Miljøministeriet
Miljøstyrelsen

Fastsættelse af kvalitetskriterier for vandmiljøet

Ketosyre

CAS nr. 70223-33-5

Vandkvalitetskriterium	$VKK_{ferskvand}$	1,95 µg/l
Vandkvalitetskriterium	$VKK_{saltvand}$	0,195 µg/l
Korttidsvandkvalitetskriterium	$KVKK_{ferskvand}$	19,5 µg/l
Korttidsvandkvalitetskriterium	$KVKK_{saltvand}$	0,195 µg/l
Sedimentkvalitetskriterium	$SKK_{ferskvand}$	Ikke relevant
Sedimentkvalitetskriterium	$SKK_{saltvand}$	Ikke relevant
Biota-kvalitetskriterie, sekundær forgiftning	$BKK_{sek.forgiftn.}$	Ikke relevant
Biota-kvalitetskriterie, sundhed	$BKK_{sundhed}$	Ikke relevant

23 November 2021

Indholdsfortegnelse

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 miljøkvalitetskriterie er harmoniseret i EU og baserer sig på vandrammedirektivet (EU, 2000), EU's vejledning til fastsættelse af kvalitetskriterier i vandmiljøet (EU, 2018) 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).

Miljøstyrelsen har haft mulighed for at kommentere et udkast til databladet inden den endelige udgave. Kommentarerne findes her: link

Den sidste litteratursøgning er foretaget den 07-09-2020.

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Faglig kvalitetssikring: John Jensen, Bioscience, Aarhus Universitet

Kvalitetssikring, DCE: Susanne Boutrup

English Summary and conclusions

There is a REACH registration for the compound (1R,3S)-2,2-dimethyl-3-(2-oxopropyl) cyclopropanecarboxylic (https://echa.europa.eu/da/substance-information/-/substanceinfo/100.119.855) the ecotoxicological data from this is used for the assessment. Furthermore, the (Q)SAR profile from the Danish (Q)SAR is also attached (appendix B). The use in Denmark has been registered since 2003 in the SPIN database, but the information is confidential. The use in EU is only as an intermediate according to the REACH registration dossier.

Based on these data sources we discerned the following conclusions in light of the EU Technical Guidance Document (EU, 2018) for (1R,3S)-2,2-dimethyl-3-(2-oxopropyl) cyclopropanecarboxylic acid:

$AA\text{-}QS_{freshwater}$ = 1.95 µg/L

$AA\text{-}QS_{saltwater}$ = 0.195 µg/L

$MAC\text{-}QS_{freshwater}$ = 19.5 µg/L

$MAC\text{-}QS_{saltwater}$ = 0.195 µg/L

$QS_{sediment,\ freshwater}$ = Not relevant

$QS_{sediment,\ saltwater}$ = Not relevant

$QS_{biota,\ secondary\ poisoning}$ = Not relevant

$QS_{biota,\ human\ health}$ = Not relevant

1 Indledning

Identiteten af ketosyre fremgår af tabel 1.1. Det benyttes som intermediate i den kemiske industri. Tonnagen og den direkte anvendelse af ketosyre er fortrolig, og der er ingen data tilgængelig om anvendelsen i Danmark.

Tabel 1.1. Identitet af Ketosyre

IUPAC navn	(1R,3S)-2,2-dimethyl-3-(2-oxopropyl) cyclopropanecarboxylic acid
Strukturformel	
CAS nr.	70223-33-5
EINECS nr.	615-083-4
Kemisk formel	$C_9H_{14}O_3$
SMILES	C(=O)(O)C1C(C)(C)C1CC(C)=O

2 Fysisk kemiske egenskaber

De fysisk kemiske egenskaber for ketosyre fremgår af tabel 2.1.

Tabel 2.1. Fysisk kemiske egenskaber for ketosyre.

Parameter	**Værdi**	**Reference**
Molekylevægt, M_w ($g \cdot mol^{-1}$)	170,21	Danish (QSAR) database, 2020
Smeltepunkt, T_m (°C)	55-55,6	EU REACH Dossier, 2020
Kogepunkt, T_b (°C)	279,1 [1]	Danish (QSAR) database, 2020
Damptryk, P_v (Pa)	0,2506 [1 2]	Danish (QSAR) database, 2020
Henry's konstant, H ($pa \cdot m^3 \cdot mol^{-1}$)	$6,7 \cdot 10^{-10}$ [1]	Danish (QSAR) database, 2020
Vandopløselighed, S_w ($g \cdot L^{-1}$)	17,370 [1]	Danish (QSAR) database, 2020
Dissociationskonstant, pK_a	4,7 [1]	Danish (QSAR) database, 2020
Octanol/vand fordelingskoefficient, log K_{ow}	1,55	EU REACH Dossier, 2020
K_{oc} ($L \cdot kg^{-1}$)	9,115 (log K_{oc} = 0,96) [1]	Danish (QSAR) database, 2020

[1] Estimeret

[2] Ved 20 °C

3 Skæbne i miljøet

3.1 Nedbrydelighed

Der findes ingen hydrolyse nedbrydelighedsdata (fx i e-chem portalen) for ketosyre og det er heller ikke muligt at prædiktere hydrolysen ved hjælp af anerkendte (Q)SAR metoder. Der er ingen eksperimentelle nedbrydelighedsdata for ketosyre. QSAR analysen (Danish Q(SAR) Database, 2020, se bilag B) estimerer ketosyre som værende let bionedbrydelig med varighed fra dage til uger ifølge BIOWIN.

3.2 Bioakkumulering

Der er ingen eksperimentelle data for bioakkumulering af ketosyre (fx i e-chem portalen). (Q)SAR resultaterne viser en BCF = 3,16 L/kg (vådvægt) pba. BIOWIN modellen og en biotransformationstid i fisk på ca. 0,1 dag (bilag B), stoffet forventes ikke at bioakkumlere.

3.3 Naturlig forekomst

Stoffet er ikke naturligt forekommende.

4 Giftighedsdata

4.1 Giftighed over for vandlevende organismer

Der forligger kun tre eksperimentelle studier på giftigheden af ketosyre over for marine organismer, og der er ingen eksperimentelle data for ferskvandslevende organismer. Der er ingen data i US EPA EcoTox databasen og heller ingen data i US EPA OPP økotoksikologi databasen for pesticider. Søgning i SciFinder returnerede ingen fund på kombinationer af: CAS 70223-33-5; toxicity; aquatic toxicity. De to eneste datakilder er EU REACH registreringen opdateret i 2013 (EU REACH registreringen, 2020) med eksperimentelle værdier, samt (Q)SAR værdier (se bilag B). Resultaterne fra de økotoksikologiske studier er samlet i tabel 4.1.

Tabel 4.1. Nominelle akutte effektkoncentrationer for marine arter. arter. Data er fra EU REACH registreringen (2020).

Art / test guideline	**Effekt konc. (mg/L)**	**Eksponeringstid**	**Effektmål**	**Klimish score**
Akut test:				
Pighvar *(Scophthalmus maximus)* (OECD 203)	>500 (LC_{50})	96 t	Overlevelse	1
Invertebrat *(Arcartia tonsa)* (ISO 14669)	62,3 (LC_{50})	48 t	Overlevelse	1
Alge (*Skelotonema costatum)* (ISO 10253)	1,95 (EC_{r50})	72 t	Vækstrate	1
Kronisk test:				
Alge (*Skelotonema costatum)* (ISO 10253)	0,75 (EC_{r10})	72 t	Vækstrate	1

Nedenfor er de estimerede værdier fra den danske QSAR database:

Exp	Battery	Leadscope	SciQSAR
Fathead minnow 96h LC50 (mg/L)	547.5143	548.1572	546.8713
Domain	IN	IN	IN
Daphnia magna 48h EC50 (mg/L)	177.5191	275.2232	79.81509
Domain	IN	IN	IN
Pseudokirchneriella s. 72h EC50 (mg/L)	222.8677	211.5364	234.1991
Domain	IN	IN	IN

DTU-developed models

	Fish 96h	Daphnid 48h	Green Algae 96h
LC50 (Fish) or EC50 (Daphnid and Algae) for Most Toxic Class (mg/L)	8912.786	4659.034	2465.408
Max. Log Kow for Most Toxic Class	5	5	6.4
Most Toxic Class	Neutral Organics-acid	Neutral Organics-acid	Neutral Organics-acid
Note			

EPI ECOSAR models

ECOSAR Classes:

4.2 Giftighed over for sedimentlevende organismer

Der findes ikke giftighedsdata for sedimentlevende organismer i EU REACH Dossier (2020) eller i den videnskabelige litteratur (SciFinder) for stoffet.

4.3 Giftighed over for pattedyr

Der er kun et resultat angående giftighed over for pattedyr nemlig et akut (oralt) rotteforsøg, hvor den akutte LD_{50} for rotter er >2000 mg/kg lgv/dag (EU REACH Dossier, 2020). (Q)SAR analyserne støtter generelt det eksperimentelle fund med hensyn til lav giftighed over for pattedyr (se tabel nedenfor og bilag B).

	LD50 (mg/kg/d)	Reliability Index
Rat Oral	660	0.38
Rat Intraperitoneal	150	0.56
Mouse Oral	760	0.35
Mouse Intraperitoneal	84.3	0.24
Mouse Intravenous	140	0.63
Mouse Subcutaneous	4000	0.51

ACDLabs models

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.

Der er ikke fundet eksperimentelle data for giftigheden af ketosyre over for fugle.

4.4 Giftighed over for mennesker

Der er ikke rapporteret nogen grænseværdier (DNEL, ADI, TDI eller RfD) for ketosyre for mennesker. QSAR-analyserne indikere ikke en maksimal acceptabel daglig dosis på ≤ 2,69 mg/kg lgv /dag for mennesker (se nedenfor og bilag B).

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

DTU-developed models

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.

5 Andre effekter

Ketosyre er selvklassificeret som Aquatic Chronic 2; H411 (Giftig for vandlevende organismer med langtidseffekter) og Skin Corr. 1C; H314 (Alvorlig forbrændinger og skader ved øjne).

6 Udledning af vandkvalitetskriterium

6.1 Vandkvalitetskriterium (VKK)

Af tabel 4.1 fremgår det, at der findes fire data for tre akutte effekter (EC_{50}) af ketosyre for tre marine arter (alge, invertebrat og fisk) og et kronisk alge studie altså dækkende i alt tre trofiske (alge, invertebrat og fisk) niveauer. Der er ingen eksperimentelle værdier for ferskvandsarter. Der skal være kroniske effektværdier fra andre trofiske niveauer end kun alger før VKK kan fastsættes på baggrund af kronisk data. Derfor anvendes den laveste akutte effektværdi til udregning af VKK. Algen, *Skelotonema costatum*, er den mest følsomme art i testsættet med en akut effektværdi på 1,95 mg/L. Der benyttes en assessment factor (AF), eller usikkerhedsfaktor, på 1000 i henhold til EU TGD på alge giftighedsværdien (EU TGD 2018, tabel 3).. VKK i ferskvand beregnes derfor som følgende:

$VKK_{ferskvand}$ = 1,95 mg/L / 1000= 0,00195 mg/L = 1,95 µg/L

$VKK_{saltvand}$ beregnes ved brug af en yderligere AF på 10 (da der ikke findes langtidsstudier for invertebrater eller fisk (tabel 4 i EU TGD#27, 2018) i forhold til ferskvandskriteriet, for at kompensere for de få data selvom disse er for saltvandsarter som et konservativt tiltag for at omfatte den typisk øgede følsomhed for visse saltvandsarter relativt til ferskvandsarter. $VKK_{saltvand}$ beregnes derfor som:

$VKK_{saltvand}$= 1,95 mg/L / 10.000 = 0,000195 mg/L = 0,195 µg/L

6.2 Korttidsvandkvalitetskriterium (KVKK)

For korttidsvandkvalitetskriterierne, KVKK, benyttes den eksperimentelle EC_{50} på 1,95 mg/L for akutte effekter på marine alge som udgangspunkt. Da standardafvigelsen på de log_{10} konverterede akutte toksicitetsdata er 1,09 og dermed større end 0,5 og da vi ikke kender den toksikologiske virkningsmekanisme (mode of action (MoA)), anvendes en AF på 100 ifølge TGD#27, tabel 5. Korttidsvandkvalitetskriterierne udledes derfor til:

$KVKK_{ferskvand}$ = 1,95 mg/L / 100 = 0,0195 mg/L = 19,5 µg/L

$KVKK_{saltvand}$ udledes ved brug af en AF på 1000 (EU, 2018, tabel 6), og derfor bliver $KVKK_{saltvand}$ således:

$KVKK_{saltvand}$ = 1,95 mg/L / 1000= 0,195 µg/L

6.3 Kvalitetskriterium for sediment (SKK)

Da log K_{oc} er mindre end 3 for ketosyre (log K_{oc} = 0,96) skal der i overensstemmelse med TGD#27 (afsnit 2.4.2 EU, 2018) ikke beregnes et SKK for ketosyre.

6.4 Kvalitetskriterium for biota (BKK)

Ketosyre har en log K_{ow} på 1,55 (tabel 2.1) og en BCF værdi på 3,16 L/kg (vådvægt). Det er ikke relevant at fastsætte et biotakvalitetskriterium, der beskytter mod sekundær forgiftning, da ketosyre ikke opfylder kriteriet (log $K_{ow} \geq 3$ eller BCF ≥ 100) ifølge TGD#27 (afsnit 2.4.3.1).

6.5 Kvalitetskriterium for human konsum af vandlevende organismer (HKK)

Ketosyre er ikke klassificeret som kræftfremkaldende, mutagent eller reproduktionstoksisk, og er heller ikke bioakkumulerende (BCF < 100 og log K_{ow} < 3). Derved opfylder stoffet ikke kriteriet for udledning af HKK ifølge TGD#27 (afsnit 2.4.3.2).

7 Konklusion

Der er fundet følgende relevante miljøkvalitetskriterier for ketosyre baseret på data fra REACH registreringsdossieret (EU REACH dossier, 2020), QSAR analyse og metoder i TGD#27, 2018:

$VKK_{ferskvand}$ = 1,95 µg/L

$VKK_{saltvand}$ = 0,195 µg/L

$KVKK_{ferskvand}$ = 19,5 µg/L

$KVKK_{saltvand}$ = 0,195 µg/L

SKK: Ikke relevant

$BKK_{sek.\ forgitn}$: Ikke relevant

$BKK_{sundhed}$: Ikke relevant

Sediment- og biotakvalitetskriterierne er ikke opfyldt og derfor ikke relevante for ketosyre.

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 (2018). Common Implementation Strategy for the Water Framework Directive (2000/60/EC). Guidance Document No. 27. Technical Guidance Document for Deriving Environmental Quality Standards.

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

EU REACH dossier (2020). Ketosyre: https://echa.europa.eu/da/substance-information/-/substanceinfo/100.119.855

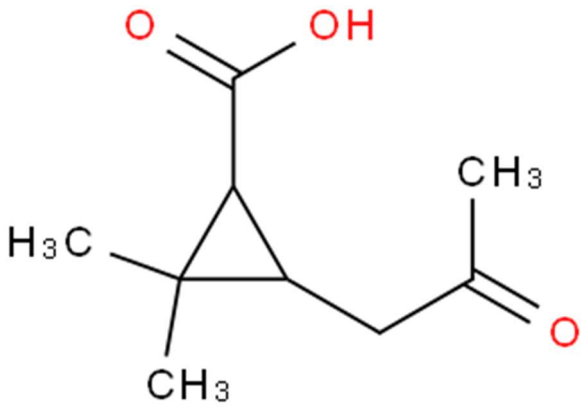
9 Bilag A. Kvalitetsevaluering af data i EU REACH Dossieret

Der er ikke adgang til rå-data bag data i EU dossieret som indeholder begrænsede testdetaljer, og derfor er en dybdegående analyse ikke mulig. Det kan dog konstateres at der er brugt nominelle koncentrationer og ikke målte værdier. De anvendte data har alle Klimisch score 1 (acceptable uden restriktioner) og er opdateret i 2013. Det er derfor ikke muligt at foretage yderligere kvalitetsevaluering af data. På grund af de få tilgængelige data er derfor også vedlagt ketosyres profil baseret på analyse i den danske (Q)SAR database (bilag B).

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

(Q)SAR predicted profile

10.1 Structure (as used for QSAR prediction):



SMILES (used for QSAR prediction): C(=O)(O)C1C(C)(C)C1CC(C)=O

10.2 ID

REACH EC Number (pre-registration, by 2013)	615-083-4	REACH EC Number (registration, by Dec. 2019)	615-083-4
Registry Number	70223-33-5	PubChem CID	
EU CLP Harmonized Classification*		DK-EPA / DTU QSAR-based CLP Advisory Classification	
REACH registration cumulated minimum annual tonnage			
Molecular Formula	C9 H14 O3	Molecular weight (g/mole)	170.21
Chemical Name			

(Annex VI to CLP up to and including the 9th ATP, and including Nordic Council of Minister SPIN list for group entries)

10.3 Melting point, Boiling point and Vapour pressure

Melting Point (deg C)	77.42	Melting Point Experimental (deg C)	
Boiling Point (deg C)	279.01	Boiling Point Experimental (deg C)	
Vapour Pressure (atm)	EPI.Estimated_VP_atm	Vapour Pressure Experimental (atm)	EPI.Exp_VP_atm
Vapour Pressure (mm Hg)	0.00188	Vapour Pressure Experimental (mm Hg)	
Vapour Pressure (Pa)	0.2506	Vapour pressure Subcooled Liquid (Pa)	0.787

EPI MPBPVP models

10.4 Henry's Law Constant

HLC Bond Method (atm-m3/mole)	6.7E-010	HLC Group Method (atm-m3/mole)	5.603E-011
HLC Via VP/WSol (atm-m3/mole)	2.424E-008	HLC Via VP/WSol (Pa-m3/mole)	0.002456
Henrys Law Const. Exp db (Pa-m3/mole)		Henrys Law Const. Exp db (atm-m3/mole)	

EPI HENRYWIN models

10.5 Water Solubility

Water solubility from Kow (mg/L)	17370	Water solubility from Fragments (mg/L)	38232
Water solubility Exp (mg/L)		Water solubility Exp Ref	

EPI WATERNT model

10.6 Hydrolysis

Hydrolysis Ka half-life pH 7		Hydrolysis Kb half-life pH 7	
Hydrolysis Ka half-life pH 8		Hydrolysis Kb half-life pH 8	

EPI HYDROWIN model

10.7 pKa

pKa Acid	4.7
- Standard deviation (±)	0.4
pKa Base	-999
- Standard deviation (±)	0

ACDLabs model

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

10.8 Partition coefficients

pH	1	4	5	6	7	8	9
LogD	1.67	1.6	1.22	0.39	-0.58	-1.53	

ACDLabs models

LogD: Log octanol-water partition coefficient, which for ionizable compounds varies with the pH-dependent amounts of neutral and ionized species

Log Koa	8.662	Log Kaw	-7.562

EPI KOAWIN models

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

Log Kow	1.1		
Log Kow Exp		Log Kow Exp Ref	

EPI WSKOW model

LogKow: log octanol-water partition coefficient

Kp (m3/ug) Mackay-based	3.81E-006	Kp (m3/ug) Koa-based	0.000113
Phi Junge-Pankow-based	0.000137	Phi Mackay-based	0.000304
Phi Koa-based	0.00894		

EPI AEROWIN models

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

Koc from MCI (L/kg)	10	Log Koc from MCI	0.6452
Koc from Kow (L/kg)	9.115	Log Koc from Kow	0.9598

EPI KOCWIN models

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

10.9 Level III Fugacity Environmental Partitioning, emission to air, water and soil

	Air	Water	Soil	Sediment
Mass Amount (%)	0.00119	30.6	69.4	0.0688
Half-Life (hr)	123	360	720	3240
Emissions (kg/hr)	1000	1000	1000	0

EPI Level III Fugacity Model

Persistence time (hr)	640
Persistence time (days)	

EPI Level III Fugacity Model

10.10 Level III Fugacity Environmental Partitioning, emission only to water

	Air	Water	Soil	Sediment
Mass Amount (%)	1.31E-009	99.8	3.61E-005	0.225
Half-Life (hr)	123	360	720	3240
Emissions (kg/hr)	0	1000	0	0

EPI Level III Fugacity Model

Persistence time (hr)	343
Persistence time (days)	14.29167

EPI Level III Fugacity Model

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

	Total removal	Biodegradation	Sludge Adsorption	Volatilization
(%)	1.9	0.09	1.8	0

EPI STPWIN model

10.12 Atmospheric oxidation (25 deg C)

	OH	Ozone
Half-Life (d)	5.115	0
Half-Life (hr)	61.379	
Overall Rate Const. (OH: E-12 cm3/molecule-sec and OZ: E-17 cm3/molecule-sec)	2.0911	

EPI AOPWIN models

10.13 Biodegradation

Biowin1 (linear model) Probability of Rapid Biodegradation	0.5621
Biowin2 (non-linear model) Probability of Rapid Biodegradation	0.2806
Biowin3 Expert Survey Ultimate Biodegradation	2.953
Biowin3 Expert Survey Ultimate Timeframe	weeks
Biowin4 Expert Survey Primary Biodegradation	3.8121
Biowin4 Exp. Survey Primary Timeframe	days
Biowin5 (MITI linear model) Biodegradation Probability	0.6478
Biowin6 (MITI non-linear model) Biodegradation Probability	0.5518
Biowin7 (Anaerobic Linear) Biodegradation Probability	0.1629
Petroleum Hydrocarbon Biodegradation Half-Life (days)	

EPI BIOWIN models

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"

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Not Ready Biodegradability (POS=Not Ready)		NEG_IN	INC_OUT	NEG_IN	NEG_IN

DTU-developed models

10.14 Bioaccumulation

BCF (L/kg wet-wt)	3.162
Log BCF (L/kg wet-wt)	0.5
Whole Body Primary Biotransformation Fish Half-Life (days)	0.1128
BCF Arnot-Gobas (upper trophic) Including Biotransformation (L/kg wet-wt)	1.981
BCF Arnot-Gobas (upper trophic) Zero Biotransformation (L/kg wet-wt)	2.253
BAF Arnot-Gobas (upper trophic) Including Biotransformation (L/kg wet-wt)	1.981
BAF Arnot-Gobas (upper trophic) Zero Biotransformation (L/kg wet-wt)	2.272

EPI BCFBAF models

BCF: Bioconcentration factor, BAF: Bioaccumulation factor

10.15 Aquatic toxicity

Exp	Battery	Leadscope	SciQSAR
Fathead minnow 96h LC50 (mg/L)	547.5143	548.1572	546.8713
Domain	IN	IN	IN
Daphnia magna 48h EC50 (mg/L)	177.5191	275.2232	79.81509
Domain	IN	IN	IN
Pseudokirchneriella s. 72h EC50 (mg/L)	222.8677	211.5364	234.1991
Domain	IN	IN	IN

DTU-developed models

	Fish 96h	Daphnid 48h	Green Algae 96h
LC50 (Fish) or EC50 (Daphnid and Algae) for Most Toxic Class (mg/L)	8912.786	4659.034	2465.408
Max. Log Kow for Most Toxic Class	5	5	6.4
Most Toxic Class	Neutral Organics-acid	Neutral Organics-acid	Neutral Organics-acid
Note			

EPI ECOSAR models

ECOSAR Classes:

10.16 Oral absorption

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

Leadscope model on Lipinski's Rule-of-five. Equation from literature on GI abs.

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

10.17 Skin absorption

Dermal absorption (mg/cm2/event)

EPI DERMWIN model

10.18 Brain/blood Distribution

Log brain/blood partition coefficient	

Equation from literature

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

10.19 Metabolism

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

DTU-developed models

10.20 Acute toxicity in Rodents

	LD50 (mg/kg/d)	Reliability Index
Rat Oral	660	0.38
Rat Intraperitoneal	150	0.56
Mouse Oral	760	0.35
Mouse Intraperitoneal	84.3	0.24
Mouse Intravenous	140	0.63
Mouse Subcutaneous	4000	0.51

ACDLabs models

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.

10.21 MRDD in Humans

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

DTU-developed models

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.

10.22 Irritation and Sensitization

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

DTU-developed models

**Based on commercial training set*

Protein binding by OASIS, alerts in:	
- parent only	No alert found
- metabolites from skin metabolism simulator only	
- metabolites from auto-oxidation simulator only	
Protein binding by OECD, alerts in:	
- parent only	No alert found
- metabolites from skin metabolism simulator only	
- metabolites from auto-oxidation simulator only	
Protein binding potency Cys (DRPA 13%), alerts in:	
- parent only	DPRA less than 9% (DPRA 13%) >> Non-Conjugated carboxylic acids and esters (non reactive)
- metabolites from skin metabolism simulator only	
- metabolites from auto-oxidation simulator only	
Protein binding potency Lys (DRPA 13%), alerts in:	
- parent only	DPRA less than 9% (DPRA 13%) >> Non-Conjugated carboxylic acids and esters (non reactive)
- metabolites from skin metabolism simulator only	
- metabolites from auto-oxidation simulator only	
Keratinocyte gene expression, alerts in:	
- parent only	Not possible to classify according to these rules
- metabolites from skin metabolism simulator only	
- metabolites from auto-oxidation simulator only	
Protein binding potency GSH, alerts in:	
- parent only	

OECD QSAR Toolbox v.4.1 profilers

Profiler predictions are supporting information to be used together with the relevant QSAR predictions

10.23 Endocrine and Molecular Endpoints

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Estrogen Receptor α Binding, Full training set (Human *in vitro*)		NEG_IN	NEG_OUT	NEG_IN	NEG_IN
Estrogen Receptor α Binding, Balanced Training Set (Human *in vitro*)		NEG_IN	NEG_OUT	NEG_IN	NEG_IN
Estrogen Receptor α Activation (Human *in vitro*)		NEG_IN	NEG_OUT	NEG_IN	NEG_IN
Estrogen Receptor Activation, CERAPP data (*in vitro*)		N/A	N/A	NEG_IN	N/A
Androgen Receptor Inhibition (Human *in vitro*)		NEG_IN	NEG_OUT	NEG_IN	NEG_IN
Androgen Receptor Binding, CoMPARA data (*in vitro*)		N/A	N/A	NEG_IN	N/A
Androgen Receptor Inhibition, CoMPARA data (*in vitro*)		N/A	N/A	NEG_IN	N/A
Androgen Receptor Activation, CoMPARA data (*in vitro*)		N/A	N/A	NEG_IN	N/A
Thyroperoxidase (TPO) inhibition QSAR1 (Rat *in vitro*)		N/A	N/A	NEG_IN	N/A
Thyroperoxidase (TPO) inhibition QSAR2 (Rat *in vitro*)		N/A	N/A	NEG_IN	N/A
Thyroid Receptor α Binding (Human *in vitro*)					
- mg/L			27226.08	1525.686	
- μM			159955.8	8963.551	
- Positive for IC_{50} ≤ 10 μM					
- Positive for IC_{50} ≤ 100 μM					
- Domain		OUT	OUT	OUT	OUT
Thyroid Receptor β Binding (Human *in vitro*)					
- mg/L			5507.891	193.2391	
- μM			32359.38	1135.298	
- Positive for IC_{50} ≤ 10 μM					
- Positive for IC_{50} ≤ 100 μM					
- Domain		OUT	OUT	OUT	OUT
Arylhydrocarbon (AhR) Activation – Rational final model (Human *in vitro*)		N/A	N/A	NEG_IN	N/A
Arylhydrocarbon (AhR) Activation – Random final model (Human *in vitro*)		N/A	N/A	NEG_IN	N/A
Pregnane X Receptor (PXR) Binding (Human *in vitro*)	N/A	NEG_IN	POS_OUT	NEG_IN	NEG_IN
Pregnane X Receptor (PXR) Binding (Human *in vitro*) NEW		N/A	N/A	NEG_IN	N/A
Pregnane X Receptor (PXR) Activation (Human *in vitro*)		N/A	N/A	NEG_IN	N/A

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Pregnane X Receptor (PXR) Activation (Rat *in vitro*)		N/A	N/A	NEG_IN	N/A
Constitutive Androstane Receptor (CAR) Activation at max. 20 µM (*in vitro*)		N/A	N/A	NEG_IN	N/A
Constitutive Androstane Receptor (CAR) Activation at max. 50 µM (*in vitro*)		N/A	N/A	NEG_IN	N/A
Constitutive Androstane Receptor (CAR) Inhibition at max. 20 µM (*in vitro*)		N/A	N/A	NEG_IN	N/A
Constitutive Androstane Receptor (CAR) Inhibition at max. 50 µM (*in vitro*)		N/A	N/A	NEG_IN	N/A

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
CYP3A4 Induction (Human *in vitro*)		N/A	N/A	NEG_IN	N/A

DTU-developed models

Estrogen Receptor Binding, alerts in:	
- parent only	Non binder, without OH or NH2 group
- metabolites from *in vivo* Rat metabolism simulator only	Non binder, without OH or NH2 group
- metabolites from Rat liver S9 metabolism simulator only	Non binder, without OH or NH2 group
rtER Expert System - USEPA, alerts in:	
- parent only	No alert found
- metabolites from *in vivo* Rat metabolism simulator only	No alert found
- metabolites from Rat liver S9 metabolism simulator only	No alert found

OECD QSAR Toolbox v.4.2 profilers

Profiler predictions are supporting information to be used together with the relevant QSAR predictions

10.24 Developmental Toxicity

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

DTU-developed models based on commercial training set

10.25 Genotoxicity - Structural Alerts for DNA Reactivity

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

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DNA binding by OASIS, alerts in:
- parent only
DNA binding by OECD, alerts in:
- parent only

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Profiler predictions are supporting information to be used together with the relevant QSAR predictions

10.26 *In vitro* Genotoxicity - Bacterial Reverse Mutation Test (Ames test)

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

DTU-developed models

* The four models (Direct Acting mutagens (without S9), Base-Pair Ames Mutagens, Frameshift Ames Mutagens, Potent Ames Mutagens) should not be used to determine if substances are Ames mutagens, but can be used for indication of mechanism or potency for cases where the main Ames model (Ames test in S. typhimurium (*in vitro*)) is POS_IN.

DNA alerts for AMES by OASIS, alerts in:
- parent only
In vitro mutagenicity (Ames test) alerts by ISS, alerts in:
- parent only
OECD QSAR Toolbox v.4.2 profilers
Profiler predictions are supporting information to be used together with the relevant QSAR predictions

10.27 Other *in vitro* Genotoxicity Endpoints

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

DTU-developed models
**Based on commercial training set*

HGPRT: Hypoxanthine-guanine phosphoribosyltransferase

DNA alerts for CA and MNT by OASIS, alerts in:
- parent only
Protein binding alerts for Chromosomal aberration by OASIS, alerts in:
- parent only
OECD QSAR Toolbox v.4.2 profilers
CA: Chromosomal aberration, MNT: Micronucleus test *Profiler predictions are supporting information to be used together with the relevant QSAR predictions*

10.28 *In vivo* Genotoxicity Endpoints

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

DTU-developed models

In vivo mutagenicity (Micronucleus) alerts by ISS, alerts in:
- parent only

OECD QSAR Toolbox v.4.2 profilers

Profiler predictions are supporting information to be used together with the relevant QSAR predictions

10.29 Carcinogenicity

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

Commercial models from CASE Ultra and Leadscope

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

Carcinogenicity (genotox and nongenotox) alerts by ISS, alerts in:
- parent only
Oncologic Primary Classification, alerts in:
- parent only

OECD QSAR Toolbox v.4.2 profilers

Profiler predictions are supporting information to be used together with the relevant QSAR predictions

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

DTU-developed models