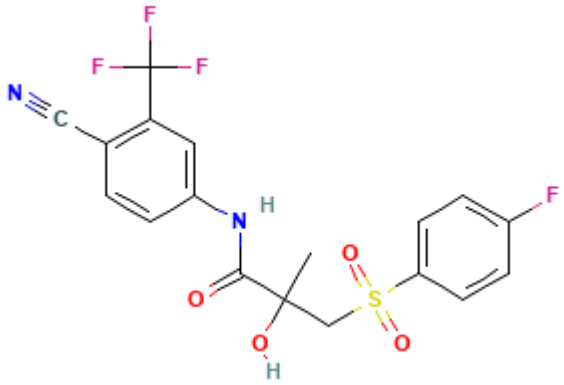
Miljø- og
Ligestillingsministeriet
Miljøstyrelsen

Fastsættelse af kvalitetskriterier for vandmiljøet

Bicalutamid

CAS nr. 90357-06-5



Vandkvalitetskriterium	$VKK_{ferskvand}$	0,092 µg/l
Vandkvalitetskriterium	$VKK_{saltvand}$	0,0092 µg/l
Korttidsvandkvalitetskriterium	$KVKK_{ferskvand}$	Ikke muligt
Korttidsvandkvalitetskriterium	$KVKK_{saltvand}$	Ikke muligt
Sedimentkvalitetskriterium	$SKK_{ferskvand}$	Ikke relevant
Sedimentkvalitetskriterium	$SKK_{saltvand}$	Ikke relevant
Biota-kvalitetskriterium, sekundær forgiftning	$BKK_{sek.forgiftn.}$	Ikke relevant
Biota-kvalitetskriterium, human konsum	HKK	Ikke muligt

Marts 2025

Indholdsfortegnelse

Forord

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

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

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, 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).

Den sidste litteratursøgning er foretaget den 15. juli 2024.

English Summary and conclusions

Derivation of environmental quality standards (EQS) for the aquatic environment is following the EU Guidance Document No. 27. Technical Guidance Document (TGD) for Deriving Environmental Quality Standards (EU, 2018).

AA-EQS for water
Only one chronic reliable study has been found for aquatic organisms. The lowest NOEC is 0.0092 mg/l for the freshwater fish Fathead minnow (*Pimephales promelas*).

Following TGD (2018, table 3) a QS for freshwater can be determined with an assessment factor of 100 when only one long-term result from either fish or crustacean are available. However, the result must be from the trophic level, which also represents the lowest short-term result. This is not the case (using QSAR data as supplementary data), but since the only reliable long-term data is also lower than the lowest supplementary acute (and chronic) data, an assessment factor of 100 for freshwater has been chosen. For saltwater an extra factor of 10 is used (TGD, 2018, table 4) resulting in the following QS values:

$\mathbf{QS_{freshwater}}$ = 0.0092 mg/l / 100 = 0.000092 mg/l = 0.092 µg/l

$\mathbf{QS_{saltwater}}$ = 0.0092 mg/l / 1000 = 0.0000092 mg/l = 0.0092 µg/l

MAC-EQS for water
No reliable acute toxicity data is available for bicalutamide. Therefore, a MAC-EQS was not derived.

QS for sediment
The criteria for setting a QS for sediment is not fulfilled since log K_{ow} and K_{oc} < 3, and no other evidence has been found, that suggest a potential for high toxicity to sediment dwelling organisms.

QS for secondary poisoning
The criteria for setting a QS for secondary poisoning is not fulfilled since log K_{ow} < 3 and BCF (and BAF) < 100, and no other evidence has been found, that suggest a potential for secondary poisoning of bicalutamid.

QS for human health
Bicalutamide has no harmonized classifications. A number of companies have registered the substance with the following self-classifications; suspected of being carcinogenic (Carc. 2, H531 – 14 companies) and being able to harm reproduction and the unborn child (Repr. 1A or 1B, H360 –

11 and 4 companies). Both classifications triggers derivation of a QS for human health following TGD (EU, 2018). However, no data have been found that can be used in the derivation, and therefore a QS for human health has not been derived.

QS_{water} based on $QS_{sec.\ pois.}$ and $QS_{human\ health}$

Since no QS for secondary poisoning or human health has been determined no QS_{water} is calculated.

In conclusion, the following EQS for the aquatic environment have been derived for bicalutamide:

AA-$EQS_{freshwater}$	= 0.092 µg/l
AA-$EQS_{saltwater}$	= 0.0092 µg/l
MAC-$EQS_{freshwater}$	Not possible
MAC-$EQS_{saltwater}$	Not Possible
$QS_{sediment,\ freshwater}$	Not relevant
$QS_{sediment,\ saltwater}$	Not relevant
$QS_{sec.\ pois.}$	Not relevant
$QS_{human\ health}$	Not possible

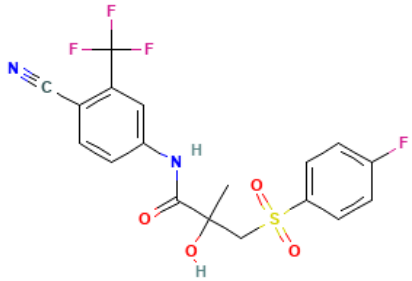
1 Indledning

Identiteten af bicalutamid fremgår af tabel 1.1.

Bicalutamid er et anti-androgen lægemiddel, som hæmmer virkningen af det mandlige kønshormon testosteron, og anvendes i behandlingen af prostatacancer (rigshospitalet.dk; produktresume.dk).

Stoffet forhandles også under navnet Casodex.

Tabel 1.1. Identitet af bicalutamid

IUPAC navn	N-[4-cyano-3-(trifluoromethyl)phenyl]-3-(4-fluorophenyl)sulfonyl-2-hydroxy-2-methylpropanamide
Strukturformel	
CAS nr.	90357-06-5
EINECS nr.	618-534-3
Kemisk formel	$C_{18}H_{14}F_4N_2O_4S$
SMILES	CC(CS(=O)(=O)C1=CC=C(C=C1)F)(C(=O)NC2=CC(=C(C=C2)C#N)C(F)(F)F)O
Harmoniseret klassificering	Bicalutamid har ikke nogen harmoniserede klassificeringer.
Selvklassificering ECHA (2023), C&L Inventory	<u>Rangeret efter antal virksomheder (angivet i parentes)[1]:</u> Skin Irrit. 2, H315 (Forårsager hudirritation) (122) Eye Irrir. 2, H319 (Forårsager alvorlig øjenirritation) (121) STOT SE 3, H335 (Kan forårsage irritation af luftveje) (121) Carc. 2, H351 (Mistænkt for at fremkalde kræft) (14) Repr. 1B, H360 (Kan skade forplantningsevnen eller det ufødte barn) (11) Aquatic Chronic 1, H410 (Meget giftig for vandlevende organismer med langvarige effekter) (8) STOT RE 1, H372 (Forårsager organskader ved længerevarende eller gentagen eksponering) (6) Repr. 1A, H360 (Kan skade forplantningsevnen eller det ufødte barn) (4) Aquatic Chronic 2, H411 (Giftig for vandlevende organismer med langvarige effekter) (3)

[1]Selvklassificeringer, som kun er angivet at en enkelt virksomhed, er ikke listet i tabellen.

2 Fysisk kemiske egenskaber

De fysisk kemiske egenskaber for bicalutamid fremgår af tabel 2.1.

Tabel 2.1. Fysisk kemiske egenskaber for bicalutamid

Parameter	**Værdi**	**Reference**
Molekylevægt, M_w ($g \cdot mol^{-1}$)	430,5	Pubchem
Smeltepunkt, T_m (ºC)	243,3 [a]	Dansk (Q)SAR Database (bilag B)
Kogepunkt, T_b (ºC)	565,72 [a]	Dansk (Q)SAR Database (bilag B)
Damptryk, P_v (Pa)	$1{,}005 \times 10^{-12}$ [a]	Dansk (Q)SAR Database (bilag B)
Henry's konstant, H ($Pa \cdot m^3 \cdot mol^{-1}$)	$3{,}682 \times 10^{-11}$ [a]	Dansk (Q)SAR Database (bilag B)
Vandopløselighed, S_w ($mg \cdot L^{-1}$)	2,77 [b] 11,75 [a,c]	AstraZenica, 2023 Dansk (Q)SAR Database (bilag B)
Dissociationskonstant, pK_a	>12 11 [b]	AstraZenica, 2023 Dansk (Q)SAR Database (bilag B)
Octanol/vand fordelingskoefficient, log K_{ow}	2,54 2,3 [a]	AstraZenica, 2023 Dansk (Q)SAR Database (bilag B)
Sediment/vand fordelingskoefficient, normaliseret til organisk karbon, K_{oc} ($L \cdot kg^{-1}$)	459,4 [d] 150,1 [c]	Dansk (Q)SAR Database (bilag B)

[a] Estimeret værdi
[b] ved pH 7
[c] beregnet ud fra K_{ow}
[d] beregnet ud fra MIC (first order Molecular Connectivity Index)

3 Skæbne i miljøet

3.1 Nedbrydelighed

Der er ikke fundet eksperimentelle data for nedbrydning af bicalutamid i miljøet.

BIOWIN modeller fra den Danske (Q)SAR Database (bilag B) estimerer generelt en langsom bionedbrydning for bicalutamid i miljøet, betydende at stoffet anses som værende ikke let bionedbrydeligt, hvilket også er den samme konklusion AstraZenica (2023) kommer frem til ud fra et vand-sediment transformeringsstudie, hvor halveringstiden blev bestemt til mellem 39 og 69 dage.

I en rapport fra 2021 udarbejdet af den tyske miljømyndighed (Umweltbundesamt, 2021) fremhæves en række stoffer, herunder bicalutamid, som værende potentielle kilder til trifluoreddikesyre (TFA) i miljøet. Helt generelt nævnes i rapporten at alle stoffer, som indeholder en C-CF_3 gruppe (se strukturformel for bicalutamid i tabel 1.1) potentielt kan være precursor til TFA.

3.2 Bioakkumulering

Der er ikke fundet eksperimentelle data for bioakkumulering af bicalutamid.

BCFBAF modeller fra den Danske (Q)SAR Database (bilag B) estimerer biokoncentrationsfaktorer (BCF) fra 15,23 til 22,08 l/kg og bioakkumuleringsfaktorer (BAF) i samme niveau med værdier fra 18,19 til 22,88 l/kg.

Ud fra det estimerede data vil bicalutamid have et lavt potentiale for at bioakkumulere.

3.3 Naturlig forekomst

Bicalutamid forekommer ikke naturligt i miljøet.

Cytostatiske stoffer, eller lægemidler mod kræft, så som bicalutamid, bliver generelt ikke metaboliseret i en særlig grad i kroppen og vil derfor blive udskilt via fæces eller urin enten i uændret form eller som metabolitter (Li et al., 2021; Gouveia, et al. 2019). Stofferne bliver herfra ledt med spildevandet fra hospitaler og private hjem, samt fra medicinske fabrikker, til renseanlæg. Mange af lægemidlerne mod kræft er genstridige, persistente eller pseudo-persistente organiske stoffer og bliver ofte ikke fjernet i behandlingen af spildevandet på renseanlæggene, hvorfor de i sidste ende vil være at finde i det akvatiske miljø (Li et al., 2021; Gouveia, et al. 2019).

4 Toksicitetsdata

Troværdigheden af studierne er vurderet ved tildelingen af en CRED (Criteria for Reporting and Evaluating Ecotoxicity Data) score fra 1 til 4 (Moermond et al., 2016). Score 1 angiver, at studiet kan anvendes uden forbehold, mens score 2 angiver at studiet kan anvendes med forbehold, f.eks. at der er tilstrækkelige oplysninger, selvom studiet ikke er udført i forhold til guideline. Studier som ikke er tilstrækkeligt beskrevet tildeles score 3 eller 4, hvor score 4 tildeles studier, hvor det ikke er muligt at vurdere kvaliteten og dermed troværdigheden. Estimeret data ved QSAR angives ligeledes en score 4, men data herfra kan anvendes supplerende.

4.1 Toksicitet over for vandlevende organismer

For bicalutamid er der begrænset data tilgængelig for vandlevende organismer. Der er fundet et studie af Panter et al. (2012), som har undersøgt effekterne af bicalutamid i et reduceret livscyklus studie med ferskvandsfisken Tykhovedet elritse (*Pimephales promelas*). Studiet anvendte testkoncentrationer fra 0,01 til 100 µg/l med en faktor 10 mellem koncentrationerne. Fire måneder gamle fisk (generation F0) blev parret op (8 par per testkoncentration), og derefter eksponeret til bicalutamid. Afkom (generation F1) fra minimum to hunner per testkoncentration blev efterfølgende inkuberet og heraf blev fire hunner og to hanner overført til en gydetank 84 dage efter klækning (to replikater per testkoncentration). Endpoints som overlevelse, udvikling, morfologi, reproduktion og vækst blev observeret. For generation F0 blev der generelt ikke observeret nogen effekter ved højeste testkoncentration, hvorfor NOEC er angivet til 0,092 mg/l (målt). For nogle endpoints (overlevelse og reproduktion) ved generation F1 blev der observeret en effekt ved højeste testkoncentration, hvorfor NOEC er angivet til 0,0092 mg/l (målt). Studiet har fået tildelt en troværdighedsscore på 2.

Derudover er der i en risikovurdering foretaget af medicinalvirksomheden AstraZenica (AstraZenica, 2023) angivet kronisk data for alger (NOEC = 1,1 mg/l) og krebsdyr (NOEC = 0,56 mg/l) og akut data for fisk (LC_{50} > 4,4 mg/l). Dog er studierapporterne ikke tilgængelige, hvorfor data herfra er angivet med en troværdighedsscore på 4.

Med et begrænset eksperimentel datasæt kan der suppleres med QSAR data. Den Danske (Q)SAR Database (bilag B) estimerer akutte data for alger (EC_{50} = 5,88 mg/l), krebsdyr (EC_{50} = 0,34 mg/l) og fisk (LC_{50} = 1,81 mg/l), samt kronisk data for krebsdyr (NOEC = 1,21 mg/l), men der bør tages højde for at det estimerede data ligger uden for domain. (Q)SAR data er også tildelt en troværdighedsscore på 4.

Der er ikke fundet data for saltvandslevende organismer.

Med det meget begrænsede datasæt kan der ikke siges noget endeligt om, hvilket taksonomisk niveau, der forventes at være mest følsomt over for eksponering til bicalutamid, dog findes laveste kroniske værdi umiddelbart for fisk.

Al tilgængelig toksicitetsdata for vandlevende organismer er angivet i bilag A.

4.2 Toksicitet over for sedimentlevende organismer

For bicalutamid er der ligeledes begrænset data tilgængeligt for sedimentlevende organismer. I risikovurderingen foretaget af AstraZenica (2023) er der angivet en NOEC på 10 mg/kg tørvægt for larver af *Chironomus reparius* (se tabel 4.1), men studiet har ikke været tilgængeligt, og derfor tildeles den en troværdighedsscore på 4.

Der er ikke fundet øvrig data for sedimentlevende organismer, heller ej ved (Q)SAR.

Tabel 4.1. Toksicitetsdata for sedimentlevende organismer i ferskvand.

Art	**Varighed**	**Effekt**	**Værdi (mg/kg tv)**	**Reference**	**Troværdighed (1-4)**
Insekt					
Chironomus reparius	28 dage	NOEC (fremkomst og udvikling)	10	Hayfield, 2009 refereret i AstraZenica, 2023	4

4.3 Toksicitet over for pattedyr og fugle

For pattedyr er der fundet to akutte studier, som begge har undersøgt effekter af bicalutamid (engelsk: flutamide) i voksne Sprague-Dawley hanrotter (stamme af *Rattus norvegicus*).

Paris et al. (1993) eksponerede rotter ved injektion under huden i fedtvævet (”subcutaneous injection”) med en koncentration på 10 mg/kg/dag (opløst i sesamolie), og observerede dem i 14 dage. Endpoints for morfologi/vækst (vægt), celler (androgen receptorer) og hormoner (testosteron) blev undersøgt, men resulterede ikke i statistisk signifikante effekter, hvorfor koncentrationen på 10 mg/kg/dag anvendes som NOEL-værdi.

Gromoll et al. (1994) eksponerede ligeledes rotter, dog ved injektion direkte i bughulen (”intraperitoneal injection”) med en koncentration på 20 mg/kg/dag, og observerede dem i 7 dage. Endpoints for morfologi/vækst (vægt), forskellige hormoner og genetik (mRNA) blev undersøgt. Overordnet blev der ikke observeret statistisk signifikante effekter, hvorfor koncentrationen på 20 mg/kg/dag anvendes som NOEL-værdi.

Da begge studier anvender injektion frem for oralt optag, anvendes de ikke i beregningen af eventuelle biotakvalitetskriterier, hvorfor der ikke er foretaget en troværdighedsvurdering af studierne.

Der er ikke fundet toksicitetsdata for fugle.

Tabel 4.2. Toksicitetsdata for pattedyr.

Art	**Varighed**	**Effekt**	**Værdi (mg/kg/dag)**	**Reference**
Rotter				
Rattus norvegicus	14 dage	NOEL (flere endpoints)	10	Paris et al., 1993
Rattus norvegicus	7 dage	NOEL (flere endpoints)	20	Gromoll et al., 1994

4.4 Toksicitet over for mennesker

Der er ikke fundet en værdi for et acceptabelt daglig indtag (ADI), et tolerabelt daglig indtag (TDI) eller øvrige referenceværdier (RfV m.m.) for bicalutamid.

Bicalutamid har fra et mindre antal registranter (ECHA, 2023) fået selvklassificeringer for at være skadelig ved indtagelse, mistænkt for at være kræftfremkaldene og at kunne skade forplantningsevnen og det ufødte barn. Til det bør nævnes at mode of action er at virke anti-androgen, og derved hæmme det mandlige kønshormon (forhindre at kræftceller i prostata bliver større), som derved kan påvirke reproduktionen.

Der er umiddelbart ikke indikationer på at bicalutamid bioakkumulerer eller biomagnificerer.

5 Andre effekter

Der er ikke kendskab til andre effekter for bicalutamid.

6 Udledning af vandkvalitetskriterium

Kvalitetskriterierne er fastsat i overensstemmelse med EU's Guidance Document no. 27: Technical Guidance Document (TGD) for Deriving Environmental Quality Standards (EU, 2018).

6.1 Vandkvalitetskriterium (VKK)

Som beskrevet i afsnit 4.1 er der et meget begrænset dataomfang for bicalutamids effekter over for vandlevende organismer. Ét enkelt kronisk studie er vurderet troværdigt, hvor laveste effektkoncentration er NOEC på 0,0092 mg/l for Tykhovedet elritse (*Pimephales promelas*).

Jf. TGD (tabel 3) kan VKK bestemmes ud fra et enkelt kronisk studie med en usikkerhedsfaktor på 100, såfremt dette trofiske niveau også repræsenterer den laveste akutte effektkoncentration. Anvendes (Q)SAR resultater supplerende, ses den laveste akutte effektkoncentration at være for krebsdyr og derfor ikke for samme trofiske niveau. TGD supplerer, at man i sådan tilfælde kan anvende en usikkerhedsfaktor på 1000 ved anvendelse af det akutte data. For bicalutamid haves der ikke troværdigt akut data. I dette tilfælde er NOEC-værdien for Tykhoved elriste også noget lavere end øvrige supplerende ((Q)SAR) værdier for alle trofiske niveauer, og den vurderes derfor, at være det mest sensitive trofiske niveau. Derfor anvendes en usikkerhedsfaktor på 100 for ferskvand. For saltvand anvendes en ekstra faktor på 10 (TGD, tabel 4). VKK bliver derfor:

$VKK_{ferskvand}$ = 0,0092 mg/l / 100 = 0,000092 mg/l = **0,092 µg/l**

$VKK_{saltvand}$ = 0,0092 mg/l / 1000 = 0,0000092 mg/l = **0,0092 µg/l**

6.2 Korttidsvandkvalitetskriterium (KVKK)

Der haves ikke troværdigt akut data for vandlevende organismer, hvorfor KVKK ikke kan beregnes.

6.3 Kvalitetskriterium for sediment (SKK)

Jf. TGD (EU, 2018) skal der udledes et sedimentkvalitetskriterie (SKK), hvis log K_{ow} eller log K_{oc} ≥3, eller der foreligger anden evidens for akkumulering i sediment eller evidens for høj toksicitet over for sedimentlevende organismer. For bicalutamid er både log K_{ow} og log K_{oc} < 3 (hhv. 2,2 til 2,7 og 2,3 til 2,54 – se tabel 2.1). Der er heller ikke fundet evidens for høj toksicitet overfor sedimentlevende organismer, hvorfor der ikke udledes et SKK.

6.4 Kvalitetskriterium for biota, sekundær forgiftning ($BKK_{sek.forgiftn.}$)

Jf. TGD (EU, 2018) skal der udledes et biotakvalitetskriterie for sekundær forgiftning ($BKK_{sek.\ forgiftn.}$), hvis BCF (BAF) ≥ 100. Der er ikke fundet eksperimentelle BCF eller BAF for bicalutamid,

men ud fra det estimerede data angivet i afsnit 3.2 er BCF og BAF < 100. Dertil er der heller ikke fundet øvrig data, som viser potentiale for sekundær forgiftning. Derfor udledes $BKK_{sek.\ forgift.}$ ikke.

6.5 Kvalitetskriterium for human konsum af vandlevende organismer (HKK)

Bicalutamid har ikke nogen harmoniserede klassificeringer, men en antal virksomheder har selvklassificereret stoffet som mistænkt for at være kræftfremkaldene (Carc. 2, H531 – 10,1% af virksomhederne) og at kunne skade forplantningsevnen og det ufødte barn (Repr. 1A, 1B, H360 – hhv. 8% og 2,9% af virksomhederne). Sidstnævnte kan være grundet mode of action, da stoffet virker antiandrogent. Begge klassificeringer opfylder de angivne triggers for udledning af HKK jævnfør afsnit 2.4.3.2 i TGD (EU, 2018).

Der er dog ikke fundet data, som kan anvendes til at udlede et HKK, hvorfor den ikke kan beregnes.

6.6 Vandkvalitetskriterium baseret på $BKK_{sek.forgiftn.}$ og HKK

Jævnfør TGD (EU, 2018) skal der laves en tilbageregning fra biotakvalitetskriterierne ($BKK_{sek.forgiftn.}$ og HKK) til en vandkoncentration, for at se om vandkvalitetskriteriet fastsat for direkte effekter, også beskytter for sekundær forgiftning gennem fødekæden, samt beskytter mod forgiftning ved human konsum af fiskeriprodukter.

Da der ikke er fastsat nogen biotakvalitetskriterier foretages der ikke en tilbageregning.

7 Konklusion

Følgende kvalitetskriterier for vandmiljøet er udregnet for bicalutamid:

Vandkvalitetskriterium

$VKK_{ferskvand}$	0,092 µg/l
$VKK_{saltvand}$	0,0092 µg/l

Korttidsvandkvalitetskriterium

$KVKK_{ferskvand}$	Ikke muligt
$KVKK_{saltvand}$	Ikke muligt

Sedimentkvalitetskriterium

$SKK_{ferskvand}$	Ikke relevant
$SKK_{saltvand}$	Ikke relevant

Biotakvalitetskriterium, sekundær forgiftning

$BKK_{sek.forgiftn.}$	Ikke relevant

Biotakvalitetskriterium, human konsum

HKK	Ikke muligt

8 Referencer

AstraZenica (2023). Environmental Risk Assessment Data – Bicalutamide. Version 2. https://www.astrazeneca.com/content/dam/az/PDF/Sustainability/era/Bicalutamide.pdf.

Dansk (Q)SAR Database. Anvendt CAS: 90357-06-5 (resultater indsat i bilag B). https://qsar.food.dtu.dk/.

ECHA (2023). Substance Infocard – CAS 90357-06-5, (2R)-N-[4-cyano-3-(trifluoromethyl)phenyl]-3-(4-fluorophenyl)sulfonyl-2-hydroxy-2-methylpropanamide, https://echa.europa.eu/da/substance-information/-/substanceinfo/100.126.100 (sidst opdateret 31/07/2023).

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. (https://circabc.europa.eu/sd/a/ba6810cd-e611-4f72-9902-f0d8867a2a6b/Guidance%20No%2027%20-%20Deriving%20Environmental%20Quality%20Standards%20-%20version%202018.pdf).

Li D, Chen H, Liu H, Schlenk D, Mu J, Lacorte S, Ying G-G & Xie L (2021). Anticancer drugs in the aquatic ecosystem: Environmental occurrence, ecotoxicological effect and risk assessment. Environment International 153, 106543.

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

Moermond CTA, Kase R, Korkaric M & Ågerstrand M (2016). CRED: Criteria for Reporting and Evaluating Ecotoxicity Data. Environ. Toxicology and Chemistry 35(5), pp. 1297-1309.

Panter GH, Glennon YC, Robinson J, Hargreaves A & Murray-Smith R (2012). Effects of the Anti-Androgen, Bicalutamide, in a Reduced Life-Cycle Study with the Fathead Minnow (*Pimephales promelas*). Aquat. Toxicol. 114-115, pp. 31-38.

Pubchem (2024). National Center for Biotechnology Information. PubChem Compound Summary for CID 2375, Bicalutamide. Retrieved July 17, 2024 from https://pubchem.ncbi.nlm.nih.gov/compound/Bicalutamide.

Produktresume.dk. Lægemiddelstyrelsen. https://www.produktresume.dk/AppBuilder/search?utf8=%E2%9C%93&id=&type=&q=Bicalutamid&button=search (besøgt d. 6. september 2024).

Rigshospitalet.dk. Bicalutamid – behandling med. Direkte link: https://www.rigshospitalet.dk/undersoegelse-og-behandling/find-undersoegelse-og-behandling/Sider/Bicalutamid---behandling-med--31073.aspx (besøgt d. 6. september 2024).

Umweltbundesamt (2021). Reducing the input of chemicals into waters: trifluoroacetate (TFA) as a persistent and mobile substance with many sources – Sources, input pathways, environmental contamination of TFA and regulatory approaches. https://www.umweltbundesamt.de/sites/default/files/medien/11850/publikationen/hgp_reducing_the_input_of_chemicals_into_waters_v2.pdf

Bilag A

Toksicitet over for vandorganismer (EC_x, LC_x, NOEC, osv.)

Ferskvandsorganismer

Akut toksicitet

	Målt	Varighed	Effekt	Værdi (mg/l)	Bemærkning	Reference	Troværdighed (1-4)
Alger							
Pseudokirchneriella sp.	Nej	72 timer	EC_{50}	5,88	Esimeret i SciQSAR, out of domain	Danske (Q)SAR Database, bilag B	4
Pseudokirchneriella sp.	Nej	72 timer	EC_{50}	7,41	Esimeret i Leadscope, out of domain	Danske (Q)SAR Database, bilag B	4
Krebsdyr							
Daphnia magna	Nej	48 timer	EC_{50}	0,34	Estimeret i VEGA, out of domain	Danske (Q)SAR Database, bilag B	4
Daphnia magna	Nej	48 timer	EC_{50}	1,09	Estimeret i Leadscope, out of domain	Danske (Q)SAR Database, bilag B	4
Daphnia magna	Nej	48 timer	EC_{50}	3,06	Estimeret i SciQSAR, out of domain	Danske (Q)SAR Database, bilag B	4
Daphnia pp.		48 timer	EC_{50} (immobilisering)	>5		FDA-CDER, 1996 refereret i Li et al., 2021	4
Fisk							
Lepomis macrochirus (Blågællet solaborre)		96 timer	LC_{50} (dødelighed)	>4,4	Der blev ikke set en effekt ved 4,4 mg/l.	Morris et al., 1994 refereret i AstraZenica, 2023	4
Oncorhynchus mykiss (Regnbueørred)		96 timer	LC_{50} (dødelighed)	>7,1	Der blev ikke set en effekt ved 7,1 mg/l.	Morris et al., 1994 refereret i AstraZenica, 2023	4

Pimephales promelas (Fathead minnow / Tykhovedet elritse)	Nej	96 timer	LC_{50} (dødelighed)	1,81	Estimeret i SciQSAR, out of domain	Danske (Q)SAR Database, bilag B	4
Pimephales promelas (Fathead minnow / Tykhovedet elritse)	Nej	96 timer	LC_{50} (dødelighed)	6,87	Estimeret i Leadscope, out of domain	Danske (Q)SAR Database, bilag B	4

Ferskvandsorganismer
Kronisk toksicitet

	Målt	**Varighed**	**Effekt**	**Værdi (mg/l)**	**Bemærkning**	**Reference**	**Troværdighed (1-4)**
Cyanobakterier							
Microcystis aeruginosa		21 dage	NOEC (vækst)	1,1		Smyth et al., 1992 refereret i AstraZenica, 2023	4
Alger							
Selenastrum capricornutum		14 dage	NOEC (vækst)	1,1		Smyth et al., 1992 refereret i AstraZenica, 2023	4
Krebsdyr							
Daphnia magna		21 dage	NOEC (længde)	0,56		Stewart et al., 1992 refereret i AstraZenica, 2023	4
Daphnia magna		21 dage	NOEC (reproduktion)	0,96		Stewart et al., 1992 refereret i AstraZenica, 2023	4
Daphnia magna	Nej	21 dage	NOEC	1,21	Estimeret i VEGA, out of domain	Danske (Q)SAR Database, bilag B	4
Daphnia pp.		21 dage	NOEC (reproduktion)	6		FDA-CDER, 1996 refereret i Li et al., 2021	4

Fisk							
Pimephales promelas (Fathead minnow / Tykhovedet elritse)	Nej		NOEC (overlevelse, reproduktion m.m.)	0,1	Generation F0	Panter et al., 2009 refereret i AstraZenica, 2023 [a]	4
Pimephales promelas (Fathead minnow / Tykhovedet elritse)	Nej		NOEC (overlevelse, histologi m.m.)	0,01	Generation F1	Panter et al., 2009 refereret i AstraZenica, 2023 [a]	4
Pimephales promelas (Fathead minnow / Tykhovedet elritse)	Ja	28 dage	NOEC (vækst, reproduktion, dødelighed)	0,092	Generation F0 (forældre). NOEC er sat lig højeste testkoncentration.	Panter et al., 2012	2
Pimephales promelas (Fathead minnow / Tykhovedet elritse)	Ja	124 dage	NOEC (reproduktion)	0,0092	Generation F1 (afkom)	Panter et al., 2012	2
Pimephales promelas (Fathead minnow / Tykhovedet elritse)	Ja	124 dage	NOEC (vækst, udvikling)	0,092	Generation F1 (afkom)	Panter et al., 2012	2

[a] Forventeligt samme data (bare afrundet værdier) som angivet i Panter et al. (2012).

Saltvandsorganismer
Akut toksicitet
Ingen data

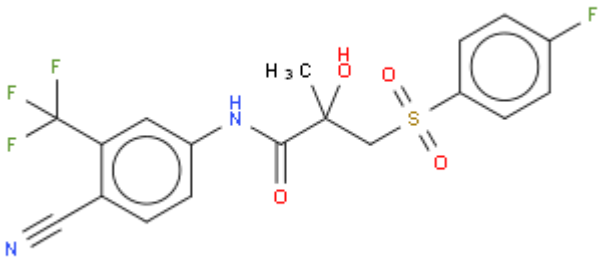
Saltvandsorganismer
Kronisk toksicitet
Ingen data

Bilag B

Danish (Q)SAR Database, https://qsar.food.dtu.dk Date: 15-07-2024

(Q)SAR predicted profile

8.1 Structure (as used for QSAR prediction):



SMILES (used for QSAR prediction): C(F)(F)(F)c1c(C#N)ccc(NC(=O)C(C)(O)CS(=O)(=O)c2ccc(F)cc2)c1

8.2 ID

Registry Number	90357-06-5	PubChem CID	
REACH EC Number (pre-registration, by 2013)	618-534-3	REACH EC Number (registration, 2019 or 2022)	
REACH registration (2022)		REACH registration cumulated minimum annual tonnage (2022)	
EU CLP Harmonized Classification*		DK-EPA / DTU QSAR-based CLP Advisory Classification	Aquatic Chronic 2
EU Biocide active substances		EU Pesticide active substances	
EU EFSA Botanical substances		US TSCA (Oct. 2021)	
Tox21 (2019)	Yes	ToxCast (Oct. 2021)	Yes
Molecular Formula	C18 H14 F4 N2 O4 S1	Molecular weight (g/mole)	430.38
Chemical Name	Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-		

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

8.3 Melting point, Boiling point and Vapour pressure

Melting Point (deg C)	243.3	Melting Point Experimental (deg C)	
Boiling Point (deg C)	565.72	Boiling Point Experimental (deg C)	
Vapour Pressure (atm)		Vapour Pressure Experimental (atm)	
Vapour Pressure (mm Hg)	7.54E-015	Vapour Pressure Experimental (mm Hg)	
Vapour Pressure (Pa)	1.005E-012	Vapour pressure Subcooled Liquid (Pa)	2.33E-010

EPI MPBPVP models

8.4 Henry's Law Constant

HLC Bond Method (atm-m3/mole)	2.816E-015	HLC Group Method (atm-m3/mole)	
HLC Via VP/WSol (atm-m3/mole)	3.634E-016	HLC Via VP/WSol (Pa-m3/mole)	3.682E-011
Henrys Law Const. Exp db (Pa-m3/mole)		Henrys Law Const. Exp db (atm-m3/mole)	

EPI HENRYWIN models

8.5 Water Solubility

Water solubility from Kow (mg/L)	11.75	Water solubility from Fragments (mg/L)	136.07
Water solubility Exp (mg/L)		Water solubility Exp Ref	

EPI WATERNT model

	Exp	Prediction	Domain
Water solubility v1.0.1 (mg/L)		1.78	mod_OUT

VEGA model

8.6 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

8.7 pKa

pKa Acid	11
- Standard deviation (±)	1.1
pKa Base	-999
- Standard deviation (±)	0

ACDLabs model

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

8.8 Partition coefficients

pH	1	4	5	6	7	8	9
LogD	2.69	2.69	2.69	2.69	2.69	2.68	2.68

Minimum LogD in the pH interval 4-9	2.68	Maximum LogD in the pH interval 4-9	2.69

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	15.238	Log Kaw	-12.938

EPI KOAWIN models

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

Log Kow	2.3		
Log Kow Exp		Log Kow Exp Ref	

EPI WSKOW model

LogKow: log octanol-water partition coefficient

Kp (m3/ug) Mackay-based	12900	Kp (m3/ug) Koa-based	425
Phi Junge-Pankow-based	1	Phi Mackay-based	1
Phi Koa-based	1		

EPI AEROWIN models

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

Koc from MCI (L/kg)	459.4	Log Koc from MCI	2.6622
Koc from Kow (L/kg)	150.1	Log Koc from Kow	2.1765

EPI KOCWIN models

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

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

	Air	Water	Soil	Sediment
Mass Amount (%)	0.00446	6.67	93.1	0.213
Half-Life (hr)	8.58	4320	8640	38900
Emissions (kg/hr)	1000	1000	1000	0

EPI Level III Fugacity Model

Persistence time (hr)	6400
Persistence time (days)	266.6667

EPI Level III Fugacity Model

8.10 Level III Fugacity Environmental Partitioning, emission only to water

	Air	Water	Soil	Sediment
Mass Amount (%)	2.39E-012	96.9	2.27E-008	3.1
Half-Life (hr)	8.58	4320	8640	38900
Emissions (kg/hr)	0	1000	0	0

EPI Level III Fugacity Model

Persistence time (hr)	888
Persistence time (days)	37

EPI Level III Fugacity Model

8.11 Air Half-Life

	Exp	Prediction	Domain
Air Half-Life (CORAL) v1.0.1 (hr)		0.0007	low_OUT

VEGA model

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

	Total removal	Biodegradation	Sludge Adsorption	Volatilization
(%)	2.64	0.1	2.54	0

EPI STPWIN model

8.13 Atmospheric oxidation (25 deg C)

	OH	Ozone
Half-Life (d)	0.3573	0
Half-Life (hr)	4.287	
Overall Rate Const. (OH: E-12 cm3/molecule-sec and OZ: E-17 cm3/molecule-sec)	29.9366	

EPI AOPWIN models

8.14 Biodegradation

Biowin1 (linear model) Probability of Rapid Biodegradation	-0.4545
Biowin2 (non-linear model) Probability of Rapid Biodegradation	0
Biowin3 Expert Survey Ultimate Biodegradation	0.9795
Biowin3 Expert Survey Ultimate Timeframe	recalcitrant
Biowin4 Expert Survey Primary Biodegradation	2.9527
Biowin4 Exp. Survey Primary Timeframe	weeks
Biowin5 (MITI linear model) Biodegradation Probability	-0.1255
Biowin6 (MITI non-linear model) Biodegradation Probability	0
Biowin7 (Anaerobic Linear) Biodegradation Probability	-0.7876
Petroleum Hydrocarbon Biodegradation Half-Life (days)	

EPI BIOWIN models
SkinBiowin1 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		INC_OUT	INC_OUT	POS_OUT	INC_OUT

DTU-developed models
POS=Not Ready

.	Exp	Prediction_Domain
Not Ready Biodegradability		POS_low_OUT

v1.0.10

VEGA model
POS=Not Ready

8.15 Bioaccumulation

BCF (L/kg wet-wt)	15.23
Log BCF (L/kg wet-wt)	1.183
Whole Body Primary Biotransformation Fish Half-Life (days)	0.3309
BCF Arnot-Gobas (upper trophic) Including Biotransformation (L/kg wet-wt)	18.19
BCF Arnot-Gobas (upper trophic) Zero Biotransformation (L/kg wet-wt)	22.08
BAF Arnot-Gobas (upper trophic) Including Biotransformation (L/kg wet-wt)	18.19
BAF Arnot-Gobas (upper trophic) Zero Biotransformation (L/kg wet-wt)	22.88

EPI BCFBAF models
BCF: Bioconcentration factor, BAF: Bioaccumulation factor

	Exp	Prediction	Domain
Log BCF (CAESAR) v2.1.15 (L/kg)		0.97	low_OUT

VEGA model

8.16 Aquatic toxicity

Exp	Battery	Leadscope	SciQSAR
Fathead minnow 96h LC50 (mg/L)		6.872142	1.806767
Domain	OUT	OUT	OUT
Daphnia magna 48h EC50 (mg/L)		1.093269	3.058173
Domain	OUT	OUT	OUT
Pseudokirchneriella s. 72h EC50 (mg/L)		7.408019	5.876952
Domain	OUT	OUT	OUT

DTU-developed models

	Exp	Prediction	Domain
Daphnia magna 48h EC50 v1.0.1 (mg/L)		0.3401	low_OUT
Daphnia magna 21d NOEC v1.0.1 (mg/L)		1.21	low_OUT
Algae Acute 72h ErC50 v1.0.1 (mg/L)		27.97	low_OUT
Sludge Classification, 3h EC50 < 100 mg/L v1.0.1*		POS_low_OUT	See prediction

Sludge 3h EC50 v1.0.1 (mg/L)	39.94	low_OUT

VEGA models

** The quantitative model should only be applied when the Sludge classification model is POS_IN*

MOA Toxicity classification (EPA T.E.S.T) v1.0.2	
- predicted Mode of action	Narcosis
- Domain	mod_OUT
- Exp, if part of training set	

VEGA model

Qualitative estimation of MOA for Fathead minnow 96h

	Fish 96h	Daphnid 48h	Green Algae 96h
LC50 (Fish) or EC50 (Daphnid and Algae) for Most Toxic Class (mg/L)	78.83	75.691	2.643
Max. Log Kow for Most Toxic Class	>8.5	>8.5	>8
Most Toxic Class	Amides	Amides	Amides
Note	Chemical may not be soluble enough	Chemical may not be soluble enough	

EPI ECOSAR models

ECOSAR Classes: Amides

8.17 Oral absorption

Lipinski's Rule-of-five score (bioavailability)	0
Absorption from gastrointestinal tract for 1 mg dose (%)	95
Absorption from gastrointestinal tract for 1000 mg dose (%)	50

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.

8.18 Skin absorption

Dermal absorption (mg/cm2/event)	2.63E-005

EPI DERMWIN model

8.19 Brain/blood Distribution

Log brain/blood partition coefficient	-0.549

Equation from literature

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

8.20 Metabolism

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

DTU-developed models

8.21 Acute toxicity in Rodents

	LD50 (mg/kg/d)	Reliability Index
Rat Oral	820	0.16
Rat Intraperitoneal	1100	0.35
Mouse Oral	760	0.21
Mouse Intraperitoneal	1900	0.24
Mouse Intravenous	93.07	0.23
Mouse Subcutaneous	950	0.29

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.

8.22 Effects in Humans

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
MRDD in Humans ≤ 2.69 mg/kg-bw/d	POS	POS_IN	POS_IN	POS_IN	POS_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.

.	Exp	Prediction_Domain
Hepatotoxicity v1.0.1	POS	POS_NA

VEGA model

Profiler-type of predictions to be used as supporting information together with relevant QSAR predictions.

8.23 Irritation and Sensitization

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR

Severe Skin Irritation in Rabbit		INC_OUT	INC_OUT	INC_OUT	NEG_OUT
Skin sensitisation GHS/CLP at least Cat. 1, LLNA-based (open data only)				INC_OUT	
Skin sensitisation GHS/CLP at least Cat. 1, LLNA-based (open data and REACH-registrations)	N/A			NEG_IN	
Skin sensitisation GHS/CLP at least Cat. 1, LLNA-based, only negative predictions (open data only)				N/A	
Skin sensitisation GHS/CLP Cat. 1A, LLNA-based (open data only)				INC_OUT	
Skin sensitisation GHS/CLP Cat. 1A, LLNA-based (open data and REACH-registrations)	N/A			NEG_IN	
Skin sensitisation GHS/CLP Cat. 1A, LLNA-based, only positive predictions (open data and REACH-registrations)	N/A			N/A	
Allergic Contact Dermatitis in Guinea Pig and Human*	N/A	INC_OUT	INC_OUT	NEG_OUT	INC_OUT
Respiratory Sensitisation in Humans		INC_OUT	INC_OUT	POS_OUT	POS_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	No alert found
- metabolites from auto-oxidation simulator only	
Protein binding by OECD, alerts in:	
- parent only	Acetates
- metabolites from skin metabolism simulator only	No alert found
- metabolites from auto-oxidation simulator only	
Protein binding potency Cys (DRPA 13%), alerts in:	
- parent only	DPRA less than 9% (DPRA 13%) >> Mono-halo arenes
- metabolites from skin metabolism simulator only	DPRA less than 9% (DPRA 13%) >> Mono-halo arenes; DPRA less than 9% (DPRA 13%) >> Non-Conjugated carboxylic acids and esters (non reactive)
- metabolites from auto-oxidation simulator only	
Protein binding potency Lys (DRPA 13%), alerts in:	
- parent only	DPRA less than 9% (DPRA 13%) >> Mono-halo arenes
- metabolites from skin metabolism simulator only	DPRA less than 9% (DPRA 13%) >> Mono-halo arenes; DPRA less than 9% (DPRA 13%) >> Non-Conjugated carboxylic acids and esters (non reactive)
- 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	Not possible to classify according to these rules
- metabolites from auto-oxidation simulator only	
Protein binding potency GSH, alerts in:	
- parent only	Not possible to classify according to these rules (GSH)

OECD QSAR Toolbox v.4.1 profilers

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

8.24 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*)		INC_OUT	INC_OUT	NEG_OUT	NEG_OUT
Estrogen Receptor α Activation (Human *in vitro*)		NEG_IN	INC_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*)	POS	POS_IN	POS_IN	POS_IN	POS_IN
Androgen Receptor Binding, CoMPARA data (*in vitro*)	POS	N/A	N/A	POS_IN	N/A
Androgen Receptor Inhibition, CoMPARA data (*in vitro*)	POS	N/A	N/A	POS_IN	N/A
Androgen Receptor Activation, CoMPARA data (*in vitro*)	NEG	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*)	NEG	N/A	N/A	NEG_IN	N/A
Sodium/iodide symporter (NIS), higher sensitivity		N/A	N/A	INC_OUT	N/A
Sodium/iodide symporter (NIS), higher specificity		N/A	N/A	INC_OUT	N/A
Thyroid Receptor α Binding (Human *in vitro*)					
- mg/L			10.18244	4363.371	20.01023
- µM			23.65919	10138.41	46.49433
- Positive for IC_{50} ≤ 10 µM					
- Positive for IC_{50} ≤ 100 µM					
- Domain		OUT	OUT	OUT	OUT
Thyroid Receptor β Binding (Human *in vitro*)					

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
- mg/L			1.802404	109.2728	96.88402
- µM			4.187935	253.8984	225.1127
- Positive for IC_{50} ≤ 10 µM					
- Positive for IC_{50} ≤ 100 µM					
- Domain		OUT	OUT	OUT	OUT
Peroxisome Proliferator-Activated Receptor gamma (PPAR-γ) Inhibition at max. 10 µM (Human *in vitro*)		N/A	N/A	INC_OUT	N/A
Peroxisome Proliferator-Activated Receptor gamma (PPAR-γ) Inhibition at any concentration (Human *in vitro*)		N/A	N/A	INC_OUT	N/A
Retinoic Acid Receptor (RAR) inhibition at max. 10 µM (Human *in vitro*)	NEG	N/A	N/A	NEG_IN	N/A
Arylhydrocarbon Receptor (AhR) Activation – Rational final model (Human *in vitro*)		N/A	N/A	NEG_IN	N/A
Arylhydrocarbon Receptor (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	POS_OUT	INC_OUT	POS_OUT	POS_IN
Pregnane X Receptor (PXR) Binding (Human *in vitro*) NEW	NEG	N/A	N/A	NEG_OUT	N/A
Pregnane X Receptor (PXR) Activation (Human *in vitro*)	NEG	N/A	N/A	NEG_IN	N/A
Pregnane X Receptor (PXR) Activation (Rat *in vitro*)		N/A	N/A	NEG_IN	N/A
CYP3A4 Induction (Human *in vitro*)	NEG	N/A	N/A	NEG_IN	N/A
Constitutive Androstane Receptor (CAR) Activation at max. 20 µM (Human *in vitro*)		N/A	N/A	NEG_IN	N/A
Constitutive Androstane Receptor (CAR) Activation at max. 50 µM (Human *in vitro*)		N/A	N/A	NEG_IN	N/A
Constitutive Androstane Receptor (CAR) Inhibition at max. 20 µM (Human *in vitro*)		N/A	N/A	INC_OUT	N/A
Constitutive Androstane Receptor (CAR) Inhibition at max. 50 µM (Human *in vitro*)		N/A	N/A	INC_OUT	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	Strong binder, NH2 group; Strong binder, OH group; Moderate binder, NH2 group
- metabolites from Rat liver S9 metabolism simulator only	Strong binder, NH2 group; Strong binder, OH group; Moderate binder, 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

8.25 Developmental Toxicity

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

DTU-developed models based on commercial training set

.	Exp	Prediction_Domain
Developmental/Reproductive Toxicity library (PG) v1.1.2		NEG_low_OUT

VEGA model

Profiler-type of predictions to be used as supporting information together with relevant QSAR predictions

8.26 Genotoxicity - Structural Alerts for DNA Reactivity

	Battery	CASE Ultra	Leadscope	SciQSAR
Ashby Structural Alerts	INC_OUT	POS_OUT	INC_OUT	NEG_OUT

DTU-developed models based on commercial training set

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

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

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

	Consensus	Mut. / Non-mut. Scores	Used models
Ames test Consensus	NEG	0.05 / 0.35	4

VEGA model

Mutagenicity (Ames) consensus model version 1.0.4 contained in VEGA version 1.4.3 with calculation core version 1.3.14

	Exp	Prediction
Ames test (ISS) v1.0.3		NEG_low_OUT
Ames test (CAESAR) - v2.1.13		NEG_mod_OUT
Ames test (SarPy) v1.0.8		POS_low_OUT
Ames test (KNN/Read-Across) v1.0.1		NEG_mod_OUT

VEGA models

DNA alerts for AMES by OASIS, alerts in:	
- parent only	No alert found
In vitro mutagenicity (Ames test) alerts by ISS, alerts in:	
- parent 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

8.28 Other *in vitro* Genotoxicity Endpoints

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Chromosome Aberrations in Chinese Hamster Ovary (CHO) Cells*	N/A	INC_OUT	INC_OUT	NEG_OUT	NEG_OUT
Chromosome Aberrations in Chinese Hamster Lung (CHL) Cells		INC_OUT	POS_OUT	NEG_OUT	NEG_OUT

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

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

HGPRT: Hypoxanthine-guanine phosphoribosyltransferase

.	Exp	Prediction_Domain
Micronucleus (VERMEER) v1.0.1		NEG_low_OUT

VEGA model

DNA alerts for CA and MNT by OASIS, alerts in:	
- parent only	No alert found
Protein binding alerts for Chromosomal aberration by OASIS, alerts in:	
- parent only	No alert found

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

8.29 *In vivo* Genotoxicity Endpoints

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

DTU-developed models

In vivo mutagenicity (Micronucleus) alerts by ISS, alerts in:	
- parent only	H-acceptor-path3-H-acceptor

OECD QSAR Toolbox v.4.2 profilers

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

8.30 Carcinogenicity

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

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	Halogenated benzene (Nongenotox); Structural alert for nongenotoxic carcinogenicity
Oncologic Primary Classification, alerts in:	
- parent only	Not classified

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	NEG_OUT

DTU-developed models

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 from QSAR models training sets.

N/A: Not applicable, either because training set data cannot be released for commercial or proprietary models / training sets, or because the model was not developed in a given QSAR software (i.e. a given prediction is not available as the model version does not exist).

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, VEGA 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: https://www.multicase.com/case-ultra

Leadscope: https://www.leadscope.com/

VEGA: https://vegahub.it

ToxSuite: https://www.acdlabs.com/

Copyright notice, terms and conditions of use

Copyright notice, terms and conditions of use

Permission is granted to use information from the database as is. The database is an expert tool where the final assessment of properties is not dictated by the (Q)SAR estimates, but by the user's own scientific judgment. Aside from the fact that models are never perfect, the (Q)SAR field is under rapid development and models are regularly updated and improved. It is also impossible to provide the detailed information accompanying each individual prediction that is available to those who do not own licences to the software platforms. The structural information in the database stems from many sources and in some cases it may be wrong. The structures are also in some cases abbreviated in that possible anions and cations have been removed. This can have important toxicological significance (e.g. for Heavy Metal salts).
All access to the database should happen through the provided client-side software and without any use of automated workflow or scripting.

Reproduction of information from the database is permitted provided the source is acknowledged as follows:

Danish (Q)SAR Database, National Food Institute, Technical University of Denmark, https://qsar.food.dtu.dk.

The Technical University of Denmark (DTU) is not responsible for any errors or inaccuracies the database may contain and is not liable for any use that may be made of the information contained therein. DTU do not warrant, and hereby disclaim any warranties, with respect to the accuracy, adequacy or completeness of any information obtained from this database. Nor do we warrant that the site will operate in an uninterrupted or error-free manner or that the site and its components are free of viruses or other harmful components. Use of information obtained from or through this site is at your own risk.

As a user of this database, you agree to indemnify and hold DTU harmless from any claims, losses or damages, including legal fees, resulting from your use of this database, and to fully cooperate in DTU's defense against any such claims.

The user requests are processed by the server hosting the database which in the process stores information. Only authorized employees have authorized access to the server and reasonable measures are in place to protect the server from unauthorized access. DTU uses the stored user request information solely for error tracking and to collect anonymized statistics (number of users, number of searches, number of report downloads etc.), and we do not release any information at the level of individual searches. However, as any server/PC/network that the requests pass through may be compromised by unauthorized access, we cannot guarantee that the information submitted by users does not fall into the hands of third parties.
These terms are governed by Danish Law, with the exception of international private law and conflict of law rules, to the extent that such rules would result in the application of another country's law. Any dispute arising between the parties in connection with the use of this database, including the interpretation of the

above terms, which cannot be settled amicably by negotiation between the parties, shall be settled by the Court of Lyngby, Denmark, as the court of first instance.