ECHA
EUROPEAN CHEMICALS AGENCY

Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the Opinion proposing harmonised classification and labelling at EU level of

Proquinazid

EC number: n.a.

CAS number: 189278-12-4

ECHA/RAC/CLH-O-0000002607-72-01/A2

Adopted

9 March 2012

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

[ECHA has compiled the comments received via internet that refer to several hazard classes and entered them under each of the relevant categories/headings as comprehensive as possible. Please note that some of the comments might occur under several headings when splitting the given information is not reasonable.]

Substance name: **Proquinazid**
EC number: **n.a.**
CAS number: **189278-12-4**

General comments

Date	Country / Person/ Organisation/ MSCA	Comment	MSCA Response to comment	RAC response to comment
13/07/2011	Denmark / National Authority	The Danish EPA agrees with the proposed classification regarding the human health effects.(Carc Cat 3; R40)	Thank you for your support	noted
13/07/2011	France / MSCA	France is in full agreement with the conclusions reached by the RMS regarding the classification of Proquinazid.	Thank you for your support	noted
19/07/2011	Spain / MSCA	Spain supports the United Kingdom proposal.	Thank you for your support	noted
21/07/2011	Sweden / Ing-Marie Olsson / MSCA	The Swedish Chemicals agency (KemI) supports the suggested classification Carc. toxicity category 2, according to Reg. 1272/2008 and Carc. category 3 according to Dir. 67/548/EEC. Editorial: Page numbers in table of contents is not correct There is an inconsistency as to the number of impurities reported in the substance. Page 15 in section 1.2 it says that there are "7 process impurities" and in section 1.2.1 it says "…, containing 4 of the 6 identified impurities)…" and "…(98 % and all 6 impurities)…". On page 18 section 4 it says "..with 7 identified impurities,..", ".., containing 4 of the 7 identified impurities),.." and "..(98 % and all 6 impurities)." The inconsistency should be corrected.	Thank you for this comment. We can confirm this substance has 7 impurities. The reporting of 6 impurities was due to an error in the DAR.	Thanks for the correction

Carcinogenicity

Date	Country / Person / Organisation/ MSCA	Comment	MSCA Response to comment	RAC response to comment
11/07/2011	Germany / Jan Averbeck / MSCA	The German CA agrees with the proposed classification for Carc Cat 3; R40 according to directive 67/548/EEC and Carc 2 – H351 according to CLP regulation, respectively. It is justified to classify Proquinazid in this category (i.e. suspected human carcinogen) because it shows neither in in-vitro tests nor in in-vivo studies genotoxic effects. Relating to tumour occurrence in mice, we share the opinion that the tumour incidences are not very marked, albeit above historical control data. Additionally, indications for a dose-dependent increase in the incidence of hepatocellular adenoma in female rats may indeed be challenged by the concurrent observation of significant signs for general toxicity.	Thank you for your support	noted
19/07/2011	Spain / MSCA	p. 38 Summary and discussion on carcinogenicity The Spanish CA supports the proposed classification of proquinazid as Carc Cat 3; R40 (Harmful; Limited evidence of a carcinogenic effect) according to Directive 67/548/EC and as Carc 2; H351 (Suspected of causing cancer) according to Regulation EC 1272/2008. This classification is based on the increased incidence of hepatocellular carcinomas in mice, intestinal-type cholangiocarcinomas in rats and hepatocellular adenomas and thyroid follicular cell adenomas in both rats and mice. Thyroid: an increase in the incidence of follicular cell adenomas was found in male rats (more sensitive than females) from 1000 ppm (43 mg/kg bw). It is proposed that the thyroid effects observed in rats exposed to proquinazid occur as a result of a dual mechanism (induction of UDP glucuronyltransferase and Inhibition of hepatic 5'-deiodinase) that result in an increased in serum TSH followed by hypertrophy, hyperplasia and adenoma of the thyroid follicular cell. Induction of the liver enzyme, UDP glucuronyltransferase, in rats results in an increased clearance of thyroid hormones with a compensatory increase in TSH. In humans, however, the presence of TBG can compensate for the physiological disturbance and the thyroid will remain unaffected. Therefore, follicular adenomas secondary to liver enzyme induction are considered to be not relevant to humans. The inhibition of hepatic 5´-deiodinase at high dose levels of proquinazid causes an hormonal imbalance, as T4 cannot be converted to T3. Characteristic effects produced by this inhibition include increased serum levels of TSH and T4 and decreased serum	Thank you for supporting our classification proposal. With regards reduced 5'-deiodinase activity, the decrease in enzyme activity could result in lower T3 levels, which in turn may lead to an increase in TSH secretion. However, as increased TSH is not considered to be of particular concern in	We agree that the findings on thyroid cancer in rats are not directly applicable to humans. However, we consider that the comment from MSCA gives further support to our proposed classification STOT RE 2 (thyroid, oral). They conclude that there is an effect of thyroid hormone balance, but that it is not

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		levels of T3. This mechanism is relevant for human because although excess T4 may be buffered by TBG, there may be effects on the negative feedback system in the pituitary which will cause thyroid stimulation. In mice, an increase in the incidence of thyroid follicular cell adenomas was observed in females at the highest dose level of 2000 ppm (415 mg/kg bw) outside the historical control data. The increased tumour incidence may be consistent with prolonged TSH stimulation as, similar to rats, mice also lack thyroid hormone globulin protein. However, as the tumours were observed in females and the mode of action for mice is not as well established as in the rats, human relevance cannot be ruled out. Overall, the increase incidence of follicular cell adenoma observed in rat and mice is of potential relevance to humans. Liver: An increased incidence of intestinal-type cholangiocarcinomas and hepatocellular adenomas were found in female rats from 600 ppm (35 mg/kg bw) in the presence of substantial systemic toxicity (reduced bodyweight gain and liver toxicity). The mode of action of hepatocellular adenomas is not known, so a potential risk for human health can not be discarded. For the development of cholangiocarcinomas, hepatotoxicity such as chronic liver toxicity leading to oval cell proliferation and metaplasia of pluripotent oval cells is needed. These kind of tumours (cholangiocarcinomas) differ in rats and humans for its different histopathology. However, a potential risk for humans depends on the level of exposure. It is appropriate to be precautionary especially as both types of tumours in rats were increased at a relatively low dose level (35 mg/kg bw/day) In mice, an increase of hepatocellular carcinomas in males and hepatocellular adenomas in females were observed at 2000 ppm (282 and 415 mg/kg bw/day in males and females respectively) in absence of generalized toxicity and above the historical control range (carcinomas only slightly above). There is no data on a potential mechanism, so a potential relevance to humans can not be excluded. Overall, carcinogenic effects observed in the liver of rats and mice are relevant to humans.	humans (for the reasons given in Annex I), we did not consider this mode of action to be of particular concern to humans.	likely to induce cancer in humans.

Mutagenicity

Date	Country/ Person/ Organisation/ MSCA	Comment No comment	MSCA Response to comment	RAC response to comment

Toxicity to reproduction

Date	Country / Person / Organisation/ MSCA	Comment No comment	MSCA Response to comment	RAC response to comment

Respiratory sensitisation

Date	Country / Person / Organisation/ MSCA	Comment No comment	MSCA Response to comment	RAC response to comment

Other hazards and endpoints

Date	Country / Person / Organisation/ MSCA	Comment	MSCA Response to comment	RAC response to comment
11/07/ 2011	Belgium / Frederic Denauw / MSCA	Based on the results of the aquatic toxicity test on the most sensitive species (Americamysis bahia 96hEC50 =0.11 mg/l, Daphnia magna21dNOEC=0.0018mg/l) the fact that the substance is not rapidly biodegradable and that the substance shows potential to bioaccumulate (BCF=821), it is justified to classify, following the classification criteria of the 2nd ATP, as Aquatic Acute 1, H400 and Aquatic chronic 1, H410. In view of the proposed classification and the toxicity band for acute toxicity between 0.1mg/l and 1 mg/l, an M-factor for acute toxicity of 1 could be assigned, and an M-factor for chronic toxicity of 10 (not-rapidly degradable substance and toxicity band between 0.001mg/l and 0.01mg/l). Based on the classification and labelling criteria in accordance with dir. 67/548/EEC,	Thank you for your support.	noted

Date	Country / Person / Organisation/ MSCA	Comment	MSCA Response to comment	RAC response to comment
		proquinazid should be classified as N, R50/53. In conclusion : we agree with the proposed environmental classification by the UK MSCA.		
13/07/2011	France / MSCA	Page 15 - point 1.2. and 1.2.1 : composition of the test material. The number of identified not relevant impurities is confidential as well as the number of identified impurities in the batches used for toxicological studies. Page 18: despite the fact that no classification for physical and chemical properties is proposed for the active substance Proquizanid, details for explosive and oxidizing properties, auto-inflammability, flammability and flash point must be given in table 10. Moreover, explanation must be provided for these properties.	Thank you for your comments. Details on the explosive, oxidising, flammability, autoflammability and flash point are provided in table 9; it is felt un-necessary to duplicate the same information in table 10. However, we have added further text to section 3 discussing these data in relation to the criteria.	Thanks for the correction
29/06/2011	Spain / Manuel Carbo / MSCA	*ECHA comment: The comment has been transferred from "General comments" to "Other hazards and endpoints" by ECHA.* We are in agreement with the environmental proposal made by UK.	Thank you for your support.	noted