 42.8 and 1480 days, 26.2 and 178 days and 2.13 and 24.4 days, respectively.

Aerobic degradation of KIF-230-M-4

The degradation of non-labelled 1-(6-fluoro-1,3-benzothiazol-2-yl)ethanone (KIF-230-M-4) was studied in silt loam, sandy loam and clay loam soils (pH 5.5 - 8.0; 1.3 - 4.5% organic carbon) from the United Kingdom for 90 days under aerobic conditions in the dark at 20°C and 45% of maximum water holding capacity at the rate of 1 mg/kg soil.

The mass balance for the study was not completed because CO_2 and other organic volatiles were not recovered. In the first six hours, the concentration of KIF-230-M-4 decreased from 79 - 86% of the applied amount to 13 - 40% of the applied amount and then decreased very slowly to 4 - 7% of the applied amount at study termination.

The half-lives (DT_{50}) of metaboliteKIF-230-M-4 in the silt loam, sandy loam and clay loam soil were respectively 1, 2 and 4 hours, while the periods to reach 90% dissipation (DT_{90}) were respectively 34, 82 and 64 days.

Aerobic degradation of KIF-230-M-3

The degradation of non-labelled 1-(6-fluoro-1,3-benzothiazol-2-yl)ethanol (KIF-230-M-3) was studied in silt loam, sandy loam and clay loam soils (pH 5.5 - 8.0; 1.4 - 4.5% organic carbon) from the United Kingdom for 30 days under aerobic conditions in darkness at 20°C and 45% of maximum water holding capacity at a rate of 1 mg/kg soil.

The mass balance was not completed because CO_2 and other organic volatiles were not recovered. The concentrations of metabolite KIF-230-M-3 were 88 - 90% of the applied amount at day 0 and decreased to 4.9 - 8.4% of the applied amount at the end of the study period.

The calculated half-lives (DT_{50}) for metabolite KIF-230-M-3 in aerobic soils ranged between2and 7 days, and the time for 90% degradation ranged between 20 and 24 days.

Aerobic degradation of KIF-230-M-1

The degradation of non-labelled 6-fluoro-2-hydroxy-1,3-benzothiazole (KIF-230-M-1) was studied in silt loam, sandy loam and clay loam soils (pH 5.5 - 8.0, 1.4 - 4.5% organic carbon) from the United Kingdom for up to 120 days under aerobic conditions in the dark and 45% of maximum water holding capacity at a rate of 1 mg/kg soil.

A mass balance was not completed for the study because CO_2 and other volatile compounds released were not recovered. The concentrations of metabolite KIF-230-M-1 decreased from 80 - 89% of the applied amount at day 0 to 5.6 - 32% of the applied amount at day 30. The sampling was continued in the sandy loam and clay loam soils where the concentrations declined slowly to 5.4% of the applied amount in the sandy loam soil at day 90 and 19% of the applied amount in the clay loam soil at day 120.

The half-life (DT_{50}) values for metabolite KIF-230-M-1 in soils ranged from 4 to 13 days and the time required to reach 90% degradation (DT_{90}) ranged from 16 to 249 days.

Aerobic degradation of KIF-230-M-8

The degradation of non-labelled N-[1-(6-fluoro-1,3-benzothiazol-2-yl)ethyl]ethanamide (KIF-230-M-8) was studied in silt loam, loamy sand and loam soils (pH 5.4 - 7.2, 1.2 - 2.0% organic carbon) from Germany for up to 28 days under aerobic conditions in darkness at 21°C and 14.8 - 31.9% moisture at a rate of 1.004 mg/kg soil.

No mass balance was completed because CO_2 and other volatile compounds released were not recovered. The concentration of metabolite KIF-230-M-8 decreased rapidly to 2 - 4% of the applied amount after 14 days in the silt loam and loam soils. In the loamy sand soil, the concentration decreased more slowly and represented 8% of the applied amount after 28 days.

The half-lives (DT_{50}) for metabolite KIF-230-M-8 in soil were 2 to 7 days.

11.1.4.4 Photochemical degradation

Direct photodegradation

The aqueous photolysis of benthiavalicarb-isopropyl was studied under intermittent artificial light for 12 hours per day for 30 days at 25°C in sterile aqueous buffered solutions at pH 5, pH 7 and pH 9 with an initial concentration of 4 µg a.s./ml.

The photolytic half-life for benthiavalicarb-isopropyl was calculated to be 16.2 days at pH 5, 543 days at pH 7 and 191 days at pH 9. The overall mass balance was 96% for the irradiated samples and 98% for the dark control samples.

The study indicated that the active R-L isomer was not converted to the S-L isomer following irradiation at any pH. Many minor photolytic degradation products were formed at pH 5 in amounts of ≤ 5% of the applied radioactivity and were not identified. Evolution of CO2 accounted for 28% of the applied radioactivity at pH 5, for 2.2% at pH 9 and 0.5% at pH 7. Other volatile organic compounds accounted for < 0.5% of the applied radioactivity.

Indirect photodegradation

In an indirect photolysis screening study, the aqueous photolysis of benthiavalicarb-isopropyl was studied in synthetic humic water at an initial concentration of 1 µg/ml under natural sunlight for 16 days.

The photolytic half-life (DT50) calculated assuming first-order linear reaction kinetics was 795 days (rate constant of 0.000872 d-1, the correlation coefficient of 0.0619).

Mass balance at each sampling point ranged from 92.2 to 99.4% of the applied radioactivity over the 16 days. No photolytic degradation products were formed. Indirect photolysis is unlikely to be a significant mechanism for dissipation of benthiavalicarb-isopropyl in aquatic environments.

11.2 Environmental transformation of metals or inorganic metals compounds

Not applicable.

11.2.1 Summary of data/information on environmental transformation

Not applicable.

11.3 Environmental fate and other relevant information

Overall, even though benthiavalicarb-isopropyl was not readily biodegradable and inherent biodegradability was not tested, the active substance demonstrated biodegradation under soil laboratory studies, aerobic mineralisation study and water/sediment studies. Major metabolites that were identified included KIF-230-M1, KIF-230-M3, KIF-230-M-4 and KIF-230-M-5. The degradation rates of these metabolites were tested in soil aerobic degradation studies.

Degradation rates were all below the trigger values for persistence. In soil, KIF-230-M-5 (Voelkel, 2015) and KIF-230-M-1 (Wright DR, 2001) had DT90 values > 200 days. However, both have low maximum predicted environmental concentrations in soil following application of benthiavalicarb-isopropyl to potatoes based on the recommended use rate of 75 g a.s./ha and a realistic worst-case exposure scenario ranged between 0.010 and 0.089 mg/kg soil (see point CP B.8.2.2). Additionally, in a field rotational crop study (Grolleau, 2011) conducted at two sites in France and Italy, benthiavalicarb-isopropyl was applied to a preceding potato crop at a seasonal rate of 450 g as/ha. Residues of KIF-230-M-5 were detected at the two sites until one year after application and the levels ranged from < 0.01 to 0.02 mg/kg. Residues of KIF-230-M-1 were not detected in the French site and only in small amounts (< 0.01 mg/kg) in the Italian site. It is of note that accumulation over many years of repeated application is taken into account in PECS calculations. These calculations can be regarded as sufficiently protective as these are based on laboratory degradation rates.

11.4 Bioaccumulation

The summary of partition coefficient test data evaluated during Annex I inclusion of benthiavalicarb-isopropyl and submitted for the purposes of EU renewal is reported below. Only information considered adequate, reliable and relevant for the classification proposal has been included.

The available partition coefficient test data for relevant metabolites of benthiavalicarb-isopropyl (KIF-230-M-1, KIF-230-M-3, KIF-230-M-4, KIF-230-M-5, KIF-230-M-8,) revealed logPow values <4 (trigger for CLP). Therefore, studies with these metabolites are not described here in detail.

Table 31: Summary of relevant information on bioaccumulation

Method	Results	Remarks	Reference
EEC A.8 / OECD 117 - Partition coefficient n-octanol/water (logPow)	KIF-230R-L pure a.s. Batch No: lot 34 Purity: 100% 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 (distill H2O), 20-25 °C: 2.56 (range 2.28 – 2.86)	The study is considered acceptable	DRAR Vol. 3CA, B.2.7/01 Bates, 1999 Report Nr 535/41-D2141 (amended 2003)
OECD 107 - Partition coefficient n-octanol/water (logPow)	KIF-230-M-1 Batch No.: lot 4, Purity: 100% 2.30±0.01 at 20°C	The study is considered acceptable	DRAR Vol. 3CA, B.2.7/02 Inoue, 2000a Report Nr 2000-72
OECD 107 - Partition coefficient n-octanol/water (logPow)	KIF-230-M-3 Batch No.: lot 3 Purity: 99.5% 2.26±0.01 at 20°C	The study is considered acceptable	DRAR Vol. 3CA, B.2.7/03 Inoue, 2000b Report Nr 2000-73
OECD 107 -	KIF-230-M-4	The study is	DRAR Vol. 3CA, B.2.7/04

Method	Results	Remarks	Reference
Partition coefficient n-octanol/water (logPow)	Batch No.: lot 3 Purity: 100% 2.58±0.01 at 20°C	considered acceptable	Inoue, 2000c Report Nr 2000-74
OECD 117 - Partition coefficient n-octanol/water (logPow)	KIF-230-M-5 Batch No.: lot 2 Purity: 100% 1.7 at 25ºC	The study is considered acceptable	DRAR Vol. 3CA, B.2.7/05 Matsumoto 2001b Report Nr 81892
OECD 107 - Partition coefficient n-octanol/water (logPow)	KIF-230-M-8 Batch No.: lot 4 Purity: 100% 1.84±0.01 at 25ºC	The study is considered acceptable	DRAR Vol. 3CA, B.2.7/06 Okazaki, 2015 (2015-002)

11.4.1 Estimated bioaccumulation

Taking into account that log Pow values for benthiavalicarb and its relevant metabolites are all < 4 (trigger for CLP being 4), there is low potential for bioaccumulation and therefore no bioaccumulation studies were conducted.

11.4.2 Measured partition coefficient and bioaccumulation test data

Partition coefficients octanol/water for benthiavalicarb-isopropyl was determined by the High Performance Liquid Chromatography (HPLC) method according to the OECD Test Guideline 117 giving the results as follow: 2.63 at pH 5 and 20-25 °C, 2.62 at pH 9 and 20-25 °C and 2.56 at pH unadjusted (distill H2O), 20-25 °C.

The study is considered valid and reliable. It is relevant for classification purposes.

The study (Bates, M 1999) with benthiavalicarb-isopropyl and studies (Inoue, J 2000a, 2000b, 2000c, Matsumoto, T 2001b,) with metabolites respectively KFI-230-M-1, KIF-230-M3, KIF-230-M-4 and KIF-230-M-5, were already evaluated during Annex I inclusion of Benthiavalicarb-isopropyl and they were accepted. The study (Okazaki, R 2015) for metabolite KIF-230-M-8 was submitted for the purpose of EU renewal.

11.5 Acute aquatic hazard

The summary of the aquatic toxicity studies evaluated during Annex I inclusion of benthiavalicarb-isopropyl and submitted for the purposes of EU renewal is reported below. Only information considered adequate, reliable and relevant for the classification proposal has been included.

The available acute toxicity data for relevant metabolites of benthiavalicarb-isopropyl (KIF-230-M-1, KIF-230-M-3, KIF-230-M-4, KIF-230-M-5, KIF-230-M-8,) revealed toxicity values > 1 mg/L. Therefore, the studies with these metabolites are not described here in detail.

Table 32: Summary of relevant information on acute aquatic toxicity

Method	Species	Test material	Results[1]	Remarks	Reference
Fish					
Acute toxicity to fish. OECD 203, (flow-through, mortality)	Rainbow trout *Oncorhynchus mykiss*	benthiavalicarb-isopropyl, purity: 87.9% as KIF-230R-L	96h LC_{50} **>10.0 mg a.s./L (nom)**	Accepted	DRAR Vol. 3CA, B.9.2.1.1/01 Anonymous 47 (2000a) Rep. No. 535/49-D2145
Acute toxicity	Common carp	benthiavalicarb-	96h LC_{50} >10.0 mg	Accepted	DRAR Vol. 3CA,

to fish. OECD 203, (flow-through, mortality)	*Cyprinus carpio*	isopropyl, purity: 87.9% as KIF-230R-L	a.s./L (nom)		B.9.2.1.1/02 Anonymous 48 (2000b) Rep. No. 535/50-D2145
Acute toxicity to fish. OECD 203, (flow-through, mortality)	Bluegill *Lepomis macrochirus*	benthiavalicarb-isopropyl, purity: 87.5% as KIF-230R-L	96h LC_{50} >10.0 mg a.s./L (nom)	Accepted	DRAR Vol. 3CA, B.9.2.1.1/03 Anonymous 49 (2000) Rep. No. 131/147
Acute toxicity to fish. OECD 203, (static, mortality)	Rainbow trout *Oncorhynchus mykiss*	metabolite KIF-230-M-1, purity: 100%	96h LC50 = 14.2 mg pm/L (nom)	Accepted	DRAR Vol. 3CA, B.9.2.1.2/01 Anonymous 50 (2014a) Rep. No. S14-02339 (KCI 150005)
Acute toxicity to fish. OECD 203, (static, mortality)	Rainbow trout *Oncorhynchus mykiss*	metabolite KIF-230-M-3, purity: 99.9%	96h LC_{50} = 40.5 mg pm/L (nom)	Accepted	DRAR Vol. 3CA, B.9.2.1.2/02 Anonymous 51 (2014b) Rep. No. S14-02340 (KCI 150006)
Acute toxicity to fish. OECD 203, (static, mortality)	Rainbow trout *Oncorhynchus mykiss*	metabolite KIF-230-M-4, purity: 100%	96h LC_{50} >3.36 mg pm/L (mm)	Accepted	DRAR Vol. 3CA, B.9.2.1.2/03 Anonymous 52 (2014c) Rep. No. S14-02341 (KCI 150007)
Acute toxicity to fish. OECD 203, (semi-static, mortality)	Rainbow trout *Oncorhynchus mykiss*	metabolite KIF-230-M-5, purity: 99.86%	96h LC_{50} >10.0 mg pm/L (nom)	Accepted	DRAR Vol. 3CA, B.9.2.1.2/04 Anonymous 53 (2014d) Rep. No. S14-02342 (KCI 150008)
Acute toxicity to fish. OECD 203, (semi-static, mortality)	Rainbow trout *Oncorhynchus mykiss*	metabolite KIF-230-M-8, purity: 100%	96h LC50>100.0 mg pm/L (nom)	Accepted	DRAR Vol. 3CA, B.9.2.1.2/05 Anonymous 54 (2014[e]) Rep. No. S14-02343 (KCI 150009)
Daphnids					
Acute toxicity to aquatic invertebrates. OECD 202 (static, immobilisation)	Water flea *Daphnia magna*	benthiavalicarb-isopropyl, purity: 87.9% as KIF-230R-L	48h EC_{50} **>10.0 mg a.s./L (nom)**	Accepted	DRAR Vol. 3CA, B.9.2.4.1/01 Mattock (2000c) Rep. No. 535/48-D2145
Acute toxicity to aquatic invertebrates. OECD 202 (semi-static, immobilisation)	Water flea *Daphnia magna*	metabolite KIF-230-M-1, purity: 100%	48h EC_{50} = 14.0 mg pm/L (nom)	Accepted	DRAR Vol. 3CA, B.9.2.4.2/01 Eser (2015a) Rep. No. S14-02345 (KCI 150014)

Acute toxicity to aquatic invertebrates. OECD 202 (static, immobilisation)	Water flea *Daphnia magna*	metabolite KIF-230-M-3 purity: 99.5%	48h EC_{50} = 55.3 mg pm/L (nom)	Accepted	DRAR Vol. 3CA, B.9.2.4.2/02 Mattock (2001b) Rep. No. 535/86-D2145
Acute toxicity to aquatic invertebrates. OECD 202 (static, immobilisation)	Water flea *Daphnia magna*	metabolite KIF-230-M-4 purity: 100%	48h EC_{50} = 6.28 mg pm/L (mm)	Accepted	DRAR Vol. 3CA, B.9.2.4.2/03 Mattock (2001c) Rep. No. 535/87-D2145
Acute toxicity to aquatic invertebrates. OECD 202 (semi-static, immobilisation)	Water flea *Daphnia magna*	metabolite KIF-230-M-5 purity: 100%	48h EC_{50}>10.0 mg pm/L (nom)	Accepted	DRAR Vol. 3CA, B.9.2.4.2/04 Oishi (2001) Rep. No. 5327 (001-281)
Acute toxicity to aquatic invertebrates. OECD 202 (static, immobilisation)	Water flea *Daphnia magna*	metabolite KIF-230-M-8, purity: 100%	48h EC_{50}>100.0 mg pm/L (nom)	Accepted	DRAR Vol. 3CA, B.9.2.4.2/05 Eser (2015b) Rep. No. S14-02346 (KCI 150015)
Algae					
Acute toxicity to algae OECD 201 (static, growth)	Green alga *Selenastrum capricornutum*	benthiavalicarb-isopropyl, purity: 87.5% as KIF-230R-L	72h ErC50 >10.0 mg a.s./L (nom) 72h EyC50 >10.0 mg a.s./L (nom)	Accepted	DRAR Vol. 3CA, B.9.2.6.1/01, Mattock (2000e), Rep. No. 535/52-D2145
Acute toxicity to algae OECD 201 Growth Inhibition Test	Green algae *Pseudokirchneriella subcapitata*	metabolite KIF-230-M-1, purity: 100%	72h ErC50 = 38.6 mg pm/L (nom) 72h EyC50 = 30.1 mg pm/L (nom)	Accepted	DRAR Vol. 3CA, B.9.2.6.2/01, Falk (2014a), Rep. No. S14-02347 (KCI 150016)
Acute toxicity to algae OECD 201 Growth Inhibition Test	Green algae *Pseudokirchneriella subcapitata*	metabolite KIF-230-M-3, purity: 99%	72h ErC50 = 90.9 mg pm/L (nom) 72h EyC50 = 42.0 mg pm/L (nom)	Accepted	DRAR Vol. 3CA, B.9.2.6.2/02, Falk (2014b), Rep. No. S14-02348 (KCI 150017)
Acute toxicity to algae OECD 201 Growth Inhibition Test	Green algae *Pseudokirchneriella subcapitata*	metabolite KIF-230-M-4, purity: 100%	72h ErC50 >10.0 mg pm/L (nom) 72h EyC50 = 7.42 mg pm/L (nom)	Accepted	DRAR Vol. 3CA, B.9.2.6.2/03, Falk (2014c), Rep. No. S14-02349 (KCI 150018)
Acute toxicity to algae OECD 201	Green algae *Pseudokirchneriella subcapitata*	metabolite KIF-230-M-5, purity: 99.86%	72h ErC50 = 71.1 mg pm/L (nom) 72h EyC50 = 44.0 mg pm/L (nom)	Accepted	DRAR Vol. 3CA, B.9.2.6.2/04, Falk (2015a), Rep. No. S14-02350 (KCI 150019)

Growth Inhibition Test					
Acute toxicity to algae OECD 201 Growth Inhibition Test	Green algae *Pseudokirchneriella subcapitata*	metabolite KIF-230-M-8, purity: 100%	72h ErC50 >100.0 mg pm./L (nom) EyC50 >100.0 mg pm./L (nom)	Accepted	DRAR Vol. 3CA, B.9.2.6.2/05, Falk (2015b), Rep. No. S14-02351 (KCI 150020)

[1] Indicate if the results are based on the measured or on the nominal concentration

11.5.1 Acute (short-term) toxicity to fish

Benthiavalicarb-isopropyl was tested in 3 acute toxicity tests (Anonymous 472000a and Anonymous 48 200b, Anonymous2000) on fish (*Oncorhynchus mykiss*, *Cyprinus carpio*, *Lepomis macrochirus*) under flow-through conditions for 96 hours at the sole concentration of 10 mg a.s./L (limit test). The content was analysed in the three studies and found to be within the ± 20% interval of deviation from the nominal concentration, therefore endpoints were derived based on the nominal concentration. In the three studies, the LC_{50} was found to be above 10 mg a.s./L.

These studies were already evaluated during Annex I inclusion of benthiavalicarb-isopropyl and they were accepted. All studies for metabolites (Anonymous50, 2014a; Anonymous 51, 2014b; Anonymous 52, 2014c; Anonymous 53, 2014d; Anonymous 54, 2014e) were submitted for the purpose of EU renewal.

11.5.2 Acute (short-term) toxicity to aquatic invertebrates

One acute toxicity study (Mattock 2000c) was conducted on daphnids (*Daphnia magna*) with benthiavalicarb-isopropyl under static conditions at the nominal concentration of 10 mg a.s./L. The content was analysed and found to be within the ± 20% interval of deviation from the nominal concentration, therefore endpoint was derived based on the nominal concentration. The EC_{50} for immobilisation was found to be above 10 mg a.s./L.

The study (Mattoc 2000c) with benthiavalicarb-isopropyl and studies (Mattock 2001b, 2001c, Oishi, N. (2001) with metabolites respectively KIF-230-M3, KIF-230-M-4 and KIF-230-M-5, were already evaluated during Annex I inclusion of Benthiavalicarb-isopropyl and they were accepted. The studies (Eser 2015a, and 2015b) for metabolites KIF-230-M-1 and KIF-230-M-8 were submitted for the purpose of EU renewal.

11.5.3 Acute (short-term) toxicity to algae or other aquatic plants

One study (Mattock 2000e) was conducted on green algae (*Selenastrum capricornutum*) with benthiavalicarb-isopropyl at different concentrations (0.63, 1.25, 2.5, 5.0 and 10 mg KIF-230/L, control and solvent control, 3 replicates with an initial cell density of $1x10^4$ cells/mL per treatment) under static conditions to detect possible growth inhibition of the algae population. The content was analysed and found to be within the allowed deviation for the endpoint to be derived on the nominal concentrations. Effective concentrations inhibiting 50 per cent of the growth rate and the yield was above the highest tested concentration of 10 mg a.s./L while NOEC for growth rate was found to be equal to 2.50 mg a.s./L. As for fish and daphnids, based on the available study, benthiavalicarb-isopropyl is shown to be moderately toxic for algae.

This study was already evaluated during Annex I inclusion of benthiavalicarb-isopropyl and was accepted. The studies (Falk 2014a, 2014b, 2014c, 2015a and 2015b) with metabolites, respectively KIF-230-M-1, KIF-230-M-3, KIF-230-M-4, KIF-230-M-5, and KIF-230-M-8, were submitted for the purpose of EU renewal.

11.5.4 Acute (short-term) toxicity to other aquatic organisms

No other aquatic organisms were tested.

11.6 Long-term aquatic hazard

The summary of the aquatic toxicity studies evaluated during Annex I inclusion of benthiavalicarb-isopropyl and submitted for the purposes of EU renewal is reported below. Only information considered adequate, reliable and relevant for the classification proposal has been included.

Regarding the metabolites of benthiavalicarb-isopropyl, only metabolites KIF-230-M-1, KIF-230-M-3, KIF-230-M-4, KIF-230-M-5 and KIF-230-M-8 toxicity data to algae are presented. The studies with these metabolites are described below.

Table 33: Summary of relevant information on chronic aquatic toxicity

Method	Species	Test material	Results[1]	Remarks	Reference
Fish					
ELS, semi-static, hatching, length, weight, mortality OECD 210	Zebrafish *Danio rerio*	KIF-230, purity: 97.0% as KIF-230R-L	35-day NOEC ≥ 5.0 mg a.s./L (nom) No ECx derivation due to lack of effect	Acceptable	DRAR Vol. 3CA, B.9.2.2.1/01, Anonymous 55 (2015) Rep. No. S14-02344 (KCI 150075)
Fish juvenile growth test, flow-through, weight OECD 215	Rainbow trout *Oncorhynchus mykiss*	KIF-230, purity: 87.9% as KIF-230R-L	28-day NOEC = **1.0 mg a.s./L (nom)** EC10 weight = 3.50mg a.s./L (95% CI: 1.84 – 6.65mg a.s./L) No reliable EC10 for growth rate	Acceptable despite flows in design and statistical analysis	DRAR Vol. 3CA, B.9.2.2.2/01, Anonymous 56 (2001a) Rep. No. 535/61-D2149
Daphnids					
Long term and chronic toxicity to aquatic invertebrates. semi-static, reproduction OECD 211	Water flea *Daphnia magna*	KIF-230, purity: 87.9% as KIF-230R-L	21-day NOEC = **3.0 mg a.s./L** $EC_{10offspring}$ = 4.30mg a.s./L (nom) (95% CI: 4.28 – 4.31 mg a.s./L)	Acceptable	DRAR Vol. 3CA, B.9.2.5/01, Mattock (2000d), Rep. No. 535/53-D2145
Algae					
Acute toxicity to algae or other aquatic plants. Growth Inhibition Test OECD 201	Green alga *Selenastrum capricornutum*	KIF-230, purity: 87.5% as KIF-230R-L	72h NOE_rC = **2.5 mg a.s./L (nom)**	Acceptable	DRAR Vol. 3CA, B.9.2.6.1/01, Mattock (2000e), Rep. No. 535/52-D2145
Acute toxicity to algae or	Green algae *Pseudokirchneriella subcapitata*	metabolite KIF-230-M-1, purity: 100%	72h NOE_rC = 20.0 mg pm/L (nom)	Acceptable	DRAR Vol. 3CA, B.9.2.6.2/01,

other aquatic plants. Growth Inhibition Test OECD 201					Falk (2014a), Rep. No. S14-02347 (KCI 150016)
Acute toxicity to algae or other aquatic plants. Growth Inhibition Test OECD Guideline 201	Green algae *Pseudokirchneriella subcapitata*	metabolite KIF-230-M-3, purity:99%	72h NOE_rC = 16.0 mg pm/L (nom)	Acceptable	DRAR Vol. 3CA, B.9.2.6.2/02, Falk (2014b), Rep. No. S14-02348 (KCI 150017)
Acute toxicity to algae or other aquatic plants. Growth Inhibition Test OECD Guideline 201	Green algae *Pseudokirchneriella subcapitata*	metabolite KIF-230-M-4, purity: 100%	72h NOE_rC = 5.0 mg pm/L (nom)	Acceptable	DRAR Vol. 3CA, B.9.2.6.2/03, Falk (2014c), Rep. No. S14-02349 (KCI 150018)
Acute toxicity to algae or other aquatic plants. Growth Inhibition Test OECD Guideline 201	Green algae *Pseudokirchneriella subcapitata*	metabolite KIF-230-M-5, purity: 99.86%	72h NOE_rC = 25.0 mg pm/L (nom)	Acceptable	DRAR Vol. 3CA, B.9.2.6.2/04, Falk (2015a), Rep. No. S14-02350 (KCI 150019)
Acute toxicity to algae or other aquatic plants. Growth Inhibition Test	Green algae *Pseudokirchneriella subcapitata*	metabolite KIF-230-M-8, purity: 100%	72h NOE_rC = 33.3 mg pm/L (nom)	Acceptable	DRAR Vol. 3CA, B.9.2.6.2/05, Falk (2015b), Rep. No. S14-02351 (KCI 150020)

OECD Guideline 201					

[1] Indicate if the results are based on the measured or on the nominal concentration

11.6.1 Chronic toxicity to fish

Two chronic toxicity studies are available (Anonymous 55,2015; Anonymous 56,2001a) on fish (*Danio rerio* and *Oncorhynchus mykiss*). One test was an early life stage test under semi-static conditions were fertilised eggs were exposed to different concentrations: 0.05, 0.15, 0.49, 1.56 and 5.00 mg a.s./L, control and solvent control, 4 replicates of 20 eggs per treatment. The other test was a fish juvenile test under flow-through conditions where juvenile fish were exposed to different concentrations of benthiavalicarb-isopropyl: 0.1, 0.32, 1.0, 3.2 and 10 mg a.s./L, control and solvent control, 1 replicate of 10 fish per treatment. In both studies, the content was analysed and found in the ± 20% interval of deviation from the nominal concentrations. Consequently, endpoints were derived based on nominal concentrations. In the early life stage test, no toxic effect was observed up to 5 mg a.s./L, setting the NOEC above this value. In the fish juvenile test, the strong effects were observed on growth and weight at 10 mg a.s./L, and at 3.2 mg a.s./L effects were observed in weight and pseudo specific growth in one fish, with impact on the average growth values, therefore the NOEC was set at 1 mg a.s./L. Based on the available studies, benthiavalicarb-isopropyl was shown to be moderately toxic to fish for chronic parameters.

The study (Anonymous 56,2001a) was already evaluated during Annex I inclusion of benthiavalicarb-isopropyl, and it was accepted. The study (Anonymous 55, 2015) was submitted for the purpose of EU renewal.

11.6.2 Chronic toxicity to aquatic invertebrates

One reproduction test (Mattock 2000d) was realised on daphnids (*Daphnia magna*) under semi-static conditions. Young daphnids were exposed to different concentrations of benthiavalicarb-isopropyl (0.1, 0.3, 1.0, 3.0, and 10 mg KIF-230/L, control and solvent control, 10 replicates of 1 daphnid per treatment) and observed for reproduction for 21 days. The content was analysed and found to be within the allowed deviation for the endpoint derived on the nominal concentrations. NOEC for reproduction and length was set at 3 mg a.s./L and was found to be the most critical endpoint. Based on the available study, benthiavalicarb-isopropyl is shown to be moderately toxic for daphnids for chronic endpoints.

This study was already evaluated and accepted during Annex I inclusion of benthiavalicarb-isopropyl.

11.6.3 Chronic toxicity to algae or other aquatic plants

Please refer to previous point 11.5.3 where the toxicity tests with the parent and metabolites on algae are included.

11.6.4 Chronic toxicity to other aquatic organisms

No other aquatic organisms were tested.

11.7 Comparison with the CLP criteria

11.7.1 Acute aquatic hazard

Table 34: Summary of information on acute toxicity relevant for classification

Method	Species	Test material	Results	Remarks	Reference
OECD 203, (flow-through, mortality)	Rainbow trout *Oncorhynchus mykiss*	KIF-230, purity: 87.9% as KIF-230R-L	96h LC50 > 10.0 mg a.s./L (nom)	Acceptable	DRAR Vol. 3CA, B.9.2.1.1/01 Anonymous 47 2000a Rep. No. 535/49 D2145
OECD 202 (static immobilisation)	Water flea *Daphnia magna*	KIF-230, purity: 87.9% as KIF-230R-L	48h EC50>10.0 mg a.s./L (nom)	Acceptable	DRAR Vol. 3CA, B.9.2.6.1/01 Mattock (2000c) Rep No. 535/48-D2145
OECD 201	Green alga *Selenastrum capricornutum*	KIF-230, purity: 87.9% as KIF-230R-L	72h ErC50 and EyC50>10.0 mg a.s./L (nom)	Acceptable	DRAR Vol. 3CA, B.9.2.6.1/01 Mattock (2000e) Rep. No. 535/52-D2145

In order to be classified for aquatic acute toxicity under CLP, 50% lethal/effect concentrations should be below or equal to 1 mg a.s./L. Therefore, there is no classification of benthiavalicarb-isopropyl proposed. Additionally, M factor is derived by taking the lowest endpoints and to compare it to set interval. The first interval for acute toxicity starts at [0.1 – 1mg/L] (M =1), therefore there is no M factor for acute toxicity for benthiavalicarb-isopropyl.

11.7.2 Long-term aquatic hazard (including bioaccumulation potential and degradation)

Table 35: Summary of information on long-term aquatic toxicity relevant for classification

Method	Species	Test material	Results[1]	Remarks	Reference
OECD 215 (fish juvenile growth test, flow-through, weight)	Rainbow trout *Oncorhynchus mykiss*	KIF-230, purity: 87.9% as KIF-230R-L	28-day NOEC=1.0 mg a.s./L (nom)	The study was considered acceptable despite flows in design and statistical analysis	DRAR Vol. 3CA, B.9.2.2.2/01 Anonymous 56 (2001a) Rep. No.535/61-D2149
OECD 211 (semi-static, reproduction)	Water flea *Daphnia magna*	KIF-230, purity: 87.9% as KIF-230R-L	21-day NOEC= 3.0 mg a.s./L (nominal)	Acceptable	DRAR Vol. 3CA, B.9.2.5/01 Mattock (2000d) Rep. No. 535/53-D2145
OECD 201	Green alga *Selenastrum capricornutum*	KIF-230, purity: 87.9% as KIF-230R-L	72h NOE_rC=2.5 mg a.s./L (nom)	Acceptable	DRAR Vol. 3CA, B.9.2.6.1/01 Mattock (2000e) Rep. No. 535/52-D2145

Benthiavalicarb-isopropyl, is not rapidly degradable (degradation in water: DT50 on the whole study period was 49.9 days (HS). In water/sediment system DegT50 water and sediment were respectively: 17.2 and 21.7

days (SFO), in one system and 25.7 and 9.63 days (SFO) in the other system). Benthiavalicarb-isopropyl is not expected to be bioaccumulative based on its log Pow of ~2.6 (trigger for CLP being 4).

The lowest endpoint was determined in the chronic fish study with rainbow trout and is equal to 1 mg a.s./L.

Based on the parameters mentioned above, benthiavalicarb-isopropyl is classified as hazardous to the aquatic environment for chronic toxicity category 2, but with no M factor.

11.8 CONCLUSION ON CLASSIFICATION AND LABELLING FOR ENVIRONMENTAL HAZARDS

Benthiavalicarb-isopropyl has no classification for aquatic acute toxicity and no M factor.

Benthiavalicarb-isopropyl is classified as hazardous to the aquatic environment for chronic toxicity, category 2, but with no M factor.

The H statement for aquatic chronic toxicity category 2 is H411: Toxic to aquatic life with long lasting effects with the pictogram GSH09 but no signal word. Three precautionary statements: P273 - Avoid release to the environment (prevention), P391 - Collect spillage (response) and P501 - Dispose of contents/container in accordance with local/regional/national/international regulation (storage).

12 EVALUATION OF ADDITIONAL HAZARDS

12.1 Hazardous to the ozone layer

No data available and none required, benthiavalicarb-isopropyl and its metabolites are not gaseous under environmental conditions.

12.1.1 Short summary and overall relevance of the provided information on ozone layer hazard

Not relevant.

12.1.2 Comparison with the CLP criteria

Not relevant.

12.1.3 Conclusion on classification and labelling for hazardous to the ozone layer

No data are available and none are required as benthiavalicarb-isopropyl and its metabolites are not gaseous under environmental conditions. Therefore, the active substance is not classified hazardous to the ozone layer.

13 ADDITIONAL LABELLING

Not applicable.

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15 ANNEXES

Benthiavalicarb_DRAR_04_Volume_3CA_B-2_2018-10-04

Benthiavalicarb_DRAR_08_Volume_3CA_B-6_korekta_E V A_2019-07-12

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