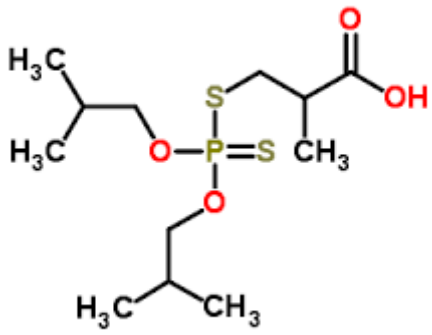
Miljø- og
Fødevareministeriet
Miljøstyrelsen

Fastsættelse af kvalitetskriterier for

Irgalube (353)

CAS nr. 268567-32-4



Vandkvalitetskriterium	$VKK_{ferskvand}$	72 µg/l
Vandkvalitetskriterium	$VKK_{saltvand}$	7,2 µg/l
Korttidsvandkvalitetskriterium	$KVKK_{ferskvand}$	3800 µg/l

Indhold

Forord

Et kvalitetskriterium i vandmiljøet er det højeste koncentrationsniveau, ved hvilket der skønnes, at der ikke vil forekomme uacceptable negative effekter på vandøkosystemer.

Miljøstyrelsen (MST) udarbejder kvalitetskriterier for kemikalier i vandsøjlen (vandkvalitetskriterium), i sediment og i dyr og planter (biota).

Miljøstyrelsen bruger kvalitetskriterierne som det faglige grundlag til at kunne fastsætte miljøkvalitetskrav, hvorved der forstås den endelige koncentration af et bestemt forurenende stof i vand, sediment eller biota, som ikke må overskrides af hensyn til beskyttelsen af miljøet og menneskers sundhed.

Metodikken, der anvendes til udarbejdelse af miljøkvalitetskrav er harmoniseret i EU og baserer sig på vandrammedirektivet (EU 2000), EU's vejledning til fastsættelse af kvalitetskriterier i vandmiljøet (EU 2011) og Miljøstyrelsens vejledning til fastsættelse af vandkvalitetskriterier (Miljøstyrelsen 2004). Metodikken er endvidere i overensstemmelse med EU's vejledning til risikovurdering under REACH forordningen (EU 2008).

Den sidste litteratursøgning er foretaget den 28-11-2018.

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Faglig kvalitetssikring: John Jensen, Institut for Bioscience, Aarhus Universitet

Kvalitetssikring, DCE: Susanne Boutrup

English Summary and conclusions

There is a REACH registration for the compound Irgalube which contains data for the compound. It was not possible to derive relevant EQS data from other literature sources or databases. Hence, the (Q)SAR profile from the Danish (Q)SAR is also attached. It is not biodegradable within 28 days in water. There is no data on degradability in sediment and soil. An analysis of BDF (OECD 305) found the BCF to be 2 to 10 L/kg (ww). The total tonnage in Denmark in 2016 was 33.1 tons and 100-1000 tons in the EU. The EQS values are the following:

$AA\text{-}EQS_{freshwater}$ =..... 72 µg/L

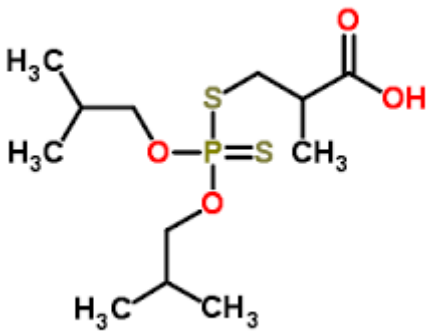
AA-EQSsaltwater = ... 7.2 µg/L

MAC = ... 3800 µg/L

1 Indledning

Identiteten af Irgalube fremgår af tabel 1.1. Der findes flere forskellige formuleringer af Irgalube. CAS nummer 268567-32-4 dækker over Irgalube 353. Irgalube er et olie produkt, der benyttes som smøreprodukt i gear og turbiner samt som hydraulisk væske. Det kan desuden anvendes i fremstillingen af pesticider, Cheminova fik i 2014 et tillæg til miljøgodkendelse af beslægtede Irgalube 62 og 63. I 2016 benyttedes 33,1 tons Irgalube i Danmark (SPIN database). Total tonnage i EU er mellem 100-1000 tons/år. Dette datablad dækker kun Irgalube 353 - i det følgende i databladet benævnt Irgalube.

Tabel 1.1. Identitet

IUPAC navn	Propanoic acid, 3-((bis(2-methylpropoxy)phosphinothioyl)thio)-2-methyl-
Strukturformel	
CAS nr.	268567-32-4
EINECS nr.	434-070-2
Kemisk formel	$C_{12}H_{25}O_4PS_2$
SMILES	C(CSP(=S)(OCC(C)C)OCC(C)C)(C)C(=O)O

2 Fysisk kemiske egenskaber

De fysisk kemiske egenskaber for Irgalube fremgår af tabel 2.1. Stoffet er mindre vandopløseligt.

Tabel 2.1. Fysisk kemiske egenskaber for Irgalube

Parameter	**Værdi**	**Reference**
Molekylevægt, M_w ($g \cdot mol^{-1}$)	328,42	EPI Suite
Smeltepunkt, T_m (°C)	Flydende indtil -45	EU REACH Registreringen (2018)
Kogepunkt, T_b (°C)	>175	EU REACH Registreringen (2018)
Damptryk, P_v (Pa) (20 °C)	6,5E-5	EU REACH Registreringen (2018)
Henry's konstant, H ($pa \cdot m^3 \cdot mol^{-1}$)	4,54E-9	EPI Suite
Vandopløselighed, S_w ($mg \cdot L^{-1}$)	7,8[1]	EU REACH Registreringen (2018)
Dissociationskonstant, pK_a	4,27 (udenfor normal pH 5-9) ved 25C – kan ikke dissocieres ved relevant forhold.	EU REACH Registreringen (2018)

[1] Ved 20°C

Octanol/vand fordelingskoefficient, log K_{ow}	3,9	EU REACH Registreringen (2018)
K_{oc} (L·kg-1)	213-504	EPI Suite

[#1]Nedbrydes inden kogepunktet

3 Skæbne i miljøet

3.1 Nedbrydelighed

Irgalube har en hydrolyse halveringstid på 11 dage ved pH 4 og 25C, ved lavere temperaturer og højere pH er stoffets hydrolyse halveringstid over 1 år. Stoffet er ikke bionedbrydeligt indenfor 28 dage i vand. Der er ingen data på nedbrydelighed i jord og sediment (EU REACH registreringen, 2018). Ud fra (Q)SAR data er stoffet ikke hurtigt bionedbrydeligt (bilag B).

3.2 Bioakkumulering

Stoffet er testet på *Cyprinus carpio* (japansk karpe) ved to forskellige koncentrationer i henhold til OECD 305, BCF er fundet til mellem 2 og 10 L/kg (ww). Det konkluderes at stoffet ikke akkumuleres i karpe (EU REACH Registreringen, 2018). (Q)SAR resultaterne viser en BCF = 3,1 L/kg (ww) og en biotransformationstid i fisk på ca. 2,5 dage (bilag B).

3.3 Naturlig forekomst

Stoffet er ikke naturligt forekommende.

4 Giftighedsdata

4.1 Giftighed over for vandlevende organismer

Der forligger kun få studier af Iraglubes giftighed over for vandlevende organismer. Søgning i SciFinder og google scholar returnered ingen fund på kombinationer af: Irgalube; Irgalube 353; CAS 268567-32-4; toxicity; aquatic toxicity. Ingen relevante andre databaser (fx ecotox mfl.) har giftighedsdata på stoffet. De to eneste datakilder er EU REACH registreringen opdateret i 2018 (EU REACH registreringen, 2018) med målte værdier, samt (Q)SAR værdi for *Daphnia magna*, der er også værdier for fisk og alger men disse er statistisk set mindre robuste og derfor ikke medtaget her. Resultaterne er samlet i tabel 4.1 nedenfor.

Tabel 4.1. Effekt koncentrationer anvendt i fastsættelsen af vandkvalitetskriterium, målte koncentrationer, (EU REACH Registreringen (2018)), samt (Q)SAR værdier.

Art / test guideline	**Effekt konc. (mg/L)**	**Eksponerings-tid**	**Effektmål**	**CRED score**
Zebrafisk *(Danio rerio)* (OECD 203)	38 (EC_{50})	96 t	Overlevelse	1
Daphnia magna (OECD 202)	53 (EC_{50})	48 t	Overlevelse	1
Daphnia magna (OECD 211)	3,6 (NOEC)	21 d	Reproduktion/vækst	1
Algae (*Desmodesmus subspicatus)* OECD 201)	66 (EC_{10})	72 t	Vækstrate	1
Algae (*Desmodesmus subspicatus)* OECD 201)	>100 (EC_{50})	72 t	Vækstrate	1
Daphnia magna (QSAR)[2]	1,2 (EC_{50})	48	Overlevelse	2

4.2 Giftighed over for sedimentlevende organismer

Ingen data (EU REACH Registreringen, 2018).

4.3 Giftighed over for pattedyr og fugle

Der er få giftighedsdata for pattedyr og fugle, primært rotteforsøg med følgende resultater. Akut LD_{50} for rotter er >2000 mg/kg lgv/d og $NOAEL_{rotter\ 92\text{-}d}$ = 125 mg/kg lgv/d (EU REACH Registreringen, 2018). Der er ikke fundet sub-letal toksicitet ved pattedyr og fugle i de forsøg dossieret præsenterer.

[2] Se bilag B QSAR data.

(Q)SAR analyserne støtter generelt de negative eksperimentelle fund med hensyn til mutagenicitet. Der er dog også enkelte positive fund som er fremhævet i gult i bilag B og listet nedenfor:

- Estrogen Receptor α Binding, Full training set (Human *in vitro*)
- Ashby Structural Alerts
- Syrian Hamster Embryo (SHE) Cell Transformation
- Sex-Linked Recessive Lethal (SLRL) Test in Drosophila m
- Dominant Lethal Mutations in Rodents
- Comet Assay in Mouse
- Liver Specific Cancer in Rat or Mouse

4.4 Giftighed over for mennesker

Irgalube har følgende Derived No Effect Levels (DNELs) for den generelle befolkning på baggrund af rotteforsøg (EU REACH Registreringen, 2018): Inhalation DNEL = 1,09 mg/m^3; Oral og dermal DNEL = 0,6 mg/kg lgv/d.

5 Andre effekter

H317: Kan forårsage hudallergi

H318: Skadeligt for øjne

6 Udledning af vandkvalitetskriterium

6.1 Vandkvalitetskriterium (VKK)

Af tabel 4.1 fremgår det, at der findes tre akutte datasæt for tre trofiske niveauer, samt et kronisk datasæt for *Daphnia magna. D. magna* er ikke den mest følsomme art i akut-testsættet, men da EC_{50} for *D. magna* (53 mg/l) ikke er væsentligt større end EC_{50} for Zebrafisk (*D. rerio)* (38 mg/L) (faktor 1,4) er toksiciteten over for *D. magna* på linje med toksiciteten for *D. rerio*. I henhold til Guidance Document No. 27 (EU 2011) (TGD#27) anvendes derfor en usikkerhedsfaktor på 50 på det kroniske resultat for *D. magna*. Vandkvalitetskriteriet for saltvand findes ved yderligere en ekstrapolationsfaktor på 10:

$PNEC/VKK_{ferskvand}$ = 3,6 mg/L/50 = 0,072 mg/L = 72 µg/L

$PNEC/VKK_{saltvand}$ = $PNEC/VKK_{ferskvand}$ /10 = 0,0072 mg/L = 7,2 µg/L

6.2 Korttidsvandkvalitetskriterium (KVKK)

For korttidskriteriet KVKK for både fersk- og saltvand benyttes data for akut effekt på fisk på 38 mg/L som data udgangspunkt. Da standardafvigelsen på de Log10-konverterede toksicitetsdata er mindre end 0,5 anvendes ifølge TGD#27 en ekstrapolationsfaktor på 10 så KVKK for både fersk- og saltvand = 38 mg/L/10 = 3,8 mg/L = 3800 µg/L.

6.3 Kvalitetskriterium for sediment (SKK)

Log K_{oc} er 2,7 (og dermed mindre end 3) og det er derfor ifølge TGD#27 ikke relevant, at fastsætte et SKK.

6.4 Kvalitetskriterium for biota (BKK)

Irgalube har en Log K_{ow} på 3,9 (Tab 2.1), men en BCF værdi på 2-10 L/kg (ww) og det er derfor ikke nødvendigt at fastsætte et biota kvalitetskriterium, der beskytter mod sekundær forgiftning ifølge TGD#27 (Tab 2.4.3.1).

6.5 Kvalitetskriterium for human konsum af vandlevende organismer (HKK)

Der er ingen kriterier (fx CMR) eller faresætninger, der indikerer mistanke om høj toksicitet over for mennesker, og det er derfor ikke relevant at fastsætte et kriterium af hensyn til human konsumption.

7 Konklusion

Der er fundet følgende miljøkvalitetskriterier for Irgalube baseret på data fra REACH registreringsdossieret (EU, 2018) og TGD#27 metoder:

$VKK_{ferskvand}$ = 72 µg/L

$VKK_{saltvand}$ = 7,2 µg/L

$KVKK_{ferskvand}$ = 3800 µg/L

8 Referencer

EU 2000. Europa-Parlamentets og Rådets Direktiv 2000/60/EF om fastsættelse af en ramme for fællesskabets vandpolitiske foranstaltninger af 23. oktober 2000.

EU 2008. ECHA: Guidance on information requirements and chemical safety assessment
Chapter R.10: Characterisation of dose [concentration]-response for environment
(https://echa.europa.eu/documents/10162/13632/information_requirements_r10_en.pdf/bb902be7-a503-4ab7-9036-d866b8ddce69)

EU 2011. Common Implementation Strategy for the Water Framework Directive (2000/60/EC). Guidance Document No. 27. Technical Guidance Document for Deriving Environmental Quality Standards.

EU 2018. Irgalube ECHA registration: https://echa.europa.eu/registration-dossier/-/registered-dossier/5213/7/1

Miljøstyrelsen 2004. Principper for fastsættelse af vandkvalitetskriterier for stoffer i overfladevand. Vejledning fra Miljøstyrelsen nr. 4, 2004.

Miljøstyrelsen 2014. J. Nr. MST-1270-01158. Tillæg til miljøgodkendelse for Cheminova:

https://mst.dk/.../20140331_cheminova_milj_godkendelse-fremstilling-irgalube_62_o...

9 Bilag A. Kvalitetsevaluering af data

De relativt få studier på stoffet findes i EU registreringsdossieret (EU,2018). De anvendte data har alle Klimish 1 scores (acceptable uden restriktioner) og opdateret i 2018. Vedlagt er evalueringsrapporten for den kritiske kroniske test med *Daphnia magna*. Der er kun adgang til robust study summary i dossieret med begrænsede detaljer hvorfor en dybdegående analyse ikke er mulig. Er anført som et GLP studie derfor CRED 1 som anført i dossieret. På grund af de få tilgængelige data er derfor også vedlagt Irgalubes profil baseret på den danske (Q)SAR database.

Evaluated study (full reference):	Long term toxicity to aquatic invertebrates. REACH study report from REACH dossier
Test substance:	Irgalube (CAS#268567-32-4)
Evaluated test:	Long term exposure of *D magna* to Irgalube
Evaluated test species:	Waterflea (*Daphnia magna*)
Evaluated test endpoint(s):	Reproduction
Evaluator (institution):	Hans Sanderson, Department of Environmental Science, Aarhus University

Relevance of the data *For each question, mark one appropriate answer with x.*

Remark: Relevance of a study mainly depends on the scope of the assessment / the regulatory framework, for which the study is evaluated. The following 12 questions should therefore be answered in the context of the overall assessment.

	Yes	No
Is the tested species relevant for the compartment under evaluation?	X	

Example: An aquatic species should be tested to evaluate risks for the aquatic environment.

	Yes	No
Are the tested organisms relevant for the tested compound?	X	

Example: In case of an ERA for an antibiotic, cyanobacteria should be used as test species instead of algae.

	Yes	No
Are the reported endpoints appropriate for the regulatory purpose?	X	

Example: Acute effects on aquatic organisms are not relevant for the environmental risk assessment of human pharmaceuticals.

	Yes	No
Are the reported endpoints appropriate for the investigated effects or the mode of action of the test substance?	X	

Explanation: When a risk assessment is performed for a substance, for which information is available on a specific mode of action that is considered relevant for environmental organisms, studies including endpoints assessing this particular mode of action are most appropriate. For instance, if an API is known to affect reproduction of vertebrates, the endpoints of the fish early life stage test may not be appropriate. Instead, fish tests should include endpoints such as vitellgenin levels, secondary sex characteristics, sex ratio and reproduction depending on the specific mode of action of the substance (OECD 2012).

	Yes	No
Is the effect relevant on a population level?	X	

Explanation: Endpoints of the guideline studies, on which the ERA of human pharmaceuticals is based, are generally population relevant. For non-standard tests, population relevance has to be evaluated on a case by case basis.

	Yes	No
Is the recorded effect statistically significant, biologically relevant and appropriate for the regulatory purpose?	X	

Explanation: In the context of environmental risk assessment, a biologically relevant effect is an effect that is important and meaningful for environmental health (EFSA 2011). In a test system with relatively little control variation, minor changes may be statistically significant without necessarily being biologically relevant. To evaluate risks caused by chronic exposure, NOEC or EC_{10} values are used, while EC_{50} values are not appropriate. For the EC_{10}, it has to be evaluated on a case by case basis, if the effect is within biological variation of the control response. To evaluate risks caused by acute exposure (note that this is only relevant for some terrestrial tests with human pharmaceuticals), EC_{50} values are preferred.

	Yes	No
Are appropriate life-stages studied?	X	

Explanation/example: The tested life stage should be (a) appropriate for the selected test and test design and (b) relevant for the expected effect of the API. For instance, fish early life stages are not appropriate for studying effects on reproduction.

	Yes	No
Are the test conditions appropriate for the tested species and relevant for the assessment?	X	

Explanation/example: Test organisms should be tested under appropriate conditions. For instance, freshwater species should be tested in freshwater, and saltwater species in saltwater. If a test with freshwater or saltwater species is required depends on the scope of the assessment.

	Yes	No
Is the timing and duration of exposure relevant and appropriate for the studied endpoints and species?	X	

Explanation: The required exposure time should be appropriate for the test organism and the studied endpoint. Chronic studies should include sensitive life stages or cover the whole life cycle.

	Yes	No
If recovery is studied, is this relevant for the framework for which the study is evaluated?		**NA**

Explanation: In most regulatory frameworks (including the environmental risk assessment of human pharmaceuticals), recovery is not relevant (exception: authorisation of plant protection products).

	Yes	No
Is the substance tested representative and relevant for the substance being assessed?	**X**	

Explanation: Sufficient information should be provided to allow a clear identification of the test item. A substance may be tested as pure active substance or in a formulation. Tests performed with formulations are relevant for plant protection products, but less relevant within many other regulatory frameworks. Studies with mixtures of different substances are relevant for assessing toxicity of these mixtures, but not for assessing the individual substances contained in the mixture. For salts, the counter ion may influence toxicity. For pro-drugs, the active moiety and, if entering the environment in >10% of the administered does, the pro-drug need to be assessed (EMA/CHMP 2011). Depending on the regulatory framework, effects of transformation products may need to be considered. If the substance causing the effect is not the substance being assessed, expert judgement is needed to decide on how to deal with the results of the study and the resulting risk assessment.

	Yes	No
Is the tested exposure route relevant for the assessment?	**X**	

Explanation/example: The exposure route should be appropriate for the assessment. For instance, exposure by injection is generally not appropriate (Harris et al. 2014). For pharmaceuticals, exposure should be continuous. Intermittent exposure is generally not relevant. Exposure duration has to be sufficiently long. However, note that acute tests with some terrestrial organisms are also required in the environmental risk assessment of human pharmaceuticals.

Assigned relevance class	**R1**

Reliability of the data

General information

Remark: Before evaluating the test, please check the physico-chemical characteristics of the test substance (what is the solubility, log K_{OW}, pK_a, is the compound volatile, does it hydrolyse, photolyse etc.?)

For each question, mark one appropriate answer with x.

Is a standard method (e.g. OECD, ISO, US EPA) or modified standard used? Please specify:

	Yes	**No**
A standard method is used.	**X OECD211**	
A slightly modified standard method is used.		**X**
A substantially modified standard method is used.		**X**

Is the test, including chemical analysis of the test substance where required, performed under GLP conditions?		**X**	
Validity criteria:			
		Yes	**No**
a	**Are all validity criteria fulfilled if applicable?**	**X**	
	Explanation: For standard tests, compliance with the validity criteria of the guideline is crucial for a study to be considered as reliable. Please check the corresponding test guideline where relevant. For non-guideline tests with standard species, validity criteria as described in a guideline for a similar test should be met if applicable.		
		Yes	**No**
b	**Are validity criteria clearly failed?**		**X**
	Explanation: If validity criteria are clearly failed, a test is classified as '3' (not reliable).		
Inclusion of appropriate controls:			
	Explanation: It depends on the test substance and test type which controls should be included; please check the corresponding test guideline where relevant. In addition to the negative control, a solvent control has to be included in all cases where a solvent is used. The concentration of solvent in the solvent control should correspond to the highest solvent concentration used in the test treatments. In some tests, a positive control with a reference substance is required. For standard tests, the corresponding guidelines provide information on how the controls should perform, e.g. with regard to survival, growth or reproduction. For non-standard tests and non-standard test organisms, expert judgement is needed to decide if performance of the controls is acceptable. Performance of the solvent control should preferably not differ significantly from performance of the negative control.		
		Yes	**No**
a	**Was a negative control included, and was its performance acceptable?**	**X**	
b	**Was a positive control included, if required, and was its performance acceptable?**		**X**

c	**Was a solvent control included, if a solvent was used, and was its performance acceptable?**		**NA**
Test substance			
		Yes	**No**
Is the test substance clearly identified with name, CAS-number or SMILES code and, where relevant, information on stereochemistry?		**X**	
	Explanation/example: If the salt of an API was tested, information on the type of salt should be provided. It should be specified if test concentrations relate to free acid / free base or salt. If the test substance is not clearly identified, a test is classified as '3' (not reliable).		
		Yes	**No**
a	**Is the purity of the test substance reported and in an acceptable range (>95%)?**		**X**
b	**Is the source of the test substance reported and trustworthy?**	**X**	
If a formulation is used or if impurities are present:			
		Yes	**No**
a	**Can it be excluded that other ingredients in the formulation or impurities exert an effect?**	**X**	
b	**Is the amount of test substance in the formulation indicated?**	**X**	
Test organism			
Description of the test organisms:			
		Yes	**No**
a	**Is the test species clearly identified?**	**X**	
	Explanation: If the test species is not clearly identified, a test is classified as '3' (not reliable).		
		Yes	**No**

b	**For algae: is mean cell density at the test start within an appropriate range? For other test organisms: Is mean body weight/length of the test organism in an appropriate range?**	**NA**	
	Explanation for 8 b-e: For standard tests, the corresponding guidelines provide information on required range of mean cell densities, age / life stage of the test organisms etc. at the test start.		
		Yes	**No**
c	**Is age/life stage of the organisms at test start reported and in the required range, where appropriate (e.g. not for algae)?**	**X**	
d	**Is sex of the test organisms reported and is sex ratio appropriate, where relevant (e.g. when evaluating sexual-endocrine effects)?**	**NA**	
e	**Is the species strain reported where required?**	**X**	
a	**Are the test organisms from a reliable source? For field collected organisms: is the site of origin well-described?**	**X**	
b	**Have the organisms been acclimatized to test conditions (e.g. water type, temperature) before the start of exposure, where relevant? For tests with embryonic stages: have the parental organisms been held at appropriate conditions?**	**X**	
c	**Are the test organisms exempt from previous exposure or any other kind of stressor?**	**X**	
Test conditions and chemical analysis			
Appropriateness of the experimental system for the test substance:		**Yes**	**No**
	Is the type of exposure (e.g. static, semi-static, flow-through) appropriate for the test substance, taking its physico-chemical characteristics into account?	**X**	

Explanation: Static systems are in most cases only appropriate for short-term tests (exception: water/sediment tests). Where appropriate, guideline requirements should be followed.

	Yes	No
In case that the test substance is a difficult substance as defined in OECD (2000): is the selected test system appropriate for testing of this substance?	X	

Explanation: Difficult test substances are substances which are e.g. poorly water soluble, volatile, photo-degradable, hydrolytically unstable, oxidizable, biodegradable, complexing or strongly adsorbing to surfaces of test vessels etc. In order to obtain reliable test results with such substances, test systems generally have to be adapted to take the difficult properties of the substance into account (e.g. by using a closed test system without headspace for volatile substances). For further details, please see OECD (2000). It has to be verified on a case-by-case basis, if the used test system is appropriate for the test substance.

	Yes	No
For ionisable substances: has the test been performed in an appropriate pH-range?	X	

Explanation: Relatively small changes in pH can significantly alter the balance between dissociated and non-dissociated forms of some substances. An altered dissociation equilibrium may significantly affect the water solubility and the partition coefficient of the substance and hence, its bioavailability and toxicity. Tests with such substances should therefore be performed at a pH, within the pH range required for maintaining the health of the test organisms, at which the more toxic form of the test substance prevails (as far as possible). For further guidance, see OECD (2000).

	Yes	No
Is the experimental system appropriate for the test organism (e.g. choice of medium / test water or soil, feeding, water or soil characteristics, temperature, light/dark conditions, pH, oxygen content)? Have conditions been stable during the test?	X	

Explanation: The general requirements of the test species should be considered with regard to the characteristics of the selected test medium etc. Temperature, pH and oxygen content should be stable and within the appropriate range for the organism (where applicable, check the corresponding guideline). If control performance is not good (e.g. high mortality), this may indicate that test conditions were not appropriate. Where applicable, feeding should follow the guideline requirements, and all excess should be removed after feeding to avoid decreased bioavailability of the test substance.

		Yes	No
a	**For aquatic tests: were exposure concentrations below the limit of water solubility?**	X	
b	**For aquatic tests: if a solvent was used, was solvent concentration within the appropriate range (i.e. not higher than 0.01%)?**	NA	
	Is a correct spacing between exposure concentrations applied?	X	

Explanation: For standard tests, the corresponding guidelines provide information on the spacing factor. A factor of 3.2 is often recommended. As rule of thumb, the spacing factor should not be >10.

	Yes	No
Is the exposure duration defined and appropriate?	X	

Chemical analysis

	Yes	No
Are chemical analyses performed to verify test substance concentrations over the duration of the study where required?	X	

Explanation: If required in the corresponding test guideline, nominal test substance concentrations should be verified by chemical analysis. Non-guideline test should be evaluated based on test guidelines for similar tests where appropriate.

	Yes	No
Is an appropriate analytical method used to measure test substance concentrations?		NA

Are the measured test substance concentrations within the calibration range of the analytical method?		**NA**
Are samples analysed from a sufficient number of treatments and controls, and from a sufficient number of time intervals?		**NA**

Explanation: The frequency of chemical analyses should be evaluated based on the requirements of the corresponding test guideline or, for non-guideline studies, on a guideline for a similar test if appropriate.

	Yes	**No**
Are test substance concentrations sufficiently stable during the course of the exposure ?		**NA**

Explanation: Please evaluate according to the requirements of the corresponding test guideline or, for non-guideline studies, a test guideline for a similar test where appropriate.

	Yes	**No**
Is the biomass loading of the organisms in the test system within an appropriate range?		**NA**

Explanation: For standard tests, the corresponding guidelines provide information on maximum biomass loading. For non-standard tests / non-standard test species, expert knowledge is required to decide if the loading rate is appropriate.

Statistical design		**Yes**	**No**
a	**Is a sufficient number of replicates used for all controls and treatments?**	**X**	
b	**Is a sufficient number of organisms per replicate used for all controls and test concentrations?**	**X**	

Explanation for 17 a and b: For standard tests, the guideline requirements should be followed. When a non-guideline study is evaluated, expert judgement is needed to assess if the study design is appropriate to obtain statistically reliable results.

	Yes	**No**
Are appropriate statistical methods used to derive the effect concentrations?	**X**	

Explanation: Generally, a description of the statistical methods is needed to assess the reliability of the test results. For standard tests, the corresponding guideline requirements should be followed. Further guidance is e.g. provided by OECD (2006). When a non-guideline study is evaluated, expert judgment may be needed. EC_X values should not be extrapolated considerably beyond the range of tested concentrations.

		Yes	No
a	**Is a concentration-response curve observed?**	**NA**	

Explanation: The requirement for a concentration-response relationship depends on the objective of the study. If a limit test is performed at one (or two) concentration(s) to verify the lack of toxicity and no toxicity is recorded, a concentration-response relationship is obviously not needed to conclude that the LC_{50} or NOEC is above the highest tested concentration. However, if the intention of the study is to demonstrate an effect, reliability of the test results is higher, if (1) a sufficient number of concentrations have been tested and (2) the observed effect is regularly increasing (or regularly decreasing) with increasing test concentration (i.e. the concentration-response relationship is monotonous). Expert knowledge is needed, if an effect is only observed at the highest tested concentration. Expert knowledge is also needed in the case of non-monotonous concentration-response curves (e.g. U-, J- or inverted U-shaped curves). In such cases, the underlying mechanisms of effects and the reproducibility of the results should be considered (Harris et al. 2014).

		Yes	No
b	**Is the observed effect statistically significant?**		

Explanation: The significance level and the statistical method used to evaluate the specific effect should be indicated.

	Yes	No
Are sufficient data available to check the calculation of endpoints and (if applicable) fulfilment of the validity criteria (e.g. control data, concentration-response curves)?	**X**	

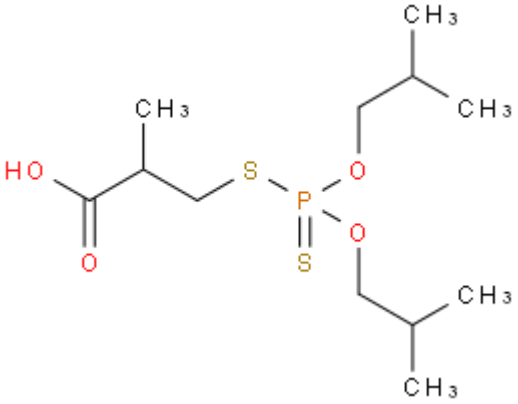
Explanation: If enough data are presented, additional endpoints may be calculated by the assessor if not reported by the author of the study.

Assigned reliability class	**R1**

10 Bilag B. (Q)SAR profil fra Danish (Q)SAR database

(Q)SAR predicted profile

11 Structure (as used for QSAR prediction):



SMILES (used for QSAR prediction): C(=O)(O)C(C)CSP(=S)(OCC(C)C)OCC(C)C

12 ID

EC Number (pre-registration)	608-009-7	EC Number (registration)	434-070-2
Registry Number	268567-32-4	PubChem CID	
Chemical Name	Propanoic acid, 3-[[bis(2-methylpropoxy)phosphinothioyl]thio]-2-methyl-;3-(Diisobutoxy-thiophosphorylsulfanyl)-2-methylpropionic acid		
Molecular Formula	C12 H25 O4 P1 S2	Molecular weight (g/mole)	328.42

13 Physical-chemical properties

EPI MPBPVP

Melting Point (deg C)	69.5	Melting Point Experimental (deg C)	
Boiling Point (deg C)	395.64	Boiling Point Experimental (deg C)	
Vapour Pressure (mm Hg)	4.04E-006	Vapour Pressure Experimental (mm Hg)	
Vapour Pressure (Pa)	0.0005386	Vapour pressure Subcooled Liquid (Pa)	0.00141

EPI HENRYWIN

HLC Bond Method (atm-m3/mole)	4.54E-009	HLC Group Method (atm-m3/mole)	
HLC Via VP/WSol (atm-m3/mole)	9.965E-007	HLC Via VP/WSol (Pa-m3/mole)	0.101
Henrys Law Const. Exp db (Pa-m3/mole)		Henrys Law Const. Exp db (atm-m3/mole)	

HLC: Henry's Law Constant

EPI WSKOW, WATERNT and HYDROWIN

Water solubility from Kow (mg/L)	1.752	Water solubility from Fragments (mg/L)	19.028
Water solubility Exp (mg/L)		Water solubility Exp Ref	
Hydrolysis Ka half-life pH 7		Hydrolysis Kb half-life pH 7	
Hydrolysis Ka half-life pH 8		Hydrolysis Kb half-life pH 8	
Log Kow	4.77		
Log Kow Exp		Log Kow Exp Ref	

LogKow: log octanol-water partition coefficient

ACDLabs

pKa Acid	4.9
- Standard deviation (±)	0.4
pKa Base	-999
- Standard deviation (±)	0

pKa estimate 999: no acidic moiety found. pKa estimate -999: no basic moiety found.

14 Environment

15 Partition coefficients

ACDLabs, pH	1	4	5	6	7	8	9
LogD	4.04	3.99	3.68	2.91	1.94	0.98	0.24

EPI KOAWIN

Log Koa	11.501	Log Kaw	-6.731

Koa: octanol-air partition coefficient. Kaw: air-water partition coefficient

EPI AEROWIN

Kp (m3/ug) Mackay-based	0.00212	Kp (m3/ug) Koa-based	0.0778
Phi Junge-Pankow-based	0.0712	Phi Mackay-based	0.145
Phi Koa-based	0.862		

Kp: particle-gas partition coefficient. Phi: fraction of substance sorbed to atmospheric particulates

EPI KOCWIN

Koc from MCI (L/kg)	213.6	Log Koc from MCI	2.3296
Koc from Kow (L/kg)	504	Log Koc from Kow	2.7024

Koc: soil adsorption coefficient of organic compounds. Kow: octanol-water partition coefficient. MCI: first order Molecular Connectivity Index

16 Level III Fugacity Environmental Partitioning

EPI Level III Fugacity Model	Air	Water	Soil	Sediment
Mass Amount (%)	0.0606	20.3	79.4	0.203
Half-Life (hr)	1.95	360	720	3240
Emissions (kg/hr)	1000	1000	1000	0

Persistence time (hr): 633

Persistence time (days): 26.375

17 Sewage Treatment Plant (STP) overall chemical mass balance using 10,000 hr

EPI STPWIN	Total removal	Biodegradation	Sludge Adsorption	Volatilization
(%)	69.1	0.62	68.48	0

18 Atmospheric oxidation (25 deg C)

EPI AOPWIN	OH	Ozone
Half-Life (d)	0.08129	0
Half-Life (hr)	0.976	
Overall Rate Const. (OH: E-12 cm3/molecule-sec and OZ: E-17 cm3/molecule-sec)	131.5709	

19 Biodegradation

EPI BIOWIN

Biowin1 (linear model) Probability of Rapid Biodegradation	0.9778
Biowin2 (non-linear model) Probability of Rapid Biodegradation	1
Biowin3 Expert Survey Ultimate Biodegradation	2.9917
Biowin3 Expert Survey Ultimate Timeframe	weeks
Biowin4 Expert Survey Primary Biodegradation	4.2248
Biowin4 Exp. Survey Primary Timeframe	days
Biowin5 (MITI linear model) Biodegradation Probability	0.0692
Biowin6 (MITI non-linear model) Biodegradation Probability	0.0265
Biowin7 (Anaerobic Linear) Biodegradation Probability	0.7324
Petroleum Hydrocarbon Biodegradation Half-Life (days)	

Biowin1 and Biowin2: ≥0.5: “Rapid” <0.5: “Slow”
Biowin3 and Biowin4: 5 ~ hours; 4 ~ days; 3 ~ weeks; 2 ~ months; 1 ~ years.
Biowin5 and Biowin6: ≥0.5: “Readily”, <0.5: “Not readily”.
Biowin7: ≥0.5: “Fast”, <0.5: “Slow”

DK	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Not Ready Biodegradability (POS=Not Ready)		INC_OUT	INC_OUT	POS_OUT	NEG_OUT

20 Bioaccumulation

EPI BCFBAF

BCF (L/kg wet-wt)	3.162
Log BCF (L/kg wet-wt)	0.5
Whole Body Primary Biotransformation Fish Half-Life (days)	2.449
BCF Arnot-Gobas (upper trophic) Including Biotransformation (L/kg wet-wt)	863.2
BCF Arnot-Gobas (upper trophic) Zero Biotransformation (L/kg wet-wt)	5205
BAF Arnot-Gobas (upper trophic) Including Biotransformation (L/kg wet-wt)	878.6
BAF Arnot-Gobas (upper trophic) Zero Biotransformation (L/kg wet-wt)	44100

BCF: Bioconcentration factor, BAF: Bioaccumulation factor

21 Aquatic toxicity

DK	Exp	Battery	Leadscope	SciQSAR
Fathead minnow 96h LC50 (mg/L)		6.819669	11.14704	2.492296
Domain		IN	IN	IN
Daphnia magna 48h EC50 (mg/L)		1.281434	1.352996	1.209872
Domain		IN	IN	IN
Pseudokirchneriella s. 72h EC50 (mg/L)		33.57108	63.4994	3.642752
Domain		IN	IN	IN

EPI ECOSAR	Fish 96h	Daphnid 48h	Green Algae 96h
LC50 (Fish) or EC50 (Daphnid and Algae) for Most Toxic Class (mg/L)	0.8	0	1.382
Max. Log Kow for Most Toxic Class	5	5	6.4
Most Toxic Class	Esters, Dithiophosphates-ac	Esters, Dithiophosphates-ac	Neutral Organic SAR
Note			

ECOSAR Classes: Esters, Dithiophosphates-acid

22 ADME

23 Oral absorption

Equation from literature

Lipinski's Rule-of-five score (bioavailability)	0
Absorption from gastrointestinal tract for 1 mg dose (%)	100
Absorption from gastrointestinal tract for 1000 mg dose (%)	90

Lipinski scores of 0 or 1: the substance may be bioavailable. Lipinski scores of 2, 3 or 4: the substance may not be bioavailable.

24 Skin absorption

EPI DERMWIN

Dermal absorption (mg/cm2/event)	0.000334

25 Distribution

Equation from literature

Log brain/blood partition coefficient	0.4604

Partitioning between the two tissues at equilibrium. >1: high, >0 to <1: medium, >-1 to <0, fair, <-1: low.

26 Metabolism

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
CYP2C9 substrates (Human clinical data)		NEG_IN	NEG_IN	INC_OUT	NEG_IN
CYP2D6 substrates (Human clinical data)		NEG_IN	NEG_OUT	NEG_IN	NEG_IN

27 Human Health

28 Acute toxicity in Rodents

ACDLabs	LD50 (mg/kg/d)	Reliability Index
Rat Oral	580	0.42
Rat Intraperitoneal	41.88	0.5
Mouse Oral	82.02	0.53
Mouse Intraperitoneal	100	0.1
Mouse Intravenous	290	0.6
Mouse Subcutaneous	440	0.29

Reliability index: <0.3 = Not reliable prediction quality; 0.3-0.5 = borderline prediction quality; 0.5-0.75 = moderate prediction quality; >0.75 = high prediction quality.

29 MRDD in Humans

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
MRDD in Humans ≤ 2.69 mg/kg-bw/d		NEG_OUT	INC_OUT	NEG_IN	STR_OUT

Model based on data on pharmaceuticals. Maximum recommended daily dose in pharmaceutical clinical trials employing primarily oral route of exposure and daily treatments, usually for 3-12 months.

30 Irritation and Sensitisation

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Severe Skin Irritation in Rabbit		NEG_OUT	NEG_OUT	POS_OUT	NEG_IN
Allergic Contact Dermatitis in Guinea Pig and Human	NA	INC_OUT	INC_OUT	NEG_OUT	INC_OUT
Respiratory Sensitisation in Humans		INC_OUT	INC_OUT	INC_OUT	NEG_OUT

31 Endocrine and Molecular Endpoints

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Estrogen Receptor α Binding, Full training set (Human *in vitro*)		INC_OUT	NEG_OUT	NEG_IN	POS_IN
Estrogen Receptor α Binding, Balanced Training Set (Human *in vitro*)		NEG_OUT	NEG_OUT	INC_OUT	NEG_IN
Estrogen Receptor α Activation (Human *in vitro*)		INC_OUT	NEG_OUT	NEG_OUT	NEG_OUT
Androgen Receptor Antagonism (Human *in vitro*)		NEG_IN	NEG_IN	NEG_IN	NEG_IN
Thyroperoxidase (TPO) inhibition QSAR1 (Rat *in vitro*)		NA	NA	NEG_OUT	NA
Thyroperoxidase (TPO) inhibition QSAR2 (Rat *in vitro*)		NA	NA	NEG_OUT	NA
Thyroid Receptor α Binding (Human *in vitro*) (mg/L)			52532.69	1077.853	429.1702
Domain		OUT	OUT	OUT	OUT
Thyroid Receptor β Binding (Human *in vitro*) (mg/L)			10627.47	28.96341	62.63681
Domain		OUT	OUT	OUT	OUT
Pregnane X Receptor (PXR) Binding (Human *in vitro*)	NA	NEG_IN	NEG_IN	NEG_IN	NEG_IN

32 Developmental Toxicity

	Battery	CASE Ultra	Leadscope	SciQSAR
Teratogenic Potential in Humans	NEG_IN	INC_OUT	NEG_IN	NEG_IN

33 Genotoxicity

34 Ashby Structural Alerts for DNA Reactivity

	Battery	CASE Ultra	Leadscope	SciQSAR
Ashby Structural Alerts	INC_OUT	POS_OUT	POS_IN	NEG_IN

35 Bacterial Reverse Mutation Test (Ames test)

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Ames test in S. typhimurium (*in vitro*)		NEG_IN	NEG_IN	NEG_IN	INC_OUT
- Direct Acting Mutagens (without S9)	NA	INC_OUT	POS_OUT	INC_OUT	INC_OUT
- Base-Pair Ames Mutagens	NA	NEG_OUT	INC_OUT	INC_OUT	NEG_IN
- Frameshift Ames Mutagens	NA	NEG_IN	NEG_OUT	NEG_IN	NEG_IN
- Potent Ames Mutagens, Reversions ≥ 10 Times Controls	NA	INC_OUT	POS_OUT	POS_IN	NEG_IN

For the four Ames ”submodels” (Direct Acting Mutagens (without S9), Base-Pair Ames Mutagens, Frameshift Ames Mutagens, Potent Ames Mutagens) only use the predictions if the main Ames model (Ames test in S. typhimurium (*in vitro*)) is POS_IN.

36 Other *in vitro* Genotoxicity Endpoints

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Chromosome Aberrations in Chinese Hamster Ovary (CHO) Cells	NA	NEG_IN	INC_OUT	NEG_IN	NEG_IN
Chromosome Aberrations in Chinese Hamster Lung (CHL) Cells		NEG_OUT	NEG_OUT	NEG_IN	NEG_OUT
Mutations in Thymidine Kinase Locus in Mouse Lymphoma Cells		NEG_IN	NEG_IN	NEG_IN	INC_OUT
Mutations in HGPRT Locus in Chinese Hamster Ovary (CHO) Cells		NEG_IN	INC_OUT	NEG_IN	NEG_IN
Unscheduled DNA Synthesis (UDS) in Rat Hepatocytes		NEG_IN	INC_OUT	NEG_IN	NEG_IN
Syrian Hamster Embryo (SHE) Cell Transformation		INC_OUT	INC_OUT	NEG_IN	POS_IN

HGPRT: Hypoxanthine-guanine phosphoribosyltransferase

37 *In vivo* Genotoxicity Endpoints

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Sex-Linked Recessive Lethal (SLRL) Test in Drosophila m.		INC_OUT	NEG_OUT	POS_IN	NEG_IN
Micronucleus Test in Mouse Erythrocytes		NEG_IN	NEG_IN	NEG_IN	INC_OUT
Dominant Lethal Mutations in Rodents		POS_OUT	INC_OUT	INC_OUT	POS_IN
Sister Chromatid Exchange in Mouse Bone Marrow Cells		NEG_IN	INC_OUT	NEG_IN	NEG_IN
Comet Assay in Mouse		POS_IN	POS_IN	NEG_IN	POS_IN

38 Carcinogenicity

	CASE Ultra	Leadscope
FDA RCA Cancer Male Rat	NEG_IN	NEG_IN
FDA RCA Cancer Female Rat	NEG_IN	NEG_IN
FDA RCA Cancer Rat	NEG_IN	NEG_IN
FDA RCA Cancer Male Mouse	NEG_IN	NEG_IN
FDA RCA Cancer Female Mouse	NEG_IN	NEG_IN
FDA RCA Cancer Mouse	NEG_IN	NEG_IN
FDA RCA Cancer Rodent	NEG_IN	NEG_OUT

FDA RCA: Data from US Food and Drug Administration as part of Research Cooperation Agreement

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Liver Specific Cancer in Rat or Mouse		INC_OUT	POS_OUT	NEG_IN	POS_IN

Abbreviations

INC: inconclusive. A definite call within the defined applicability domain could not be made.

NEG: negative

POS: positive

IN: inside applicability domain

OUT: outside applicability domain

Exp: Experimental values, from EpiSuite experimental databases or DK DTU QSAR models training sets.

NA: Not applicable, because training set data cannot be released for commercial models.

Important notes

This is an automatically generated report from the Danish (Q)SAR Database, http://qsar.food.dtu.dk.

For predictions from CASE Ultra, Leadscope, SciQSAR as well as the Acute toxicity in rodent from ACDLabs information on the software versions can be found in the QMRFs. For the other predicted properties the software versions are:

EPI MPBPWIN v1.43

EPI HENRYWIN v3.20

EPI WSKOW v1.42

EPI WATERNT v1.01

EPI KOAWIN v1.10

EPI AEROWIN v1.00

EPI KOCWIN v2.00

EPI Level III Fugacity Model (EPI Suite v4.11)

EPI STPWIN (EPI Suite v4.11)

EPI AOPWIN v1.92

EPI BIOWIN v4.10

EPI BCFBAF v3.01

EPI ECOSAR v1.11

EPI DERMWIN v2.02

ACD/ ToxSuite 2.95.1 Ionization\pKa

ACD/ ToxSuite 2.95.1 Ionization\ LogD

ACD/ ToxSuite 2.95.1

It is recommended to run the latest version of the EPI Suite Programs in preference of the predictions given in this document when these endpoints are of importance and new versions have been released from the United States Environmental Protection Agency in comparisons. EPI Suite can be downloaded from the US EPA homepage: http://www.epa.gov/oppt/exposure/pubs/episuitedl.htm

For further information on the applied systems, see the following homepages:

CASE Ultra: http://www.multicase.com/case-ultra

Leadscope: http://www.leadscope.com/

SciQSAR: http://lhasa-llc.com/

ToxSuite: http://www.acdlabs.com/