ECHA
EUROPEAN CHEMICALS AGENCY

Committee for Risk Assessment

RAC

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/F

Adopted

9 March 2012

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OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37(4) of the Regulation (EC) No 1272/2008 (CLP Regulation), the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling of

Substance Name: **proquinazid**

EC Number: **n.a.**

CAS Number: **189278-12-4**

The proposal was submitted by **United Kingdom** and received by RAC on **7 June 2011**

The proposed harmonised classification:

	CLP Regulation (EC) 1272/2008	**Directive 67/548/EEC**
Current entry in Annex VI of CLP Regulation (EC) No 1272/2008	-	-
Proposal by dossier submitter for consideration by RAC	Carc. 2; H351 Aquatic Acute 1; H400 Aquatic Chronic 1; 410 M-factor 10	Carc. Cat. 3; R 40 N; R50/53
Resulting harmonised classification (future entry in Annex VI of CLP Regulation) as proposed by dossier submitter	Carc. 2 - H351 Aquatic Acute 1; H400 Aquatic Chronic 1; H410 Acute M=1 Chronic M=10	Carc. Cat. 3; R 40 N; R50/53

PROCESS FOR ADOPTION OF THE OPINION

United Kingdom has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at

http://echa.europa.eu/web/guest/harmonised-classification-and-labelling-previous-consultations on **7 June 2011.** Parties concerned and MSCAs were invited to submit comments and contributions by **22 July 2011.**

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Benjamin Pina**

Co-rapporteur, appointed by RAC: **Zhivka Halkova**

The opinion takes into account the comments of MSCAs and parties concerned provided in accordance with Article 37(4) of the CLP Regulation.

The RAC opinion on the proposed harmonised classification and labelling has been reached on **9 March 2012,** in accordance with Article 37(4) of the CLP Regulation; giving parties concerned the opportunity to comment. Comments received are compiled in Annex 2.

The RAC opinion was adopted by **consensus.**

OPINION OF RAC

The RAC adopted the opinion that **proquinazid** should be classified and labelled as follows:

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
				Hazard Class and Category Code(s)	Hazard state ment Code(s)	Pictogram, Signal Word Code(s)	Hazard state ment Code(s)	Suppl. Hazard statement Code(s)		
	Proquinazid	n.a.	189278-12-4	Carc 2 Aquatic Acute 1 Aquatic Chronic 1	H351 H400 H410	GHS08 GHS09 Wng	H351 H410		Acute M=1 Chronic M=10	

Classification and labelling in accordance with the criteria of Directive 67/548/EEC

Index No	International Chemical Identification	EC No	CAS No	Classification	Labelling	Concentration Limits	Notes
	Proquinazid	n.a.	189278-12-4	Carc Cat 3; R 40; N; R50/53	Xn; N; R: 40-50/53 S: (2-)36/37-46-60-61		

SCIENTIFIC GROUNDS FOR THE OPINION

Proquinazid is a new active substance in the scope of Directive 91/414/EEC. There have been no previous classification and labelling discussions for this substance.

At the time of RAC opinion adoption, no registration dossiers were available for this substance.

HEALTH HAZARDS

Acute toxicity

Summary of dossier submitter's proposal

The dossier submitter proposed not to classify proquinazid for acute toxicity. Dossier submitter's proposal not to classify proquinazid for acute toxicity was based on three studies where rats were exposed via oral, inhalation and dermal routes. All the reported studies were performed according to OECD test protocols.

Comments received during public consultation

No comments were received regarding this classification during public consultation.

Outcome of RAC assessment - comparison with criteria and justification

According to a protocol OECD Guideline No. 401 (Filiben, 1999a), the oral LD50 value for male and female rats is above 2000 mg/kg bw and, therefore, no classification or labelling is required for acute oral toxicity.

According to a protocol OECD Guideline No. 402 (Filiben, 1999b), the dermal LD50 value for male and female rats is above 2000 mg/kg bw and, therefore, no classification or labelling is required for acute dermal toxicity.

According to a protocol OECD Guideline No. 403 (Kegelman, 2003), the inhalation LC50 value for male and female rats is above 5.2 mg/l (rats, 4 hour), above threshold levels for aerosols and particulates (≤1 mg/l) and for dusts and mists (≤ 5 mg/l). Therefore, no classification or labelling is required for acute inhalation toxicity.

Specific target organ toxicity – single exposure (STOT SE)

Summary of dossier submitter's proposal

The dossier submitter proposed not to classify proquinazid for specific target organ toxicity – single exposure (STOT SE).

Comments received during public consultation

No comments were received regarding this classification.

Outcome of RAC assessment - comparison with criteria and justification

Black ocular discharge was observed in female rats from the oral study and in one rat in the inhalation study. All other clinical signs were considered to be non-specific signs of general acute toxicity. Based on the results of the acute toxicity, no classification or labelling is required for acute toxicity according to Directive 67/548/EEC and CLP Regulation.

Skin irritation

Summary of dossier submitter's proposal

The dossier submitter proposed not to classify proquinazid for skin irritation. The proposal was based on one study in white rabbits which was performed according to the OECD Guideline 404.

Comments received during public consultation

No comments were received regarding this classification.

Outcome of RAC assessment - comparison with criteria and justification

In the reported study on white rabbits, erythema, but not oedema, was observed. The average erythema and oedema scores were < 2, therefore no classification is required under Directive 67/548/EEC. Desquamation and erythema were observed in the 28-dermal study. As these effects were only observed from day 24, they are considered indicative of proquinazid's weak irritating potential and are not considered relevant for classification.

Based on the results, no classification or labelling is required according to Directive 67/548/EEC and CLP Regulation (EC) 1272/2008 as regards the irritation of skin.

Eye irritation

Summary of dossier submitter's proposal

The dossier submitter proposed not to classify proquinazid for eye irritation. The eye irritation potential of proquinazid was investigated in a standard guideline study.

Comments received during public consultation

No comments were received regarding this classification.

Outcome of RAC assessment - comparison with criteria and justification

No effects on the cornea or iris were noted in the reported study. Effects on the conjunctivae were limited to erythema and mild oedema. Clear conjunctival discharge was noted after 1 h, but not at later time points. Based on the results, no classification or labelling is required according to Directive 67/548/EEC and CLP Regulation (EC) 1272/2008 as regards eye irritation.

Respiratory tract irritation

Summary of dossier submitter's proposal

The dossier submitter proposed not to classify proquinazid for respiratory track irritation.

Comments received during public consultation

No comments were received regarding this classification.

Outcome of RAC assessment - comparison with criteria and justification

Although not experimentally tested, proquinazid was assumed not to be a respiratory irritant from acute toxicity experiments. No specific information is given, RAC agrees that no classification is needed.

Corrosivity

Summary of dossier submitter's proposal

The dossier submitter proposed not to classify proquinazid for corrosivity.

Comments received during public consultation

No comments were received regarding this classification.

Outcome of RAC assessment - comparison with criteria and justification

Dossier submitter stated that no signs of corrosivity were observed in an *in vivo* skin irritation study of proquinazid. Given the available data, RAC agrees with the DS proposal that no classification or labelling is required for corrosivity.

Skin sensitisation

Summary of dossier submitter's proposal

The dossier submitter proposed not to classify proquinazid for skin sensitisation. The proposal not to classify proquinazid for skin sensitisation was based on a standard maximisation study performed according to the OECD 406 test Guideline.

Comments received during public consultation

No comments were received regarding this classification.

Outcome of RAC assessment - comparison with criteria and justification

According to the Guinea pig maximisation test (OECD Guideline No. 406), proquinazid induced skin sensitisation in 3/18 animals compared to 1/10 in the control. Given that less than the 30% positive responses were obtained in the test, RAC agrees that no classification for skin sensitisation is required under Directive 67/548/EEC or the CLP Regulation.

Respiratory sensitisation

Summary of dossier submitter's proposal

The dossier submitter proposed not to classify proquinazid for respiratory sensitisation.

Comments received during public consultation

No comments received.

Outcome of RAC assessment - comparison with criteria and justification

Data is lacking and RAC concludes that no classification is required.

Repeated dose toxicity (DSD) and specific target organ toxicity – repeated exposure (STOT RE) (CLP)

Summary of dossier submitter's proposal

The dossier submitter proposed not to classify proquinazid for repeated dose toxicity (DSD) or specific target organ toxicity – repeated exposure (STOT RE) (CLP). The proposal not to classify proquinazid for this hazard class was based on several studies where repeated dose toxicity of proquinazid was tested in two 90-day studies and one chronic study in the rat, one chronic study in the mouse, and one 90-day and one 1-year study in the dog.

Comments received during public consultation

Specific comments on repeated dose toxicity (DSD) or specific target organ toxicity – repeated exposure (STOT RE) (CLP) were not received. However, effects on thyroid and liver were commented.

Outcome of RAC assessment - comparison with criteria and justification

The repeated dose toxicity of proquinazid was investigated in two 90-day and one chronic study in rats, one chronic study in mice, and one 90-day and one 1-year study in dogs. Liver and thyroid were considered target organs of proquinazid toxicity, whereas reductions in bodyweight gain and food consumption, and ocular discharges were observed in dogs. The latter effects were not considered relevant for classification, thyroid toxicity not relevant for humans and hepatic effects were considered secondary to the liver carcinogenic activity. The observed liver effects are consistent with the carcinogenic effect, and warrant the Carc. classification (see below).

Classification according to DSD criteria

Only thyroid and liver toxicity occurred below the 50 mg/kg bw/day limit for classification. The observed liver effects are consistent with the carcinogenic effect, and warrant the Carc. classification (see the section concerning carcinogenicity). Thyroid effects in rats occur just below the cut-off dose (20 mg/kg bw/day, and the proposed Mode of Action (MoA) (the same as for thyroid tumours) is assumed not to apply to humans. In addition, DAR explicitly reports no effects in the thyroid gland in dogs. Therefore, no repeated dose toxicity classification according to DSD is proposed.

Classification according to CLP criteria

No dermal effects were observed below the CLP cut-off dose. Effects on bodyweight and eyes were observed below the cut-off dose 100 mg/kg bw/day, but not considered severe enough to support classification. Relative liver weight increase and other negative effects (fatty change, biliary tract hyperplasia) were considered as related to the carcinogenic activity. Effects in the thyroid (relative weight changes, follicular hypertrophy and thyroid hormone alterations) were not considered relevant to humans and therefore not relevant for classification.

Whereas the effects in rats (and with less extend, in mice) may warrant a STOT RE classification for thyroid, the MoA of proquinazid for observed thyroid effects in rodents is considered not applicable to humans according to the existing information, a position favoured in the comments given during the public consultation. Therefore, RAC agrees with the dossier submitter's proposal not to classify for STOT RE according to the CLP Regulation.

Germ cell mutagenicity (Mutagenicity)

Summary of dossier submitter's proposal

The dossier submitter proposed not to classify proquinazid for germ cell mutagenicity. The proposal was based on two Ames tests, two mammalian cell gene mutation assays, a chromosome aberration assay and an unscheduled DNA synthesis assay.

Comments received during public consultation

No comment specifically addressed to this hazard class was received. However, one comment explicitly accepts the lack of genotoxic/mutagenic potential for proquinazid.

Outcome of RAC assessment - comparison with criteria and justification

The results of any of the reported studies indicated mutagenicity of proquinazid. The data shows that proquinazid is not mutagenic *in vitro* or *in vivo* and, therefore, RAC agrees that classification according to Directive 67/548/EEC and CLP Regulation (EC) 1272/2008 for mutagenicity is not required.

Carcinogenicity

Summary of dossier submitter's proposal

The dossier submitter proposed to classify proquinazid as Carc 2 (H351) according to CLP and Carc cat 3 (R40) according to DSD. The proposal was based on one carcinogenicity study in the rat and one study in the mouse. Human information on proquinazid's carcinogenicity was not available.

Comments received during public consultation

All comments referred to this issue, and three MSs explicitly agreed to the proposed classification.

Outcome of RAC assessment - comparison with criteria and justification

Proquinazid caused carcinogenic effects in the liver of rats (hepatocellular adenomas and cholangiocarcinomas, only females) and mice (carcinomas in males and adenomas in females). The observed thyroid tumours in rats are considered not relevant for humans (Part II RIVM report 601516009/2002), whereas follicular cell adenomas observed in mice are considered of potential relevance for humans.

Carcinogenic effects were seen in two species (rat and mouse) and in two tissues (liver and thyroid). This would warrant a Cat 1B. However, three circumstances indicate the CLP Carc. 2 labelling as more adequate: 1) Liver carcinogenicity is only observed at very high doses (600-1200 ppm); 2) Thyroid adenomas appears to be related to a MoA not applicable to humans; 3) Proquinazid demonstrated no mutagenic potential.

From the data and arguments of the dossier submitter, RAC considers the proposed classification adequate. Whereas the carcinogenic effects are well established for two model species (rat and mouse), which would argue for Cat 1B classification, the high

doses required for liver carcinogenicity and the doubts about the applicability of the proposed MoA for thyroid carcinogenicity to humans (see chapter *8 Annexes* in the background document) justify the proposed CLP classification Carc 2; H351 and DSD classification Carc cat 3; R40.

Reproductive toxicity

Summary of dossier submitter's proposal

The dossier submitter proposed not to classify proquinazid for reproductive toxicity. The proposal was based on results from two fertility studies in rats and two developmental toxicity studies, one in rats and one in rabbits.

Comments received during public consultation

No comments specifically addressed to this issue.

Outcome of RAC assessment - comparison with criteria and justification

The effects of proquinazid on fertility have been investigated in two 2-generation studies in rats.

In both studies, administration of proquinazid resulted in reduced pup size. In the older study, there was also a reduction in pup viability and in the number of implantations. These effects were observed at a dose level at which significant maternal toxicity was observed (bodyweight reductions of > 10% in the top dose and > 7% in the mid dose). As such, it is considered that these effects are likely to be a non-specific secondary consequence of general toxicity and not a direct consequence of administration of proquinazid.

The developmental toxicity of proquinazid was investigated in one study in rats and one study in rabbits. No relevant malformations were observed.

Overall, the results show that proquinazid does not affect fertility, reproductive performance or development. No effects providing sufficient evidence to cause a strong suspicion of impaired fertility or developmental toxicity were observed in the absence of marked toxicity.

RAC thus concludes that classifications for fertility effects or toxicity for development are not required under Directive 67/548/EEC and Regulation (EC) 1272/2008.

ENVIRONMENTAL HAZARDS

Summary of dossier submitter's proposal

The dossier submitter proposed to classify proquinazid as Aquatic Acute 1 and Aquatic Chronic 1 with an acute M-factor 1 and a chronic M-factor 10 according to CLP, and R50/53 according to DSD. The proposed classification was based on studies on hydrolysis, ready biodegradability, bioaccumulation and both acute and chronic aquatic toxicity tests on three different trophic levels of aquatic organisms.

Comments received during public consultation

Two MSs supported the proposed classification.

Outcome of RAC assessment - comparison with criteria and justification

Proquinazid is hydrolytically stable and not readily biodegradable. The result of 1% biodegradation after 28 days is clearly lower than the 70% reference value (CLP Regulation) for biodegradable substances. Proquinazid is moderately bioaccumulative: BCF=821 (fish), Kow=5.5. These values meet the CLP criteria of BCF=500 for bioaccumulative substances.

Several proquinazid degradation products have been described and analysed. They are considered less toxic and bioaccumulative than the parental compound.

Acute toxicity: The three trophic levels represented in the data set (fish, invertebrates and algae) showed similar sensitivity to proquinazid in acute ecotoxicity tests. The mysid shrimp (*Americamysis bahia)* study (flow-through conditions, 96-hour exposure) showed the lowest EC50 (0.11 mg/L) and this value was chosen for classification in CLP as Aquatic Acute Cat 1 (EC50<1 mg/L). As 0.1<EC50<1 mg/L, an M factor of 1 should apply for acute toxicity.

Chronic toxicity: The most sensitive chronic result is from the *Daphnia magna* reproduction test showing the highest sensitivity to long-term (21 d) exposure to proquinazid, with a NOEC of 0.0018 mg/l. Long-term fish results showed a similar toxicity within an order of magnitude, whereas results from other taxa and trophic levels, albeit less sensitive, were in line with fish data. Therefore, the *Daphnia* results were chosen as criteria for classification in CLP as Aquatic Acute Cat 1 (NOEC<0.01 mg/L, not readily biodegradable). As 0.001<NOEC<0.01 mg/L, an M factor of 10 should apply for chronic toxicity.

RAC concludes that classification according to the CLP criteria as Aquatic Acute 1 (H400) with an M-factor 1), and Aquatic chronic 1 (H410) with an M-factor 10 is warranted.

As proquinazid shows EC50<1mg mg/L for aquatic species and it is not biodegradable, the classification N; R50/R53 is warranted according to the criteria in Directive 67/548/EEC.

Additional information

The Background Document, attached as Annex 1, contains the original proposal by the dossier submitter and gives the detailed scientific grounds for the Opinion.

ANNEXES:

Annex 1 Background Document (BD)[1]

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and RAC (excl. confidential information). A revised version of the CLH report submitted after PC by the dossier submitter as part of the RCOM is included in Annex 2, section 2.

[1] The Background Document (BD) gives detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the dossier submitter; the evaluation performed by RAC is contained in RAC boxes.