GreenScreen® Assessment for Medetomidine (CAS # 86347-14-0)

Method Version: GreenScreen® Version 1.3[1]

Assessment Details[2]:

Assessment Type:	GreenScreen
Assessment Prepared By:	Alex Stone
Assessment Prepared For:	Northwest Green Chemistry
Date Assessment Completed:	3 August 2017
Assessment Expiration Date:	3 August 2020
Assessor Type: (Licensed GreenScreen Profiler or equivalent, Authorized GreenScreen Practitioner or Unaccredited)	Authorized GreenScreen Practitioner

Confirm application of the *Disclosure and Assessment Rules and Best Practice*[3]: (List disclosure threshold and any deviations)

Chemical Name (CAS #): Medetomidine, CAS #: 86347-14-0

Also Called: Selektope; 5-[1-(2,3-dimethylphenyl)ethyl]-1H-imidazole; Hydrochloride, Medetomidine, Levomedetomidine, Medetomidine, Medetomidine Hydrochloride, MPV 785, MPV-785, MPV785; Medetomidina; Medetomidinum; (+-)-4-(alpha,2,3-trimethylbenzyl)imidazole;

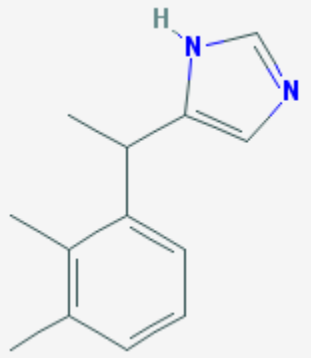
Suitable analogs or moieties of chemicals used in this assessment (CAS #'s):

Chemical Structure(s):
*Note: Include chemical structure(s) of all suitable analogs (and/or moieties) used in the assessment.

The substance is manufactured as a racemic mixture of two stereoisomers. The active isomer is dexmedetomidine whereas the other isomer, levomedetomidine, is non effective. Dexmedetomidine is a highly selective α2 adrenoceptor agonist on presynaptic neurons. The

[1] Use GreenScreen® Hazard Assessment Guidance (Guidance) v1.3
[2] **Assessment Type**: GreenScreen reports are either "UNACCREDITED" (by unaccredited person), "AUTHORIZED" (by Authorized GreenScreen Practitioner), "CERTIFIED" (by Licensed GreenScreen Profiler or equivalent) or "CERTIFIED WITH VERIFICATION" (Certified or Authorized assessment that has passed GreenScreen Verification Program); **Assessment Prepared By**: Licensed GreenScreen Profilers must provide name of organization; Authorized GreenScreen Practitioners must provide their name; **Assessment Prepared For**: Optional for Licensed GreenScreen Profilers, mandatory for Authorized Practitioners; **Date Assessment Completed**: Assessments by Licensed GreenScreen Profilers require quality control tracked via internal documentation; **Assessment Expiration Date**: Assessments expire three years from the date of completion.
[3] See GreenScreen Guidance v1.3.

stimulation of these receptors leads to a decrease in norepinephrine release from presynaptic neurons with inhibition of postsynaptic activation, which attenuates CNS (Central Nervous System) excitation, especially in the locus coeruleus of the brain. A similar mode of action (activation of specific neuro-receptors in shell-building organisms leading to an anti-settling effect) is the basis of its biocidal activity as an antifouling agent. (ECHA-CLH report, Proposal for Harmonised Classification and Labelling)



Notes related to production specific attributes[4]:

For Inorganic Chemicals and relevant particulate organics (*if not relevant, list NA*)
Define Properties:

1. Particle size (e.g., silica of respirable size): NA
2. Structure (e.g., amorphous vs. crystalline): NA
3. Mobility (e.g., water solubility, volatility): NA
4. Bioavailability: NA

Identify Applications/Functional Uses:
(e.g., Cleaning product, TV casing)

1. Antifouling agent[5]
2. Anesthetic in veterinary medicine
3. Analgesic in human medicine.

GreenScreen Benchmark Score and Hazard Summary Table:[6,7,8,9] Medetomidine was assigned a **Benchmark Score of 1** based on a very high persistence, acute mammalian toxicity and acute aquatic toxicity (criteria 1C of the GreenScreen Benchmarking Criteria). As the criteria for persistence and acute mammalian toxicity are based upon the results of laboratory studies, there is a high confidence in assigning a Benchmark 1 to this chemical. Many of the other

[4] Note any composition or hazard attributes of the chemical product relevant to how it is manufactured. For example, certain synthetic pathways or processes result in typical contaminants, by-products or transformation products. Explain any differences between the manufactured chemical product and the GreenScreen assessment of the generic chemical by CAS #.
[5] Information from ECHA-CLH report, Proposal for Harmonised Classification and Labelling
[6] See Appendix A for a glossary of hazard endpoint acronyms.
[7] See Appendix B for alternative GreenScreen Hazard Summary Table (Classification presented by exposure route).
[8] For inorganic chemicals only, see GreenScreen Guidance v1.3 Section 13. (Exceptions for Persistence)
[9] For Systemic Toxicity and Neurotoxicity, repeated exposure data are preferred. Lack of single exposure data is not a Data Gap when repeated exposure data are available. In that case, lack of single exposure data may be represented as NA instead of DG. See GreenScreen Guidance v1.3 Section 8.2.1.

hazard criteria, however, are based upon limited results as reflected by italicizing the level of concern. Additional data may change both the assessment and the justification for assigning a BM 1 score.

GreenScreen Hazard Ratings: Medetomidine																			
Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B	Rx	F
						single	repeated *	single	repeated *										
L	**L**	*L*	**L**	*L*	**vH**	DG	DG	*M*	DG	*L*	DG	*L*	*L*	*vH*	**vH**	**vH**	**vL**	**L**	**L**

Note: Hazard levels (Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL)) in *italics* reflect estimated values, authoritative B lists, screening lists, weak analogues, and lower confidence. Hazard levels in **BOLD** font are used with good quality data, authoritative A lists, or strong analogues. Group II Human Health endpoints differ from Group II* Human Health endpoints in that they have four hazard scores (i.e., vH, H, M and L) instead of three (i.e., H, M and L), and are based on single exposures instead of repeated exposures.

Environmental Transformation Products and Ratings[10]:
Identify feasible and relevant environmental transformation products (i.e., dissociation products, transformation products, valence states) and/or moieties of concern[11]

Functional Use	Life Cycle Stage	Transformation Pathway	Environmental Transformation Products	CAS #	Feasible and Relevant?	GreenScreen List Translator Score or GreenScreen Benchmark Score
Active metabolite	-	biological	dexmedetomidine	113775-47-6	Y	1*
Non-active ingredient	-	biological	levomedetomidine	106162-92-5	Y	?
-	degr	Hydrolysis	4-methylimidazole	822-36-6	Y	LT-1
-	degr	Hydrolysis	1-Ethyl-2,4-dimethylbenzene	933-98-2	Y	?

*As dexmedetomidine is the active ingredient from the metabolism of medetomidine, it can be assumed that the Benchmark Score would be equivalent to the BM 1 assigned in this report.

[10] See GreenScreen Guidance v1.3 Section 12.
[11] A moiety is a discrete chemical entity that is a constituent part or component of a substance. A moiety of concern is often the parent substance itself for organic compounds. For inorganic compounds, the moiety of concern is typically a dissociated component of the substance or a transformation product.

Hazard Classification Summary Section:

Group I Human Health Effects (Group I Human)

Carcinogenicity (C) Score (H, M or L): L

No carcinogenicity data was available . However, a European Union (2014) report indicated no carcinogenicity studies were needed as '*... the toxicological profile of medetomidine is driven by the acute effects of sedation* ' and concluded '*.... likely exposure scenarios are medium-term rather than chronic.*' Therefore, medetomidine was assigned a low (**L**) level of concern for carcinogenicity. As this level of concern is based upon professional judgment, it is italicized in the Hazard Summary Table to indicate the low level of confidence in this determination. Data may change this determination.

- Authoritative and Screening Lists
  - Authoritative: None available
  - Screening: None available

- Source
  - ECHA, 2014: **4.10 Carcinogenicity**: No data available
  - EU Assessment Report, 2015:
    - '*No carcinogenicity studies have been submitted for medetomidine. The UK CA agrees that no carcinogenicity studies are required as the available data show that the toxicological profile of medetomidine is driven by the acute effects of sedation, with no specific target organs of toxicity being identified following repeated exposure. In addition, for PT21 biocidal products the likely exposure scenarios are medium-term rather than chronic.*'

Mutagenicity/Genotoxicity (M) Score (H, M or L): L

Data on mutagenicity/genotoxicity is limited. The ECHA (2014) reviewed all available data and determined *'medetomidine is not genotoxic in vitro or in vivo'*. Medetomidine was assigned a low (L) level of concern for mutagenicity/genotoxicity based on the ECHA assessment. As this determination is based upon laboratory studies, the level of concern is bolded in the Hazard Summary Table. Additional data may change this determination.

- Authoritative and Screening Lists
  - Authoritative: None available
  - Screening: None available

- ECHA, 2014
  - **4.9 Germ cell mutagenicity (Mutagenicity)**
    4.9.1 Non-human information:
    4.9.1.1 In vitro data: The genotoxic potential of medetomidine has been investigated in vitro in an Ames test and cytogenetics assay. The result of both studies was negative. The genotoxic potential of the active isomer of medetomidine,

dexmedetomidine, has been investigated in vitro in an Ames test, cytogenetics Assay and a gene mutation assay. The results of all studies were negative.
4.9.1.2 In vivo data: No information is available on Medetomidine itself; however, information is available from a micronucleus study conducted on the active isomer of Medetomidine, dexmedetomidine. The result of this study was negative. Although there was no change in the P/N ratio, the test substance was judged to have reached the bone marrow.

4.9.2 Human information: No information available.

4.9.3 Other relevant information: No information available

4.9.4 Summary and discussion of mutagenicity: Data on medetomidine and dexmedetomidine indicate that medetomidine is not genotoxic in vitro or in vivo.

4.9.5 Comparison with criteria: Data indicate that medetomidine is not genotoxic in vitro or in vivo and does not require classification.

Reproductive Toxicity (R) Score (H, M, or L): L

Reproductive toxicity data is limited. An assessment conducted by ECHA (2014) reviewed all available data and found a single non-standard, two-generational study. No other information was available. The non-standard study determined, *'No effect on fertility was observed in the presence of significant parental toxicity*'. Based upon this evaluation, medetomidine was assigned a low (L) level of concern for reproductive toxicity. As this determination is based upon a single non-standard studies, the level of concern is italicized in the Hazard Summary Table. Additional data may affect this determination.

- Authoritative and Screening Lists
  - Authoritative: None available
  - Screening: None available

- ECHA, 2014
  - **4.11 Toxicity for reproduction**: Developmental toxicity studies are available in rabbits by the intravenous route and in rats by the subcutaneous route of administration.

4.11.1 Effects on fertility:
4.11.1.1 Non-human information: The reproductive toxicity of medetomidine has been investigated in a non-standard two-generation study conducted via the subcutaneous route in Sprague-Dawley rats (Hirsimaki, 1989). In this study, no effects on reproductive toxicity were observed. Parental toxicity in the form of clinical signs (sedation, piloerection, exophthalmos) was observed at all dose levels. Reduced food consumption and an associated decrease in bodyweight gain were observed in F0 males from 13.3 µg/kg bw/day. The reductions in prostate, testis and epididymides weight observed at all dose levels were considered secondary to the

reduced bodyweight gain. F0 dams treated with ≥ 40 µg/kg bw/day had significantly reduced bodyweight gain by up to 20 % during GD 0-20 and by up to 49 % during lactation when compared to controls. Although the number of corpora lutea, number of implantation sites, and the number of pre-implantation losses were all comparable to controls, placenta weight was significantly decreased in F0 dams (by 18 %) at the top dose. In offspring, F1 foetal bodyweight was significantly reduced in a dose dependant manner from a dose of 40 µg/kg bw/day (by up to 35 %), and there was a significant increase in the number of early embryonic deaths in the top dose group (14 vs 5 in controls). There were no effects on the F2 litter parameters of sex ratio and number of pups.

4.11.1.2 Human information: No information available.

4.11.4 Summary and discussion of reproductive toxicity: Fertility. The reproductive toxicity of medetomidine has been investigated in a two generation study (Hirsimaki, 1989). No effect on fertility was observed in the presence of significant parental toxicity (sedation, piloerection, exophthalmos, reduced food consumption and bodyweight gain).

4.11.5 Comparison with criteria: Fertility.
No effects were observed in the absence of marked toxicity that provides sufficient evidence to cause a strong suspicion of reduced fertility.

4.11.6 Conclusions on classification and labelling:
Not classified; conclusive but not sufficient for classification.

Summary:
Reproductive data is limited to a single non-standard, two-generational rat study. No reproductive toxicity effects were observed in this study although some acute mammalian toxicity was observed at all doses used.

Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M or L):

Developmental toxicity data for medetomidine is limited. An ECHA assessment (2014) reviewed all available data and determined the limited results reported *'are considered a result of acute toxicity and not a specific developmental effect'*. Based upon this evaluation, medetomidine was assigned a low (L) level of concern for developmental toxicity. As this determination is based upon laboratory studies, the level of concern is bolded in the Hazard Summary Table. Additional data may affect this determination.

- Authoritative and Screening Lists
  - Authoritative: None available
  - Screening: None available

- ECHA, 2014
  - **4.11.2 Developmental toxicity**
    4.11.2.1 Non-human information: Developmental toxicity of medetomidine has been

investigated in the rabbit via the intravenous route and in rats via the subcutaneous route of administration. There is also limited information from a poorly reported developmental study conducted via the subcutaneous route with dexmedetomidine, the active isomer of medetomidine. Rabbits In the rabbit study, maternal toxicity was observed from 24 µg/kg bw/day medetomidine and consisted of sedation and miosis (FDA, 1966). There were no treatment related effects on bodyweight gain or food consumption; however, in the top dose group daily food consumption was reduced compared to the control group from study day 7. No developmental toxicity was observed in this study. Rats In a non-guideline developmental study in female Sprague-Dawley rats, medetomidine was administered via the subcutaneous route. Maternal toxicity was observed from a dose level of ≥ 30 µg/kg bw/day and included sedation, piloerection and exopthalmos (Hirsimaki, 1988b). Dams treated with ≥ 120 µg/kg bw/day had significantly reduced body weight gain when compared to controls (by 24 and 38 % in the mid and high dose groups, respectively). Placenta weight was significantly reduced by 9 and 22 % in the mid- and top-dose dams. Foetal bodyweight was significantly reduced in a dose dependent manner from a dose level of 30 µg/kg bw/day and there was a significant increase in the number of early embryonic deaths in the top dose group (1.1 ± 0.4 vs 3.1 ± 2.6 for controls vs treatment groups, respectively). No malformations or skeletal abnormalities were observed. In another developmental study, dexmedetomidine was administered to rats via the subcutaneous route (Tariq, 2008). Similar effects were observed in this study as in other studies (food reduction in dams and reduced foetal weights), with no malformations or skeletal abnormalities observed at any CLH REPORT FOR MEDETOMIDINE 42 dose level. However, due to the small group size and limited examinations, the study is of limited use to inform on the classification of the substance. 4.11.2.2 Human information No information available

4.11.3 Other relevant information: None

4.11.4 Summary and discussion of reproductive toxicity:
Developmental toxicity. Information on the developmental toxicity of medetomidine is available from a developmental study in rabbits, one good quality developmental toxicity study in rats and a 2-generation study in rats. In rabbits, no developmental toxicity was observed at any dose level. No malformations or skeletal abnormalities were observed in the rat studies. However, pup deaths were observed at the top dose of both the rat developmental study and the 2-generation study and foetal pup weights were also significantly reduced at lower doses in both studies. Although the deaths and reduced weights were mainly observed in the presence of significant maternal toxicity (sedation, ↓ reduced bodyweight gain) they are not considered secondary to it as they are the same as observed in adult rats following single exposure (see section 4.2). As such, these effects are considered a result of acute toxicity and not a specific developmental effect relevant for classification.

4.11.5 Comparison with criteria:
Developmental toxicity. No effects were observed in the absence of marked toxicity that provides sufficient evidence to cause a strong suspicion of causing developmental toxicity.

4.11.6 Conclusions on classification and labelling:
Not classified; conclusive but not sufficient for classification.

Summary:
Reproductive toxicity data for medetomidine is limited. The 2014 ECHA assessment reported the results of three studies, a rabbit, a rat and a two-generational rat assays. No developmental toxicity was observed in the rabbit assay. Some impacts were observed in the two rat assays at the top dose including an increase in pup deaths and reduced fetal pup weights; however, these impacts were observed during single dose acute toxicity studies and the ECHA assessment concluded *'these effects are considered a result of acute toxicity and not a specific developmental effect relevant for classification'*.

Endocrine Activity (E) Score (H, M or L): L
Limited endocrine activity data is available. However, a European Union (2014) report indicated '*... there were no significant effects on endocrine organs ... in standard mammalian toxicity studies.....*' Therefore, medetomidine was assigned a low (**L**) level of concern for endocrine activity. As this level of concern is based upon limited data, it is italicized in the Hazard Summary Table to indicate the low level of confidence in this determination. Additional data may change this determination.

- Authoritative and Screening Lists
  - Authoritative: None available
  - Screening: None available

- Source
  - EU, 2015:
    - *'Available evidence at this time indicates that ..., medetomidine does not …have endocrine-disrupting properties (there were no significant effects on endocrine organs and/or reproduction in standard mammalian toxicity studies)….. Therefore, the interim criteria for endocrine disruptors are not met.*'

Group II and II* Human Health Effects (Group II and II* Human)
Note: Group II and Group II endpoints are distinguished in the v1.3 Benchmark system (the asterisk indicates repeated exposure). For Systemic Toxicity and Neurotoxicity, Group II and II* are considered sub-endpoints. When classifying hazard for Systemic Toxicity/Organ Effects and Neurotoxicity endpoints, repeated exposure results are required and preferred. Lacking repeated exposure results in a data gap. Lacking single exposure data does not result in a data gap when repeated exposure data are present (shade out the cell in the hazard table and make a note). If data are available for both single and repeated exposures, then the more conservative value is used.*

Acute Mammalian Toxicity (AT) Group II Score (vH, H, M or L): vH

An ECHA assessment (2014) reviewed all available data and assigned medetomidine hazard statements of H300 and H330 both of which equate to a very high (vH) level of concern using

GreenScreen ranking criteria. The Korean GHS, a GS screening source, assigned a similar hazard ranking of H330 (vH). Based upon these evaluations, medetomidine was assigned a very high (vH) level of concern for acute mammalian toxicity. As this determination is based upon laboratory studies, the level of concern is bolded in the Hazard Summary Table.

- Authoritative and Screening Lists
  - *Authoritative:*
    - ECHA - CLP, Acute Tox 2; H300 – Fatal if swallowed
    - ECHA - CLP, Acute Tox 2; H330 – Fatal if inhaled
  - *Screening:*
    - *Korea GHS Acute toxicity (inhalation) - Category 1 [H330 - Fatal if inhaled]*

- ECHA, 2014:
  - **4.2.1 Non-human information**

    4.2.1.1 Acute toxicity: oral: Via the **oral route**, data are available from a study in rats and a study in mice. The **LD_{50} from the rat study was > 31.25 mg/kg bw**, whereas the **LD_{50} value derived from the mouse study was 11 mg/kg bw**. In accordance with the Guidance on the Application of the CLP Criteria (pg 196), classification is, generally, based on the lowest LD_{50} value from the most sensitive species, unless a robust justification as to why this would not be appropriate can be provided. Although neither study was to guideline, they were conducted at similar times in the same laboratory, suggesting that conditions for each study would have been similar. Consequently, it is proposed to base the classification on the lowest LD_{50} value of 11 mg/kg bw.

    4.2.1.2 Acute toxicity: inhalation: An **inhalation LC_{50} of 0.14 mg/l for 4 hours** was derived from a study conducted with rats.

    4**.2.1.3 Acute toxicity: dermal**: **A dermal LD_{50} of > 2,000 mg/kg bw** was derived from a study in rats.

    4.2.2 Human information: The lead effect following administration of either medetomidine of dexmedetomidine (the active isomer of medetomidine) was sedation. This was observed from doses of 0.6 ng/ml (Abbott, 1998). Sedation was reported to be observed within 15 min of administration with recovery observed between 1 – 4 hours after administration. Other effects observed in the presence of the drug included hypotension; bradycardia; hypertension; reduced salivation; decreased blood pressure, heart rate and cardiac output. From these investigations, an i.v. **human NOAEL of 0.4 µg/kg bw was identified for medetomidine**.

    4.2.3 Summary and discussion of acute toxicity: See section 4.2.1 and 4.2.2 CLH REPORT FOR MEDETOMIDINE 23

    4.2.4 Comparison with criteria: Via the oral route, an LD50 of 11 mg/kg bw meets the criteria for classification as Acute tox 2 ($5 < ATE \leq 50$ mg/kg). Via the dermal route, the LD50 was > 2000 mg/kg bw, no classification is proposed. Via the inhalation route, an LC50 of 0.15 mg/l meets the criteria of Acute tox 2 ($> 0.05 \leq 0.5$ mg/l/ 4h for dusts and

mists).

4.2.5 Conclusions on classification and labelling CLP: Acute Tox 2; H300 Fatal if swallowed and Acute Tox 2; H330 Fatal if inhaled

Summary:
For medetomidine, two oral toxicity studies identified LD_{50} values of > 31.25 mg/kg bw and 11 mg/kg bw in separate rat and mouse studies, respectively. The LD_{50} value of 11 mg/kg bw equates to a very high (vH) level of concern. The LD_{50} value of > 31.25 mg/kg bw cannot be used as the levels of concern in the GS criteria range from <50 to > 2,000 for oral toxicity and this value does not identify a definitive level of concern.

An inhalation LC_{50} value of 0.14 mg/l (4 hours) was reported in a rat study. Although the study does not indicate whether the inhalation was due to vapor or dust/mist, the value of 0.14 mg/L equates to a very high (vH) level of concern regardless of which exposure route was used. A dermal LD_{50} value > 2,000 mg/kg bw was identified in a separate rat study. This equates to a low level (L) of concern using GreenScreen ranking criteria.

Using human data, a NOAEL of 0.4 µg/kg bw was identified for medetomidine. GreenScreen does not use NOAEL values for the determination of acute mammalian toxicity although the data may be used in the system toxicity category. Therefore this result is not pertinent to this evaluation.

As the ECHA report indicates a very high (vH) level of concern for both the oral and inhalation routes of exposure, medetomidine was assigned a very high (vH) level of concern for acute mammalian toxicity.

Systemic Toxicity/Organ Effects incl. Immunotoxicity (ST)
(ST-single) Group II Score (single dose: vH, H, M or L); DG

No single dose systemic toxicity data for medetomidine was found; therefore, medetomidine was assigned a level of concern of data gap (DG) for single dose systemic toxicity.

- Authoritative and Screening Lists
  - *Authoritative:* No data available
  - *Screening:* No data available

- ECHA, 2014:
  - **4.3 Specific target organ toxicity – single exposure (STOT SE)**

    4.3.3 Conclusions on classification and labelling: STOT SE 3: H336: May cause drowsiness or dizziness

Summary:
The ECHA (2014) assessment report assigned a systemic single exposure hazard statement of H336 due to the effects of drowsiness caused by medetomidine. GreenScreen, however,

considers this hazard to be quantified under neurotoxicity; therefore, the value is not used here to assign a level of concern to medetomidine but will be used later in this report. No other data for single dose systemic toxicity was found.

(ST-Repeated) Group II* Score (Repeated dose: H, M, L): DG

No repeat dose systemic toxicity data for medetomidine was found. The ECHA (2014) assessment did report some results; however, ECHA determined that these effects were due to acute mammalian toxicity and were not actually the result of a repeat dose toxicity. Therefore, medetomidine was assigned a level of concern of data gap (DG) for repeat dose systemic toxicity.

- Authoritative and Screening Lists
  - Authoritative: None available
  - Screening: None available

- ECHA, 2014
  - **4.8 Specific target organ toxicity (CLP Regulation) – repeated exposure (STOT RE)**
    4.8.1 Summary and discussion of repeated dose toxicity findings relevant for classification as STOT RE according to CLP Regulation: See section 4.7.1.7

    4.8.2 Comparison with criteria of repeated dose toxicity findings relevant for classification as STOT RE: The available data on repeated exposure do appear to support classification of medetomidine for repeated dose toxicity. In the oral 90-day study, death was observed in rats in both sexes from a dose level of 3.6 mg/kg bw/day, the majority from day 11 onwards. In addition to mortality, severe sedation and significant adverse effects on clinical chemistry parameters, bodyweight and organ weights were noted at this dose level. Sedation and effects on bodyweight gain were also observed in the acute toxicity studies. Consequently, whilst the criteria for repeated dose classification appear to have been met, it is considered that the effects observed are not the consequence of repeated (prolonged) exposure, but are in fact acute effects arising from a small number of single exposures, they appear to be the result of acute exposure. As classification for acute toxicity via the oral and inhalation routes is already proposed, it is not proposed to additionally classify for STOT-RE.

    4.8.3 Conclusions on classification and labelling of repeated dose toxicity findings relevant for classification as STOT RE: Not classified; conclusive but not sufficient for classification.

Summary:
The ECHA (2014) assessment reported significant impacts from an oral 90-day rat study. However, ECHA determined that these effects were not due to repeat dose system toxicity '... but are in fact acute effects arising from a small number of single exposures.' Therefore no repeat dose effects were identified.

Neurotoxicity (N)
(N-single) Group II Score (single dose: vH, H, M or L): *M*

Single dose neurotoxicity data for medetomidine is limited. An ECHA assessment (2014) reviewed all available data and identified only a single pertinent study. Using this study, ECHA assigned medetomidine a hazard statement of H336 which equates to a moderate or low level of concern using GreenScreen ranking criteria. Using a conservative approach, medetomidine was assigned a moderate (M) level of concern for single dose neurotoxicity. As this determination is based upon only a single study, the level of concern is italicized in the Hazard Summary Table. Additional data may affect this determination.

- Authoritative and Screening Lists
  - *Authoritative:*
    - ECHA - CLP, STOT SE 3; H336 – May cause drowsiness or dizziness
  - *Screening:* No data available

- ECHA, 2014:
  - **4.3 Specific target organ toxicity – single exposure (STOT SE)**
    4.3.1 Summary and discussion of Specific target organ toxicity – single exposure: Sedation and/or related clinical signs (lethargy, under activity) were observed in all species by all routes. Via the oral and inhalation routes, effects in the eyes were also observed. Via the oral route, in both rat and mice, opacity of the eyes was observed from a dose level of 6.25 mg/kg bw. Histopathological examination revealed keritits in the eyes of all rats in 31.25 mg/kg bw group, but not those dosed 6.25 mg/kg bw group. No mice survived administration with 31.25 mg/kg bw; however, keritits was evident in one (out of 3) surviving animals at 6.25 mg/kg bw. Via the inhalation route, opacity of the eyes was observed at all dose levels (≥ 0.1 mg/L). Keritits was not recorded in surviving animals, although it is not clear whether the eyes were examined microscopically. It is likely the keritits and opacity were a result of desiccation of the cornea as a result of the medetomidine-induced exophthalmos and partially close eyelids. They are therefore considered secondary effects and are not relevant for classification. No effects in the eye were observed in the dermal study. A number of changes in various organs (including haemorrhagic lungs, pale liver, congestion of the heart and distended abdomen) were observed in decedents or those killed in extremis. However, these changes were not considered to represent specific target toxicity. No effects were noted in surviving animals.

    4.3.2 Comparison with criteria: Substances that have produced significant toxicity in humans or that, on the basis of evidence from studies in experimental animals, can be presumed to have the potential to produce significant toxicity in humans following single exposure are classified in STOT-SE 1 or 2. Classification is supported by evidence associating single exposure to the substance with a consistent and identifiable toxic effect. The signs apparent after single oral, dermal and inhalation exposure to medetomidine were indicative of non-specific (or secondary to) general acute toxicity. As there was no clear evidence of specific toxic effects on a target organ or tissue, no classification for specific target organ toxicity (single exposure) 1 or 2 under CLP is

proposed. Classification in STOT-SE 3 is reserved for transient target organ effects and is limited to substances that have narcotic effects or cause respiratory tract irritation. CLH REPORT FOR MEDETOMIDINE 24 Administration of medetomidine to animals (via any route) led to signs of sedation (≥ 0.05 mg/kg bw via the oral route, 0.1 mg/L via the inhalation route and 30 mg/kg bw via the dermal route). Sedation was observed at much lower doses than those causing lethality. In surviving animals, signs of sedation also appeared to be transient. In humans, a LOAEL of 0.3 ng/ml blood, which is equivalent to an external iv dose of 1.2 µg/kg bw racemic medetomidine was identified. The sedation was again reported to be transient with recovery observed 1 – 4 hours after administration. In both humans and animals, the severity of the effect was reported to increase with dose. Since signs of sedation were observed in all studies, a simple case for classification as STOT SE 3 can be made. The LOAEL (expressed as an external iv dose) for this effect in humans is 1.2 µg/kg bw. On this basis, the recommended GCL of 20 % seems inappropriate and consideration to a much lower SCL should be given.

4.3.3 Conclusions on classification and labelling: STOT SE 3: H336: May cause drowsiness or dizziness

(N-Repeated) Group II* Score (Repeated dose: H, M, L): DG

No repeat dose neurotoxicity data for medetomidine was found; therefore, medetomidine was assigned a level of concern of data gap (DG) for repeat dose neurotoxicity.

- Authoritative and Screening Lists
  - *Authoritative:* No data available
  - *Screening:* No data available

- Source
  - No additional data available

Skin Sensitization (SnS) Group II* Score (H, M or L): *L*

Skin sensitization data for medetomidine is limited. An ECHA assessment (2014) reviewed all available data and identified only a single non-standard delayed hypersensitivity study in guinea pigs. ECHA determined *'The sensitisation response from the available study was < 30 % in all guinea-pig maximisation studies. Therefore, no classification is required* '. Based upon this limited data, medetomidine was assigned a level of concern of low (L) for skin sensitization. As this determination is based upon a single, non-standard study, the level of concern is italicized in the Hazard Summary Table to indicate the low level of confidence in this determination. Additional data may affect this evaluation.

- Authoritative and Screening Lists
  - Authoritative: None available
  - Screening: None available

- ECHA, 2014
  - **4.6.1 Skin sensitisation**
    4.6.1.1 Non-human information: The skin sensitisation potential of dexmedetomidine (the active isomer of medetomidine) has been investigated in a non-standard delayed hypersensitivity study in guinea-pigs (Hahn, 1995). Two weeks after the last induction injection, the animals were challenged with 2 intradermal injections of dexmedetomidine at 0.06 %. Dexmedetomidine did not induce skin sensitisation in any animals tested. Although the positive control gave an appropriate response, as the challenge dose was not maximal, no conclusions can be drawn about medetomidine's skin sensitisation potential at concentrations of > 0.06%. An OECD compliant local lymph node was initiated with medetomidine, but was terminated due to severe sedation and anaesthesia of the test animals (Ranta-Paula, 2010c).

    4.6.1.2 Human information: No information available

    4.6.1.3 Summary and discussion of skin sensitisation: There were no signs of sensitisation up to 0.06 % in the one available guinea-pig skin sensitisation study conducted with dexmedetomidine, the active isomer of medetomidine.

    4.6.1.4 Comparison with criteria: The sensitisation response from the available study was < 30 % in all guinea-pig maximisation studies. Therefore, no classification is required under the CLP Regulation.

    4.6.1.5 Conclusions on classification and labelling: Not classified; inconclusive

Respiratory Sensitization (SnR) Group II* Score (H, M or L): DG

ECHA (2014) identified that no respiratory sensitization data for medetomidine was available; therefore, medetomidine was assigned a level of concern of data gap (DG) for respiratory sensitization.

- Authoritative and Screening Lists
  - *Authoritative:* No data available
  - *Screening:* No data available

- ECHA, 2014
  4.6.2 Respiratory sensitisation
  4.6.2.1 Non-human information: No data are available.

  4.6.2.2 Human information: No data are available.

  4.6.2.3 Summary and discussion of respiratory sensitisation: No data are available.

  4.6.2.4 Comparison with criteria: No data are available.

  4.6.2.5 Conclusions on classification and labelling: Not classified; data lacking

Skin Irritation/Corrosivity (IrS) Group II Score (vH, H, M or L): *L*

Skin irritation/corrosivity data for medetomidine is limited. An ECHA assessment (2014) reviewed all available data and identified a single standard study using rabbits. ECHA determined *'No signs of irritation were observed....'* Based upon this limited data, medetomidine was assigned a level of concern of low (*L*) for skin irritation/corrosivity. As this determination is based upon a single, standard study, the level of concern is italicized in the Hazard Summary Table to indicate the low level of confidence in this determination. Additional data may affect this evaluation.

- Authoritative and Screening Lists
  - Authoritative: None available
  - Screening: None available

- ECHA, 2014:
  - **4.4.1 Skin irritation**
    4.4.1.1 Non-human information: The skin irritation potential of medetomidine has been investigated in a standard guideline study in rabbits. No signs of irritation were observed at any time point.

    4.4.1.2 Human information: No information available

    4.4.1.3 Summary and discussion of skin irritation: The skin irritation potential of medetomidine has been investigated in a standard guideline study in rabbits. No signs of irritation were observed at any time point.

Eye Irritation/Corrosivity (IrE) Group II Score (vH, H, M or L): *L*

Eye irritation/corrosivity data for medetomidine is limited. An ECHA assessment (2014) reviewed all available data and identified only a single standard study using rabbits. ECHA determined *'No effect on the cornea or iris was noted....'* Slight irritation was observed in a single rabbit but identified as more likely related to mechanical than chemical irritation. Based upon this limited data, medetomidine was assigned a level of concern of low (*L*) for eye irritation/corrosivity. As this determination is based upon a single, standard study, the level of concern is italicized in the Hazard Summary Table to indicate the low level of confidence in this determination. Additional data may affect this evaluation.

- Authoritative and Screening Lists
  - Authoritative: None available
  - Screening: None available

- ECHA, 2014:
  - **4.4.2 Eye irritation:**
    4.4.2.1 Non-human information: The eye irritation potential of medetomidine has been investigated in a standard guideline study in rabbits. No effect on the cornea or iris was

noted. Slight irritation-redness of the conjunctivae was noted in a single animal at 24 h after administration, although it is possible that this was caused by mechanical irritation because as much as ¼ of the dose was still present in the conjunctival sack. This residual substance was washed from the eye and the symptoms of irritation were resolved by day 7. No oedema was observed.

4.4.2.2 Human information: No information available

4.4.2.3 Summary and discussion of eye irritation: See section 4.4.2.1

4.4.2.4 Comparison with criteria: No effects in the iris or cornea were noted. The scores for erythema of the conjunctivae were less than 2 (value specified in the classification criteria). No oedema was noted. No classification is proposed.

Ecotoxicity (Ecotox)

Acute Aquatic Toxicity (AA) Score (vH, H, M or L): vH

Acute aquatic toxicity data for medetomidine is limited. An ECHA assessment (2014) reviewed all available data and identified only a single standard study using zebra fish. ECHA determined medetomidine was *'very toxic to aquatic life*' and assigned a hazard statement of H400. H400 equates to a very high level of concern for aquatic toxicity using GreenScreen ranking criteria. The Korea GHS screening list assigned a similar level of concern of Category 1 [H400] which is also a very high level of concern. Based upon this limited data, medetomidine was assigned a level of concern of very high (vH) for acute aquatic toxicity. As this determination is based upon a single, standard study and a screening list determination, the level of concern is italicized in the Hazard Summary Table to indicate the low level of confidence in this level of concern. Additional data may affect this evaluation.

- Authoritative and Screening Lists
  - *Authoritative:*
    - ECHA - CLP, Aquatic Acute 1: H400 - very toxic to aquatic life
  - *Screening:*
    - Korea GHS - Hazardous to the aquatic environment (acute) - Category 1 [H400 - very toxic to aquatic life]

- ECHA, 2014:
  - **5.4 Aquatic toxicity:**
    Medetomidine has two stereoisomers; at relevant concentrations in mammalian studies the active isomer is considered to be dexmedetomidine and levomedetomidine is the toxicologically inactive isomer. There is no evidence to indicate that differential toxicity for the two isomers exists for aquatic organisms, however, the ecotoxicological studies have been conducted with the racemate form of medetomidine, which is the form in which it is manufactured and marketed. Medetomidine is also present in two different forms dependent on pH. The pKa of medetomidine is 7.1 (ref. Table 9) so at pH 7.1 the base and salt form will be present in a 50:50 ratio; at pH 9 the base form is approximately

99% and the acid form is 1%. It has been confirmed that the medetomidine used in the ecotoxicological tests was manufactured in the same way as the proposed method for the production of commercial medetomidine. Therefore, the form of medetomidine used in these studies will be the same as that for commercial production. The base and salt ratio could, however, subsequently change depending upon the pH of the test medium. This would only be a concern if there was a differential toxicity expected between the two forms. The pH of sea water is considered to be around 8.0 and there is likely to be around 88 % of the base form and 12 % of the acid form. The pH of the ecotoxicological studies undertaken has been considered to ensure they appropriately reflect the conditions of exposure in the environment and the form medetomidine that will occur in. No significant issues were found with solubility in the reliable ecotoxicological studies presented.

The ecotoxicological test results for technical medetomidine from both acute and chronic studies are summarised in the following tables and sections. A large number of screening studies are available but generally these do not have analytical verification of concentrations, the method of CLH REPORT FOR MEDETOMIDINE 51 manufacture of the medetomidine is not always provided and they were not to GLP or strictly according to guideline. Only the valid studies are included in the following table and relevant end points from these studies are discussed in further detail below. Additional information and robust study summaries are available in the biocide CAR.

Unless otherwise stated, all the studies listed were performed on medetomidine in the commercially available racemic form and purity. The endpoint quoted is based on whether measured concentrations are within 80-120 % of nominal concentrations in which case nominal concentrations (n) are used, or if the concentrations measured depart more than this then mean measured concentrations (mm) are reported.

5.4.1 Fish 5.4.1.1 Short-term toxicity to fish:
One reliable static 96-hour acute toxicity study is available (to OECD 203 and GLP) using zebra fish Danio rerio (Bätscher, 2007a). Test concentrations of medetomidine were 83-122 % of nominals. Although the report referred to medetomidine hydrochloride being used, the batch details simply referred to medetomidine. The 96-hour LC50 was 30 mg/l based on the mean measured concentrations. It is of note that the NOEC in this study was

Conclusions on classification and labelling for environmental hazards (sections 5.1 – 5.4):
Aquatic Acute 1; H400: Very toxic to aquatic life
Acute M-factor = 1

Chronic Aquatic Toxicity (CA) Score (vH, H, M or L): vH
Chronic aquatic toxicity data for medetomidine is limited. An ECHA assessment (2014) reviewed all available data and identified a single standard study using sheepshead minnow. Additional non-standard studies on rainbow trout and mysid shrimp were mentioned but not included in the assessment as the study results were not thought to be reliable. ECHA determined

medetomidine was *'very toxic to aquatic life with long lasting effects*' and assigned a hazard statement of H410. H400 equates to a very high level of concern for aquatic toxicity. The Korea GHS screening list assigned a similar level of concern of Category 1 [H410], also a very high level of concern. Based upon this limited data, medetomidine was assigned a level of concern of very high (vH) for chronic aquatic toxicity. As this determination is based upon a single, standard study and a screening list determination, the level of concern is italicized in the Hazard Summary Table to indicate the low level of confidence in this level of concern. Additional data may affect this evaluation.

- Authoritative and Screening Lists
  - *Authoritative:*
    - ECHA - CLP, Aquatic Chronic 1: H410 – Very toxic to aquatic life with long lasting effects
  - *Screening:*
    - Korea GHS - Hazardous to the aquatic environment (chronic) - Category 1 [H410 - very toxic to aquatic life with long lasting effects]

- ECHA, 2014:
  - **5.4 Aquatic toxicity:**
    Medetomidine has two stereoisomers; at relevant concentrations in mammalian studies the active isomer is considered to be dexmedetomidine and levomedetomidine is the toxicologically inactive isomer. There is no evidence to indicate that differential toxicity for the two isomers exists for aquatic organisms, however, the ecotoxicological studies have been conducted with the racemate form of medetomidine, which is the form in which it is manufactured and marketed. Medetomidine is also present in two different forms dependent on pH. The pKa of medetomidine is 7.1 (ref. Table 9) so at pH 7.1 the base and salt form will be present in a 50:50 ratio; at pH 9 the base form is approximately 99% and the acid form is 1%. It has been confirmed that the medetomidine used in the ecotoxicological tests was manufactured in the same way as the proposed method for the production of commercial medetomidine. Therefore, the form of medetomidine used in these studies will be the same as that for commercial production. The base and salt ratio could, however, subsequently change depending upon the pH of the test medium. This would only be a concern if there was a differential toxicity expected between the two forms. The pH of sea water is considered to be around 8.0 and there is likely to be around 88 % of the base form and 12 % of the acid form. The pH of the ecotoxicological studies undertaken has been considered to ensure they appropriately reflect the conditions of exposure in the environment and the form medetomidine that will occur in. No significant issues were found with solubility in the reliable ecotoxicological studies presented.

    The ecotoxicological test results for technical medetomidine from both acute and chronic studies are summarised in the following tables and sections. A large number of screening studies are available but generally these do not have analytical verification of concentrations, the method of CLH REPORT FOR MEDETOMIDINE 51 manufacture of the medetomidine is not always provided and they were not to GLP or strictly according to guideline. Only the valid studies are included in the following table and relevant end points from these studies are discussed in further detail below. Additional

information and robust study summaries are available in the biocide CAR.

Unless otherwise stated, all the studies listed were performed on medetomidine in the commercially available racemic form and purity. The endpoint quoted is based on whether measured concentrations are within 80-120 % of nominal concentrations in which case nominal concentrations (n) are used, or if the concentrations measured depart more than this then mean measured concentrations (mm) are reported.

5.4.1.2 Long-term and sub-lethal toxicity to fish:
i) Sheepshead minnow early life stage.
Vaughan and Hutchinson (2011) investigated the toxicity of medetomidine to early life stages of sheepshead minnow (Cyprinodon variegates) according to OECD guideline 210 and GLP. This was a standard flow-through early life stage study undertaken in normal laboratory light conditions (photoperiod 16 hours); effects were reported at 28 days post-hatch. The initial nominal test concentrations used were: 0, 1.0, 3.2, 10, 32, 100 and 320 µg/l. The mean measured test concentrations in the study were 105-120 % of the nominal concentrations and therefore results are based on nominals.

NOEC values were reported for the following parameters: hatchability: 320 µg/l; survival: 320 µg/l; length: 32 µg/l; dry weight: 1.0 µg/l (0.001 mg/l). Fish of a paler colour were noted at 10 to 320 CLH REPORT FOR MEDETOMIDINE 53 µg/l but not at lower concentrations. Hence, although a statistically determined NOEC was not provided for fish pigmentation, it was considered to be 3.2 µg a.s./l. It should be noted that an effect on fish colouration is seen at a lower concentration in sheepshead minnow than in rainbow trout. The relevance of pigmentation for hazard classification is discussed further below. Overall the lowest NOEC from this study was a nominal 0.001 mg/l based on dry weight. The study was considered to be reliable.

ii) Rainbow trout sub-lethal effects:
The short-term (two hour exposure period) study by Maunder et al., 2012 was not conducted to guideline as it was a specifically designed study to examine the sub-lethal effect of medetomidine on fish pigmentation, however it was performed in accordance with GLP and is considered reliable. The study was undertaken in standard laboratory light conditions. The concentrations of medetomidine in this study were 88-100 % of nominals and hence results were based on nominal concentrations. The NOEC of 0.01 mg/l (10 µg/l) was based on a reduction in the pigmentation in fish (affected fish were paler in colour and the grey scale intensity was reduced).

Additional Studies in Fish:
A number of other studies in fish are available. These are reviewed in detail in the biocides CAR, however, due to deficiencies in the methodology and/or reporting of these studies they are not considered to be reliable and they have not been included here.

Many of these non-guideline studies were conducted to investigate the sub-lethal effects of medetomidine on pigmentation in fish. This is of uncertain relevance to hazard classification, however the issue is discussed in some detail in document IIA to the CAR

(Section 4.2.5.2). Some studies on pigmentation reported effects as low as 0.0001 mg/l, however the reliability of these data is also questioned.

Conclusion on NOEC for fish:
Overall, it is concluded in the CAR that the use of the dry weight endpoint from the standard fish early life stage (FELS) study also covers any pigmentation effects. This reliable and GLP study by Vaughan and Hutchinson (2011) using sheepshead minnow gave a NOEC of 0.001 mg/l based on fish dry weight. This chronic study does not use the same species as the key acute study (rainbow trout), however, other than pigmentation, no major differences in sensitivity between the species are highlighted in the CAR and sensitivity is expected to be broadly similar over the same time frame. This is discussed further in relation to the chronic M-factor.

ii) Rainbow trout sub-lethal effects:
The short-term (two hour exposure period) study by Maunder et al., 2012 was not conducted to guideline as it was a specifically designed study to examine the sub-lethal effect of medetomidine on fish pigmentation, however it was performed in accordance with GLP and is considered reliable. The study was undertaken in standard laboratory light conditions. The concentrations of medetomidine in this study were 88-100 % of nominals and hence results were based on nominal concentrations. The NOEC of 0.01 mg/l (10 µg/l) was based on a reduction in the pigmentation in fish (affected fish were paler in colour and the grey scale intensity was reduced).

Additional Studies in Fish:
A number of other studies in fish are available. These are reviewed in detail in the biocides CAR, however, due to deficiencies in the methodology and/or reporting of these studies they are not considered to be reliable and they have not been included here.

Many of these non-guideline studies were conducted to investigate the sub-lethal effects of medetomidine on pigmentation in fish. This is of uncertain relevance to hazard classification, however the issue is discussed in some detail in document IIA to the CAR (Section 4.2.5.2). Some studies on pigmentation reported effects as low as 0.0001 mg/l, however the reliability of these data is also questioned.

Conclusion on NOEC for fish:
Overall, it is concluded in the CAR that the use of the dry weight endpoint from the standard fish early life stage (FELS) study also covers any pigmentation effects. This reliable and GLP study by Vaughan and Hutchinson (2011) using sheepshead minnow gave a NOEC of 0.001 mg/l based on fish dry weight. This chronic study does not use the same species as the key acute study (rainbow trout), however, other than pigmentation, no major differences in sensitivity between the species are highlighted in the CAR and sensitivity is expected to be broadly similar over the same time frame. This is discussed further in relation to the chronic M-factor.

5.4.2.2 Long-term toxicity to aquatic invertebrates:

A chronic study on mysid shrimp reproduction and growth to EPA OPPTS 850.1350

(Bjørnestad, 2010) and a study on embryonic development in the mussel, Mytilus edulis (Bellas, Granmo and CLH REPORT FOR MEDETOMIDINE 55 Ohlauson, 2009) are included in the biocide CAR for medetomidine, however the UKCA considers these studies to be unreliable and so they are not included here. A reliable long-term NOEC for the invertebrate taxonomic group is not available.

5.5 Comparison with criteria for environmental hazards (sections 5.1 - 5.4):
Medetomidine is considered not rapidly degradable and not bioaccumulative for classification purposes. No metabolites were present at >5% AR in a sediment/water simulation study at any time point. Therefore, the classification is based on medetomidine ecotoxicity only. Valid data are available for acute and chronic toxicity in fish and algae, and acute toxicity in invertebrates. Algae are the most acutely sensitive trophic group with a reliable 72-hour mean measured ErC50 of 0.65 mg/l for Desmodesmus subspicatus [syn. Scenedesmus subspicatus]. Fish are the most chronically sensitive aquatic organisms with a 28-day NOEC of 0.001 mg/l for effects on dry weight in Cyprinodon variegatus. As discussed above, this is considered to cover any potential sub-lethal effect on pigmentation. No reliable or relevant chronic invertebrate NOEC is available but there is no impact on the chronic classification as the surrogate approach based on acute invertebrate toxicity would not lead to a higher M-factor. Based on available acute and chronic data (and because medetomidine is not rapidly degradable) where L(E)C50 values are below 1 mg/l, classification with Aquatic Acute 1 is applicable. Where the long-term NOEC is below 0.1 mg/l, classification with Aquatic Chronic 1 is applicable. An acute M-factor of 1 is applicable based on the algal ErC50 of 0.65mg/l is in the range 0.1 < L(E)C50 ≤ 1 mg/l. A chronic M-factor of 100 is applicable based on the fish NOEC of 0.001 mg/l being in the range 0.0001 < NOEC ≤ 0.001 mg/l for a non-rapidly degradable substance. This is also considered to help cover any differences in sensitivity between the fish species used in acute and chronic tests.

Conclusions on classification and labelling for environmental hazards (sections 5.1 – 5.4):
Aquatic Chronic 1; H410: Very toxic to aquatic life with long lasting effects
Chronic M-factor = 100

Environmental Fate (Fate)

Persistence (P) Score (vH, H, M, L, or vL): vH

ECHA (2014) reports several studies which identified a level of concern ranging from very high to moderate using data from laboratory studies. A EU report (2015) determined '... *medetomidine breaches the persistence (vP) trigger for marine sediment*.' EPA's PBT profiler provided estimates with a major of medetomidine partitioning to the sediment (high level of concern) and the water (moderate level of concern). Given preference to analytical data, medetomidine was assigned a level of concern of very high (vH) for persistence. As this

determination is based upon analytical data, the level of concern is bolded in the Hazard Summary Table to indicate the higher level of confidence in this level of concern.

- Authoritative and Screening Lists
  - Authoritative: None available
  - Screening: None available

- ECHA, 2014:
  5.1.1 Stability
  Abiotic degradation:
  A hydrolysis study (Sydney, 2011) was carried out to OECD test guideline 111 and to GLP using 100% pure medetomidine. A preliminary test was conducted at pH 4, 7 and 9 and at 50 °C and results showed less than 10 % hydrolysis after 120 hours in all samples. This is considered equivalent to a half-life of greater than one year under environmental conditions and no further testing was performed. Medetomidine is considered to be hydrolytically stable at all environmentally relevant pH and temperatures.

  An aqueous photodegradation study (Wehrhan, 2009) was carried out in accordance with OECD guideline 316 and to GLP. Test solutions were prepared in ethanol (p.a) at the concentration 1.09 g/L (pH 8.5) and 0.109 g/L (pH 8.1). Tier 1 of the guideline was conducted at 24 ºC and the UV spectrum of the test item was measured in order to estimate the maximum possible direct photolysis rate constant. Absorption of UV light between 290 and 800 nm was low for the test item and the molar decadic adsorption coefficients were below 10 L mol- 1 cm -1. The test item is therefore assumed to be photolytically stable and neither theoretical nor experimental photolytic half lives were determined.

  5.1.3 Summary and discussion of degradation:
  Medetomidine is considered stable in abiotic hydrolysis and photolysis studies.

  The substance is not readily biodegradable. In a simulation study on aerobic aquatic degradation in two marine sediment/water systems (Lewis, 2014), the geomean DT50 value for degradation in the whole system was determined to be 51.3 days (range 48.8 to 54 d). A reliable sediment degradation DT50 could not be obtained.

  No information has been submitted on degradation in soil since the principal biocidal use is in the marine environment only. For the purposes of hazard classification under CLP, medetomidine does not meet the rapid degradability criterion of >70% degradation in a 28-day period.

  Therefore, it is considered to be not rapidly degradable.

- EU, 2015:
  - Medetomidine was shown to be hydrolytically stable at all environmentally relevant pH values and temperatures. Absorption of light was low and the substance was therefore assumed to be stable to photolysis. No significant degradation occurred in a ready biodegradation test and therefore medetomidine cannot be regarded as

readily biodegradable.

The criteria for persistence according to Annex XIII of Regulation (EC) 1907 /2006 are listed below. The same criteria are listed in the TGD except there is no reference to a half-life in soil:

- the half life in marine water is higher than 60 days, or
- the half-life in fresh or estuarine water is higher than 40 days, or
- the half-life in marine sediment is higher than 180 days, or
- the half-life in fresh or estuarine water sediment is higher than 120 days, or
- the half-life in soil is higher than 120 days.

It is recommended that persistence should be assessed such that half-lives are determined under relevant environmental conditions, therefore temperature correction to 9 °C of the sediment I water study derived DT50 values is presented in the following Table. Although assessment of persistence should be based on degradation half-lives, only a sediment dissipation half-life could be determined from the water I sediment study according to FOCUS kinetics guidance. The UK CA considered that in this case the dissipation value provided a reasonable estimate of the degradation half-life as the mean Koc value for medetomidine is 2157 mL/g, indicating that back transfer into the water phase is likely to be limited and in general losses from the sediment in such cases are likely to occur by degradation or irreversible adsorption (formation of bound residues). No major metabolites were formed and therefore the persistence assessment only need consider parent medetomidine.

Table 1.13 Whole system degradation and sediment dissipation DT_{50} values at 20 °C and 9 °C

System	Compartment	DT_{50} values (days)	
		At study temp. 20°C	Adjusted to 9°C
W1	Whole system degradation	52.6	125.1
W2		47.9	113.9
Geomean values:		50.2	119.4
W1	Sediment dissipation	218.0	518.6
W2[a]		-	-

[a] *No clear decline at the end of the study*

It is not possible to ascertain from the water I sediment study whether medetomidine would breach the marine water DT 50 trigger for persistence, because a reliable water phase degradation rate could not be calculated. However, the stability of medetomidine in other tests (hydrolysis, photolysis, and ready biodegradation), and the whole system degradation DT50 values suggest that it may do so. Medetomidine breaches the sediment trigger (vP) in both water I sediment systems. The temperature adjusted dissipation DTso value is much greater than the trigger of 180 days in system Wl (vP) and also exceeds the

trigger without temperature adjustment. Persistence must be assumed for system W2 as there was no evidence of decline in concentrations in the sediment at the end of the study. It could reasonably be inferred, given the extent by which the sediment trigger was exceeded in the marine water I sediment study, that medetomidine would most likely breach the fresh or estuarine sediment trigger too.

No data was submitted on the degradation of medetomidine in soil and it is not currently possible to conclude on whether the substance would breach the persistence criteria in soil (i.e. soil DT 50 > 120 d). Since the substance breached the trigger for marine sediment, was stable to hydrolysis and photolysis, and was not readily biodegradable, in the absence of further specific information on the fate in soil, the UK CA concludes that the substance should, by default, be considered P in soil. This P classification for soil could be removed following submission of further data on degradation in soil.

In conclusion, medetomidine breaches the persistence (vP) trigger for marine sediment. The general lack of degradation in other test systems suggests that medetomidine may breach persistence triggers in other environmental compartments as well.

- PBT Profiler: Persistence Estimate

86347-14-0 (RS)-4-[1-(2,3-dimethylphenyl)ethyl]-1Himidazole

Media	Half-Life	Percent in Each Medium
Water	38	16%
Soil	75	78%
Sediment	340	5%
Air	0.16	0%

Summary:
ECHA (2014) reported several standard studies related to the persistence of medetomidine. A hydrolysis study reported a half-life of > 360 days (1 year) for pure medetomidine. This equates to a very high (vH) level of concern. A second study evaluated the aqueous photodegradation of medetomidine. Although no half-life was determine, the study indicated medetomidine was '.... photolytically stable' which suggests a very high (vH) level of concern. A simulation study in two marine sediment/water systems identified a mean half-life (DT50) of 51.3 days (moderate (M) level of concern for sediment and high (H) level of concern for water). This equates to a moderate level of concern.

A EU report (2015) determined '... *medetomidine breaches the persistence (vP) trigger for marine sediment*.'

EPA's PBT profiler estimates the persistence levels of concern for medetomidine which range from very high (sediment) to low (air) with most of medetomidine partitioning to the soil (half-life of 75 days, high (H) level of concern) and water (half-life of 38 days, moderate (M) level of concern).

The values for persistence range considerably from moderate to very high. Using a conservative approach, a very high level of concern using data from standard laboratory studies. As level of concern is based upon analytical studies, it is bolded in the Hazard Summary Table.

Bioaccumulation (B) Score (vH, H, M, L, or vL): vL

ECHA (2014) reports several studies which identified a very low level of concern for persistence from laboratory studies. This result was supported by a EU report (2015) which concluded there was no concern for bioaccumulation or biomagnification for medetomidine. EPA's PBT profiler estimated a BCF that equates to a low level of concern. Given preference to analytical data, medetomidine was assigned a very low (vL) level of concern. As this determination is based upon analytical data, the level of concern is bolded in the Hazard Summary Table to indicate the higher level of confidence in this level of concern.

- Authoritative and Screening Lists
  - Authoritative: None available
  - Screening: None available

- ECHA, 2014:
  4.1.3 Summary and discussion on toxicokinetics: Based upon biological studies in human volunteers, dogs, rats and cats, ' There was no evidence of bioaccumulation.'

  5.3.2 Summary and discussion of aquatic bioaccumulation: The measured maximum log K_{ow} for medetomidine is 3.1 at pH 9 (20 oC), which represents a worst case for aquatic systems due to the limited ionisation of the substance at this pH. This value is below the CLP log Kow trigger value of ≥ 4 intended to identify substances with a potential to bioaccumulate. Reliable information from a fish bioconcentration study shows medetomidine to have a whole fish BCF of 1.0, which is less than the CLP trigger of ≥ 500. This substance is therefore not bioaccumulative for classification purposes.

- EU, 2015:
  According to the TGD a substance is considered to have the potential to fulfill the criterion of bioaccumulation when the log K0w exceeds 4.5. For medetomidine, the maximum log K0w is 3.1 at pH 9. Therefore, medetomidine does not meet the criteria set by the TGD.

  In addition, a bioconcentration study has been conducted in sheepshead minnow that indicated that the steady state BCF was 1. 0 ml g- 1 . This value is < 2000 (trigger according to TGD) and suggests that there is no concern of bioaccumulation and biomagnification of medetomidine in the environment and the bioaccumulation criterion is not fulfilled.

- PBT Profiler: Bioaccumulation Estimate
  BCF = 160

Summary:
All data found indicate either a low or very low level of concern for persistence. ECHA (2014) stated based upon biological studies in humans, dogs, cats and rats that there was '... no evidence of bioaccumulation', a log Kow of 3.1 and a BCF of 1.0 based upon a reliable fish study, all of which equate to a very low (vL) level of concern. A EU report (2015) concluded '*...there is no concern of bioaccumulation and biomagnification....*' EPA's PBT Profiler calculated a BCF of 160 which equates to a low (L) level of concern.

Using analytical data, medetomidine is assigned a very low (vL) level of concern for bioaccumulation.

Physical Hazards (Physical)

Reactivity (Rx) Score (vH, H, M or L): L

Medetomidine was assigned a level of concern of low (L) for flammability based the determination in the ECHA (2014) assessment which indicates medetomidine is not pyrophoric, does not liberate reactive gasses and is not considered to possess explosive or oxidizing properties. In addition, the structure of medetomidine suggests that it is not reactive. As this level of concern is based upon analytical results, it is bolded in the Hazard Summary Table to indicate the high level of confidence in this determination.

- Authoritative and Screening Lists
  - Authoritative: None available
  - Screening: None available

- **ECHA, 2014.**
  - **1.3 Physico-chemical properties:**
    Table 9: Summary of physico-chemical properties

Property	Value	Reference	Comment (e.g. measured or estimated
Explosive properties	From a consideration of the structure, medetomidine is not considered to posses explosive properties.		
Oxidising properties	From a consideration of the structure, medetomidine is not considered to possess oxidising properties.		

3.1 Physical-Chemical Properties
3.1.1 Summary and discussion of Physical-Chemical Properties
.... Further, experience in handling and use indicates it is not pyrophoric and does not react with water to liberate flammable gases.

From a consideration of the structure, medetomidine is not considered to posses explosive or oxidising properties.

Flammability (F) Score (vH, H, M or L): L

Medetomidine was assigned a level of concern of low (L) for flammability based on data in the ECHA (2014) assessment. Based upon a standard flammability study, medetomidine was found to be neither flammable nor a flammable solid. In addition, the structure of medetomidine suggests that it is not flammable which is supported by a flash point of 191 degrees Celsius. As this level of concern is based upon analytical results, it is bolded in the Hazard Summary Table to indicate the high level of confidence in this determination.

- Authoritative and Screening Lists
  - Authoritative: None available
  - Screening: None available

- ECHA, 2014:
  - **1.3 Physico-chemical properties:**
    Table 9: Summary of physico-chemical properties

Property	Value	Reference	Comment (e.g. measured or estimated
Flash point	191.3 ^{o}C (calculated using Advanced Chemistry Development, ACD software)	L. Nilsson, R. Bordes, D. Ostrovskii, 2008.	Calculated
Flammability	Not highly flammable. From experience in handling and use and consideration of the chemical structure it is not pyrophoric and does not release flammable gases on contact with water	Sydney , 2011	EC, A10, GLP, Purity 100%

3.1 Physical-Chemical Properties
3.1.1 Summary and discussion of Physical-Chemical Properties
In a standard flammability study (EC A10) medetomidine was found to be not flammable and does not meet the criteria for classification as a flammable solid.

References:

ECHA, 2014: CLH report Proposal for Harmonised Classification and Labelling Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2. Substance Name: Medetomidine, CAS Number: 86347-14-0.

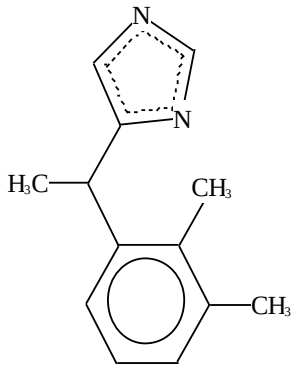
European Union (EU), 2015: Regulation (EU) No 528/2012 concerning the making available on the market and use of biocidal products, Evaluation of active substances, Assessment Report, Medetomidine, Product-type 21 (Antifouling products), 83 pages (http://dissemination.echa.europa.eu/Biocides/ActiveSubstances/1327-21/1327-21_Assessment_Report.pdf).

APPENDIX A: Hazard Benchmark Acronyms (alphabetical order)

(AA) Acute Aquatic Toxicity
(AT) Acute Mammalian Toxicity
(B) Bioaccumulation
(C) Carcinogenicity
(CA) Chronic Aquatic Toxicity
(D) Developmental Toxicity
(E) Endocrine Activity
(F) Flammability
(IrE) Eye Irritation/Corrosivity
(IrS) Skin Irritation/Corrosivity
(M) Mutagenicity and Genotoxicity
(N) Neurotoxicity
(P) Persistence
(R) Reproductive Toxicity
(Rx) Reactivity
(SnS) Sensitization- Skin
(SnR) Sensitization- Respiratory
(ST) Systemic/Organ Toxicity

EPISuite Results for Medetomidine (CAS #)

EPI Suite Results For CAS



SMILES : Cc1cccc(C(C)c2cncn2)c1C
CHEM :
MOL FOR: C13 H16 N2
MOL WT : 200.29
---------- EPI SUMMARY (v4.11) ----------
Physical Property Inputs:
Log Kow (octanol-water): ------
Boiling Point (deg C) : ------
Melting Point (deg C) : ------
Vapor Pressure (mm Hg) : ------
Water Solubility (mg/L): ------
Henry LC (atm-m3/mole) : ------

Log Octanol-Water Partition Coef (SRC):
Log Kow (KOWWIN v1.68 estimate) = 3.83

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPVP v1.43):
Boiling Pt (deg C): 386.32 (Adapted Stein & Brown method)
Melting Pt (deg C): 132.01 (Mean or Weighted MP)
VP(mm Hg,25 deg C): 1.51E-006 (Modified Grain method)
VP (Pa, 25 deg C) : 0.000201 (Modified Grain method)
Subcooled liquid VP: 1.78E-005 mm Hg (25 deg C, Mod-Grain method)
: 0.00238 Pa (25 deg C, Mod-Grain method)

Water Solubility Estimate from Log Kow (WSKOW v1.42):
Water Solubility at 25 deg C (mg/L): 23.56
log Kow used: 3.83 (estimated)
no-melting pt equation used

Water Sol Estimate from Fragments:
Wat Sol (v1.01 est) = 18.724 mg/L

ECOSAR Class Program (ECOSAR v1.11):
Class(es) found:
Imidazoles

Henrys Law Constant (25 deg C) [HENRYWIN v3.20]:
Bond Method : 5.41E-007 atm-m3/mole (5.48E-002 Pa-m3/mole)
Group Method: Incomplete
For Henry LC Comparison Purposes:
User-Entered Henry LC: not entered
Henrys LC [via VP/WSol estimate using User-Entered or Estimated values]:
HLC: 1.689E-008 atm-m3/mole (1.711E-003 Pa-m3/mole)
VP: 1.51E-006 mm Hg (source: MPBPVP)
WS: 23.6 mg/L (source: WSKOWWIN)

Log Octanol-Air Partition Coefficient (25 deg C) [KOAWIN v1.10]:
Log Kow used: 3.83 (KowWin est)
Log Kaw used: -4.655 (HenryWin est)
Log Koa (KOAWIN v1.10 estimate): 8.485
Log Koa (experimental database): None

Probability of Rapid Biodegradation (BIOWIN v4.10):
Biowin1 (Linear Model) : 0.8162
Biowin2 (Non-Linear Model) : 0.8694
Expert Survey Biodegradation Results:
Biowin3 (Ultimate Survey Model): 2.5320 (weeks-months)
Biowin4 (Primary Survey Model) : 3.3532 (days-weeks)
MITI Biodegradation Probability:
Biowin5 (MITI Linear Model) : 0.2310
Biowin6 (MITI Non-Linear Model): 0.1469
Anaerobic Biodegradation Probability:
Biowin7 (Anaerobic Linear Model): -0.5455
Ready Biodegradability Prediction: NO

Hydrocarbon Biodegradation (BioHCwin v1.01):
Structure incompatible with current estimation method!

Sorption to aerosols (25 Dec C)[AEROWIN v1.00]:
Vapor pressure (liquid/subcooled): 0.00237 Pa (1.78E-005 mm Hg)
Log Koa (Koawin est): 8.485
Kp (particle/gas partition coef. (m3/ug)):
Mackay model : 0.00126
Octanol/air (Koa) model: 7.5E-005
Fraction sorbed to airborne particulates (phi):
Junge-Pankow model : 0.0437
Mackay model : 0.0918

Octanol/air (Koa) model: 0.00596

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:
Hydroxyl Radicals Reaction:
OVERALL OH Rate Constant = 102.5921 E-12 cm3/molecule-sec
Half-Life = 0.104 Days (12-hr day; 1.5E6 OH/cm3)
Half-Life = 1.251 Hrs
Ozone Reaction:
No Ozone Reaction Estimation
Fraction sorbed to airborne particulates (phi):
0.0678 (Junge-Pankow, Mackay avg)
0.00596 (Koa method)
Note: the sorbed fraction may be resistant to atmospheric oxidation

Soil Adsorption Coefficient (KOCWIN v2.00):
Koc : 5700 L/kg (MCI method)
Log Koc: 3.756 (MCI method)
Koc : 2767 L/kg (Kow method)
Log Koc: 3.442 (Kow method)

Aqueous Base/Acid-Catalyzed Hydrolysis (25 deg C) [HYDROWIN v2.00]:
Rate constants can NOT be estimated for this structure!

Bioaccumulation Estimates (BCFBAF v3.01):
Log BCF from regression-based method = 2.191 (BCF = 155.4 L/kg wet-wt)
Log Biotransformation Half-life (HL) = 0.1714 days (HL = 1.484 days)
Log BCF Arnot-Gobas method (upper trophic) = 2.520 (BCF = 331)
Log BAF Arnot-Gobas method (upper trophic) = 2.520 (BAF = 331.3)
log Kow used: 3.83 (estimated)

Volatilization from Water:
Henry LC: 5.41E-007 atm-m3/mole (estimated by Bond SAR Method)
Half-Life from Model River: 1533 hours (63.88 days)
Half-Life from Model Lake : 1.684E+004 hours (701.8 days)

Removal In Wastewater Treatment:
Total removal: 22.97 percent
Total biodegradation: 0.26 percent
Total sludge adsorption: 22.68 percent
Total to Air: 0.02 percent
(using 10000 hr Bio P,A,S)

Level III Fugacity Model:

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.101	2.5	1000

Water 16.5 900 1000
Soil 78 1.8e+003 1000
Sediment 5.44 8.1e+003 0
Persistence Time: 1.13e+003 hr

ECOSAR Results for Chemical Name (CAS #)
ECOSAR Version 1.11 Results Page

SMILES : Cc1cccc(C(C)c2cncn2)c1C
CHEM :
CAS Num:
ChemID1:
MOL FOR: C13 H16 N2
MOL WT : 200.29
Log Kow: 3.826 (EPISuite Kowwin v1.68 Estimate)
Log Kow: (User Entered)
Log Kow: (PhysProp DB exp value - for comparison only)
Melt Pt: (User Entered for Wat Sol estimate)
Melt Pt: (deg C, PhysProp DB exp value for Wat Sol estimate)
Wat Sol: 23.56 (mg/L, EPISuite WSKowwin v1.43 Estimate)
Wat Sol: (User Entered)
Wat Sol: (PhysProp DB exp value)

Values used to Generate ECOSAR Profile

Log Kow: 3.826 (EPISuite Kowwin v1.68 Estimate)
Wat Sol: 23.56 (mg/L, EPISuite WSKowwin v1.43 Estimate)

Available Measured Data from ECOSAR Training Set

No Data Available

ECOSAR v1.1 Class-specific Estimations

Imidazoles

ECOSAR Class	Organism	Duration	End Pt	Predicted mg/L (ppm)
Imidazoles	: Fish	96-hr	LC50	0.651
Imidazoles	: Daphnid	48-hr	LC50	0.508
Imidazoles	: Green Algae	96-hr	EC50	0.095
Imidazoles	: Fish	ChV		0.011
Imidazoles	: Daphnid	ChV		0.013

Imidazoles	: Green Algae	ChV	0.075 !	
Imidazoles	: Mysid (SW)	96-hr	LC50	0.080

Neutral Organic SAR	: Fish	96-hr	LC50	3.771
(Baseline Toxicity)	: Daphnid	48-hr	LC50	2.534
	: Green Algae	96-hr	EC50	3.790
	: Fish	ChV	0.450	
	: Daphnid	ChV	0.395	
	: Green Algae	ChV	1.445	

Note: * = asterisk designates: Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported.

NOTE: ! = exclamation designates: The toxicity value was estimated through application of acute-to-chronic ratios per methods outlined in the ECOSAR Methodology Document provided in the ECOSAR Help Menu.

Class Specific LogKow Cut-Offs

If the log Kow of the chemical is greater than the endpoint specific cut-offs presented below, then no effects at saturation are expected for those endpoints.

Imidazoles:

Maximum LogKow: 5.0 (LC50)
Maximum LogKow: 6.4 (EC50)
Maximum LogKow: 8.0 (ChV)

Baseline Toxicity SAR Limitations:

Maximum LogKow: 5.0 (Fish 96-hr LC50; Daphnid LC50)
Maximum LogKow: 6.4 (Green Algae EC50)
Maximum LogKow: 8.0 (ChV)

- Other