ECHA
EUROPEAN CHEMICALS AGENCY

# Committee for Risk Assessment

# RAC

# Opinion

proposing harmonised classification and labelling
at EU level of

# Amidosulfuron

**EC Number: 407-380-0**

**CAS Number: 120923-37-7**

ECHA/RAC/CLH-O-0000002509-70-01/F

**Adopted**

**8 March 2012**

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**08/03/2012**
**CLH-O-0000002509-70-01/F**

# OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT COMMUNITY 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:** **Amidosulfuron**

**EC Number:** **407-380-0**

**CAS Number:** **120923-37-7**

The proposal was submitted by **Austria**
and received by RAC on **29 July 2011**

## The proposed harmonised classification

| | **CLP Regulation (EC) No 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** | Aquatic Acute 1; H400<br>Aquatic Chronic 1; H410<br><br>M (acute) = 100<br>M (chronic) = 10 | N; R50/53<br><br>N; R50/53: C ≥ 0.25 %<br>N; R51/53: 0.025 % ≤ C < 0.25 %<br>R52/53: 0.0025 % ≤ C < 0.025 % |
| **Resulting harmonised classification (future entry in Annex VI of CLP Regulation) as proposed by dossier submitter** | Aquatic Acute 1; H400<br>Aquatic Chronic 1; H410<br><br>M (acute) = 100<br>M (chronic) = 10 | N; R50/53<br><br>N; R50/53: C ≥ 0.25 %<br>N; R51/53: 0.025 % ≤ C < 0.25 %<br>R52/53: 0.0025 % ≤ C < 0.025 % |

## PROCESS FOR ADOPTION OF THE OPINION

***Austria*** 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/consultations/harmonised_cl/harmon_cl_prev_cons_en.asp*** on **29 July 2011**. Parties concerned and MSCAs were invited to submit comments and contributions by **12 September 2011**.

## ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC**: Norbert Rupprich**
Co-rapporteur, appointed by RAC: **Hans-Christian Stolzenberg**

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 **8 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 **amidosulfuron** 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) | | |
| | Amidosulfuron | 407-380-0 | 120923-37-7 | Aquatic Acute 1 Aquatic Chronic 1 | H400 H410 | GHS09<br>Wng | H410 | | Acute M factor =100<br>Chronic M factor =100 | |

## 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 |
|---|---|---|---|---|---|---|---|
| | Amidosulfuron | 407-380-0 | 120923-37-7 | N; R50/53 | N<br>R50/53 | N, R50/53: C ≥ 0.25%<br>N, R51/53: 0.025% ≤ C < 0.25%<br>R52/53: 0.0025% ≤ C <0.025% | |

## SCIENTIFIC GROUNDS FOR THE OPINION

This opinion on harmonised classification and labelling relates to all hazard classes. Unless otherwise specified, the following endpoint evaluations by RAC relate specifically to the proposal of the Dossier Submitter.

## HUMAN HEALTH HAZARD ASSESSMENT

### Acute oral toxicity

#### *Summary of dossier submitter's proposal*

The dossier submitter proposed not to classify amidosulfuron for any of the hazard classes related to human health.

#### Comments received during the public consultation

Comments received during public consultation did not question the dossier submitter's proposal for any of the hazard classes related to human health.

#### *Outcome of RAC assessment - comparison with criteria and justification*

Amidosulfuron has a low acute oral toxicity in rats and mice. The lowest LD50 reported was calculated to be in the range of 5000 mg/kg (female mice). Oral LD50 values need to be lower than 2000 mg/kg in order to classify a substance for acute oral toxicity (both CLP and DSD).

Thus RAC as well proposes not to classify amidosulfuron for acute oral toxicity.

### Acute toxicity by inhalation

#### *Summary of dossier submitter's proposal*

The dossier submitter proposed not to classify amidosulfuron for any of the hazard classes related to human health.

#### Comments received during the public consultation

Comments received during public consultation did not question the dossier submitter's proposal for any of the hazard classes related to human health.

#### *Outcome of RAC assessment - comparison with criteria and justification*

Amidosulfuron was tested for acute inhalative toxicity in rats. The test concentration of 1.8 mg/L air was reported to be the highest concentration that could technically be administered. At this air-borne concentration of 1.8 mg/L there was no mortality in exposed rats. Some unspecific clinical effects were reported. LC50 values need to be lower than 5 mg/L air in order to classify a substance (dust) for acute inhalative toxicity (both CLP and DSD).

Because there was no lethality at the tested air-borne concentration of 1.8 mg/L RAC as well proposes not to classify amidosulfuron for acute toxicity by inhalation.

## Acute dermal toxicity

### *Summary of dossier submitter's proposal*

The dossier submitter proposed not to classify amidosulfuron for any of the hazard classes related to human health.

### Comments received during the public consultation

Comments received during public consultation did not question the dossier submitter's proposal for any of the hazard classes related to human health.

### *Outcome of RAC assessment - comparison with criteria and justification*

Amidosulfuron has a low acute dermal toxicity in rats. No mortality occurred after dermal application of 5000 mg/kg. Dermal LD50 values need to be lower than 2000 mg/kg in order to classify a substance for acute dermal toxicity (both CLP and DSD).

Thus RAC as well proposes not to classify amidosulfuron for acute dermal toxicity.

## Specific target organ toxicity / single exposure

### *Summary of dossier submitter's proposal*

The dossier submitter proposed not to classify amidosulfuron for any of the hazard classes related to human health.

### Comments received during the public consultation

Comments received during public consultation did not question the dossier submitter's proposal for any of the hazard classes related to human health.

### *Outcome of RAC assessment - comparison with criteria and justification*

The observed effects in acute toxicity studies mostly covered clinical signs like e.g. squatting position, high-legged gait, contracted flanks, reduced spontaneous activity, piloerection and irregular breathing. These clinical signs are not considered to be the consequence of a specific non-lethal target organ toxicity.

Thus RAC as well proposes not to classify amidosulfuron for specific target organ toxicity / single exposure.

## Skin irritation

### *Summary of dossier submitter's proposal*

The dossier submitter proposed not to classify amidosulfuron for any of the hazard classes related to human health.

### Comments received during the public consultation

Comments received during public consultation did not question the dossier submitter's proposal for any of the hazard classes related to human health.

### *Outcome of RAC assessment - comparison with criteria and justification*

Amidosulfuron was tested for skin irritation in rabbits. No signs of irritation could be noted in exposed animals at any time of the examination.

Thus RAC as well proposes not to classify amidosulfuron for skin irritation.

## Eye irritation

### *Summary of dossier submitter's proposal*

The dossier submitter proposed not to classify amidosulfuron for any of the hazard classes related to human health.

### Comments received during the public consultation

Comments received during public consultation did not question the dossier submitter's proposal for any of the hazard classes related to human health.

### *Outcome of RAC assessment - comparison with criteria and justification*

Amidosulfuron was tested for eye irritation in rabbits. The results of the study indicate slight irritating effects (conjunctivae and iris). No effects on cornea could be observed. All signs of irritation did recede by day 7 after application of the test substance. For the conjunctivae (chemosis and redness) the individual mean scores (24-72 hours) did not exceed the score of 1. The minimum individual score for conjunctival effects that trigger classification is the score of 2 (both CLP and DSD). There was one animal with an iris score of 1 at 24 hours; thus for the iris the minimum score for classification of 1 is not reached at all.

Thus RAC as well proposes not to classify amidosulfuron for eye irritation.

## Respiratory tract irritation

### *Summary of dossier submitter's proposal*

The dossier submitter proposed not to classify amidosulfuron for any of the hazard classes related to human health.

### Comments received during the public consultation

Comments received during public consultation did not question the dossier submitter's proposal for any of the hazard classes related to human health.

### *Outcome of RAC assessment - comparison with criteria and justification*

There is no human evidence for respiratory tract irritation. In addition, no irritating effects on the respiratory tract were observed in the acute and subchronic rat inhalation studies.

Thus RAC as well proposes not to classify amidosulfuron for respiratory tract irritation.

## Skin sensitisation

### *Summary of dossier submitter's proposal*

The dossier submitter proposed not to classify amidosulfuron for any of the hazard classes related to human health.

### Comments received during the public consultation

Comments received during public consultation did not question the dossier submitter's proposal for any of the hazard classes related to human health.

### *Outcome of RAC assessment - comparison with criteria and justification*

For amidosulfuron the results of two valid guinea pig maximisation tests (GPMT) are available. In the first study none of the 20 test animals showed any signs of irritation on the treated skin areas (challenge phase). In the second study 3/20 test animals showed skin reactions. However, incidence and severity of these reactions were similar in control animals and in those test animals receiving vehicle (acetone) in the challenge phase alone. Thus there is no clear sensitising potential in the second study as well.

Because test results from a GPMT need to exceed a 30% incidence level RAC as well proposes not to classify amidosulfuron for skin sensitisation (CLP and DSD).

## 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 amidosulfuron for any of the hazard classes related to human health.

### Comments received during the public consultation

Comments received during public consultation did not question the dossier submitter's proposal for any of the hazard classes related to human health.

### *Outcome of RAC assessment - comparison with criteria and justification*

Incidence and severity of the adverse effects observed in different oral studies are not sufficiently strong in order to characterise the corresponding doses as "effective doses". Even comparison of NOAELs/LOAELs with the duration-adjusted cut-off levels for the different CLP/DSD RDT categories do not imply the need for RDT classification. There is only one study (28-day dog) with the LOAEL below the highest cut-off level. However, this LOAEL is not considered an "effective dose". The two dog studies with longer duration did not reveal the adverse effects seen in the 28-day dog study. In both longer-term dog studies the NOAELs are higher than the highest cut-off level for classification.

For dermal toxicity and toxicity by inhalation no adverse effects were observed at the highest dose levels tested. The corresponding NOAELs are beyond the highest cut-off levels for these routes of application.

Thus RAC as well proposes not to classify amidosulfuron for repeated dose toxicity (DSD) or specific target organ toxicity – repeated exposure (STOT RE) (CLP).

## Mutagenicity

### *Summary of dossier submitter's proposal*

The dossier submitter proposed not to classify amidosulfuron for any of the hazard classes related to human health.

### Comments received during the public consultation

Comments received during public consultation did not question the dossier submitter's proposal for any of the hazard classes related to human health.

### *Outcome of RAC assessment - comparison with criteria and justification*

Amidosulfuron was tested in a range of *in vitro* mutagenicity assays measuring different mutagenic endpoints like gene mutation in bacterial and mammalian cells, chromosomal aberration and unscheduled DNA synthesis in vitro as well as in an *in vivo* micronucleus test in mice. All mutagenicity study results were negative.

Thus RAC as well proposes not to classify amidosulfuron for mutagenicity.

**Table: Mutagenicity testing of amidosulfuron**

| |
|---|
| Reverse mutation assay (S. typhimurium TA 98, TA 100, TA 1535, TA 1537 and TA 1538; E. coli WP2uvrA) |
| Chinese hamster V79 cell/HGPRT locus gene mutation assay |
| Chromosomal aberration assay in cultured human lymphocytes |
| Unscheduled DNA synthesis assay in mammalian cells (permanent human cell line A 549) |
| Micronucleus test in NMRI mice |

## Carcinogenicity

### *Summary of dossier submitter's proposal*

The dossier submitter proposed not to classify amidosulfuron for any of the hazard classes related to human health.

### Comments received during the public consultation

Comments received during public consultation did not question the dossier submitter's proposal for any of the hazard classes related to human health.

### *Outcome of RAC assessment - comparison with criteria and justification*

Carcinogenicity of amidosulfuron was (validly) tested in rats and mice (chronic toxicity/oncogenicity study in Wistar rats; via diet up to 111 weeks, highest dose tested 1044/1300 mg/kg/d; oncogenicity study in NMRI mice, via diet up to 78/91 weeks, highest dose tested 961/1260 mg/kg/d).

The incidence data of benign and malign neoplastic findings (see histopathology tables in the CLH report) were considered to be similar in both treated and control animals; there was no statistical significance for neoplasms of treated versus control animals. Overall, amidosulfuron did not reveal a carcinogenic potential in rats and mice.

Thus RAC as well proposes not to classify amidosulfuron for carcinogenicity.

## Effects on fertility

### *Summary of dossier submitter's proposal*

The dossier submitter proposed not to classify amidosulfuron for any of the hazard classes related to human health.

### Comments received during the public consultation

Comments received during public consultation did not question the dossier submitter's proposal for any of the hazard classes related to human health.

### *Outcome of RAC assessment - comparison with criteria and justification*

Amidosulfuron was tested in a 2-generation reproduction study in Wistar/HAN rats (see the table in the section "Extended analysis of the key studies provided by the dossier submitter" in the RAC box for effects on fertility in Annex 1). No effects on fertility were observed both in the F0 and F1 parents. The findings of the developmental toxicity studies (see chapter on developmental toxicity) did not reveal any indications for amidosulfuron related effects on fertility.

Thus RAC as well proposes not to classify amidosulfuron for effects on fertility.

## Developmental toxicity

### *Summary of dossier submitter's proposal*

The dossier submitter proposed not to classify amidosulfuron for any of the hazard classes related to human health.

### Comments received during the public consultation

Comments received during public consultation did not question the dossier submitter's proposal for any of the hazard classes related to human health.

### *Outcome of RAC assessment - comparison with criteria and justification*

Developmental toxicity of amidosulfuron has been tested in Wistar rats and Himalayan rabbits; furthermore a postnatal developmental study in rats has been provided. The table in the section "Extended analysis of the key studies provided by the dossier submitter" in the RAC box for effects on fertility (Annex 1) contains studies submitted were performed at the limit dose level of 1000 mg/kg/d. Isolated developmental findings were thoroughly discussed in the CLH dossier. The following table contains those findings which showed statistical significance. The skeletal findings with significant increase in tested animals were graded as retardations and variations within historical control incidences. These findings (retardations and variations) are not considered sufficiently severe in order to trigger a classification for developmental toxicity.

Thus RAC as well proposes not to classify amidosulfuron for developmental toxicity.

## Neurotoxicity

### *Summary of dossier submitter's proposal*

The dossier submitter proposed not to classify amidosulfuron for any of the hazard classes related to human health.

### Comments received during the public consultation

Comments received during public consultation did not question the dossier submitter's proposal for any of the hazard classes related to human health.

### *Outcome of RAC assessment - comparison with criteria and justification*

In all studies provided amidosulfuron did not exhibit signs of neurotoxicity such as CNS symptoms, behaviour abnormalities or histopathological changes with respect to brain, spinal cord or peripheral nerves.

Thus RAC as well proposes not to classify amidosulfuron for neurotoxicity.

## ENVIRONMENTAL HAZARD ASSESSMENT

### *Summary of dossier submitter's proposal*

The dossier submitter proposed to classify amidosulfuron as hazardous to the aquatic environment, Acute category 1 - H400 and Chronic category 1 - H410, with M-factors 100 and 10 respectively, according to the Regulation (EC) 1272/2008 (CLP), and R50/53 (and SCLs corresponding to the acute M-factor of 100), according to Directive 67/548/EEC (DSD).

The proposal for the classification for acute aquatic hazard is based on the ecotoxicological test results from three species of fish, two species of crustaceans, two species of algae, and from two tests with the duckweed *Lemna gibba*, one with a treatment period of 14 days, the other with a treatment period of 7 days, displayed in table 50 of the Annex 1. These tests show that *Lemna gibba* is several orders of magnitude more sensitive than all other taxonomic groups tested. The EC50 values for this species are far below 1 mg/L thus fulfilling the criterion for classification for acute aquatic hazard in the category 1 (CLP) and R50 (DSD). Based on the 7d *Lemna gibba* study the dossier submitter concluded that the EC50 lies between 0.001 and 0.01 mg/L (55% inhibition at 9.2 µg/L), and proposed an acute M-factor (according to CLP) of 100.

The dossier submitter's proposal for the classification for long term aquatic hazard is based on the following additional argumentations.

Amidosulfuron is not prone to photolysis and is hydrolytically stable under pH conditions relevant for the environment. It is not readily biodegradable. In simulation tests its degradation half-time of 38 days in two water-sediment systems was well above the classification criterion of 16 days, while only around 20% mineralisation after 180 days did not indicate ultimate degradation.

Thus, based on this information the dossier submitter concluded that amidosulfuron is not rapidly degradable.

With logPow = -1.56 (pH 7; 1.07 at pH 4) amidosulfuron shows no indication of bioaccumulation potential meeting the classification criteria (BCF > 500 under CLP and BCF > 100 under DSD).

The dossier submitter proposed therefore to classify for long term aquatic hazard as R53 according to DSD.

Regarding the classification for long term aquatic hazard according to CLP, the dossier submitter proposed to base the classification on the lowest of the available toxicity values, which the dossier submitter considered to be the NOEC of 8.74 µg/L of the 14 days *Lemna gibba* study.

This finding would determine a classification for aquatic chronic category 1, accompanied by an M-factor of 10.

After the public consultation, the dossier submitter has resubmitted a new version of the CLH report, which implements some minor corrections and editorial changes pointed out during public consultation. This report is provided at the end of the response to comments (RCOM) document in the Annex 2.

## *Comments received during public consultation*

During the public consultation, comments on hazards to the aquatic environment were received from six Member States.

The comments did not question the proposal of classification as aquatic acute 1 and chronic 1. Likewise, regarding the proposed acute M-factor of 100 (and corresponding SCL under DSD criteria), only supportive comments were submitted. However, the proposed chronic M-factor of 10 was questioned by comments from one Member State. This Member State argued that in the 7 days study on *Lemna gibba* the NOEC should be well below the value of 9.2 µg/L and recommends that the chronic M-factor be modified from 10 to 100 based on 7 days acute toxicity data and on the non rapid degradation of the substance.

The other Member States generally supported the dossier submitter's proposal but indicated some minor corrections (mainly related to labelling) and editorial changes.

For the full set of comments and responses, see the response to comments (RCOM) in the Annex 2.

### *Outcome of RAC assessment - comparison with criteria and justification*

RAC supports the proposal from the dossier submitter to classify amidosulfuron as hazardous to the aquatic environment, Acute category 1 with M-factor 100.

Concerning the long term aquatic hazard, RAC supports the classification as hazardous to the aquatic environment, Chronic category 1. However, RAC does not support the proposed M-factor of 10 and proposes instead a value of 100.

RAC considered both available key studies on duckweed species *Lemna gibba* as not relevant or inconclusive for chronic classification (see the extended analysis in the RAC evaluation box of the Annex 1).

RAC concludes that, in the absence of conclusive data on chronic toxicity for the most sensitive taxonomic group, the surrogate approach according to CLP guidance Annex 1, Table 4.1.0 (b) (iii) should be applied. The key information for this approach is 1) the conclusion that amidosulfuron is not rapidly degradable, and 2) the EC50 for *Lemna gibba*.

RAC supports the conclusion of the dossier submitter that the EC50 for *Lemna gibba* is comprised between 0.001 and 0.01 mg/L.

On this basis, the aquatic hazard of amidosulfuron should be classified according to CLP criteria with

**H400, Category Acute 1, M = 100**

**H410, Category Chronic 1, M = 100**

and according to DSD criteria with

**N; R50/53** and applying specific concentration limits (SCL) as follows:

| Classification | Concentration |
|---|---|
| **N; R50/53** | **C ≥ 0.25%** |
| **N; R51/53** | **0.025% ≤ C < 0.25%** |
| **R52/53** | **0.0025% ≤ C < 0.025%** |

## 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 the 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.