17 March 2010
CLH-0-0000000955-67-03/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 ("the CLP Regulation"), the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling of

Substance Names:	***abamectin* (combination of avermectin B_{1a} and avermectin B_{1b})**	***avermectin B_{1a}* (purity more than 80 %)**
EC Number:	***n. a.***	***265-610-3***
CAS Number:	***71751-41-2***	***65195-55-3***

The proposal was submitted by ***the Netherlands***
and received by ECHA on ***01 July 2009***

PROCESS FOR ADOPTION OF THE OPINION

The Netherlands 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/doc/consultations/cl/clh_axvrep_netherlands_abamectin.pdf*** on ***02 September 2009***. Parties concerned and MSCAs were invited to submit comments and contributions by ***17 October 2009***.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: ***Bert-Ove Lund***
Co-rapporteur, appointed by RAC: ***Stephen Dungey***

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 ***17 March 2010,*** 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 **abamectin/avermectin B_{1a}** should be classified and labelled as follows:

Classification & labelling in accordance with Directive 67/548/EEC

Classification[1]: Repr. Cat.3; R63

T+; R26/28

T ; R48/23/25

N; R50/53

Specific concentration limits: Cn ≥ 5% **T ; R48/23**

0.5% ≤ Cn <5% **Xn; R48/20**

Classification of the preparation		
N; R50-53	**N; R51-53**	**R52-53**
Cn ≥ 0.0025%	**0.00025% ≤ Cn <0.0025%**	**0.000025% ≤ Cn <0.00025%**

where Cn is the concentration of abamectin/avermectin B_{1a} in the preparation.

Notes: **None**

Labelling: **Symbol:** **T+, N**
Risk phrases: **R26/28-R48/23/25-R63-R50/53**
Safety phrases: **S28-S36/37-S45-S60-S61**

Classification & Labelling in accordance with the Classification, Labelling and Packaging Regulation (Regulation (EC) 1272/2008):

Classification **Repr. 2** **H361d**

Acute Tox. 2 H300

Acute Tox. 1 H330

STOT-RE 1 H372 ("Causes damage to the nervous system through prolonged or repeated exposure")

Aquatic Acute 1 **H400**

Aquatic Chronic 1 **H410**

Specific concentration limits:

Cn ≥ 5% **STOT-RE 1; H372 Causes damage to the nervous system through prolonged or repeated exposure**

[1] This section should reflect all relevant entries for the C&L: classification, R-phrases, S-phrases, concentrations limits, nota.

0.5% ≤ Cn <5% STOT-RE 2; H373 May cause damage to the nervous system through prolonged or repeated exposure

Classification of the mixture		
H400, H410	**H411**	**H412**
Cn ≥ 0.0025%	**0.00025% ≤ Cn <0.0025%**	**0.000025% ≤ Cn <0.00025%**

where Cn is the concentration of abamectin/avermectin B_{1a} in the mixture.

M-factors: **10,000**

Notes: **none**

Labelling: **GHS06, GHS08, GHS09; Dgr; H300, H330, H361d, H372, H400, H410**

Opinion on justification for need for action at Community level

As an active ingredient in plant protection products (Dir. 91/414/EEC) and biocidal products (Dir. 98/8/EC), there is a requirement for harmonisation of all classification end points.

SCIENTIFIC GROUNDS FOR THE OPINION

The extensive data set presented in the Annex VI dossier for abamectin has already been reviewed by other European technical committees, and so their reliabilities are taken at face value. Studies have generally been conducted using either abamectin or avermectin B_{1a} as the test substance. Due to the close structural similarity of avermectin B_{1b} to avermectin B_{1a} (B_{1a} has an ethyl group whereas B_{1b} has a methyl group at the 26-C position), the results are considered to be equally applicable to both abamectin and avermectin B_{1a}, regardless of which substance was tested.

Reproductive Toxicity

In a developmental toxicity study on rabbits, an increase in malformations (clubbed fore-foot) is occurring at the highest dose tested. The incidence is above the concurrent and historic controls and therefore considered as treatment related. The increased incidence in these malformations was small (5 in the high dose group versus 1 in the control) but considered as evidence of developmental toxicity, although not being clear evidence. These effects were observed in presence of only slight maternal toxicity, unlikely to be related to the increased incidence in malformations.

AFSSA opposed this proposal during the public consultation. AFSSA believes this effect should be disregarded, because of species differences with regard to when the protective transport protein p-glycoprotein starts to appear during pregnancy. However, it is unknown whether there are differences in p-glycoprotein development between rabbits and humans. Therefore, it is prudent to assume that this effect is relevant to humans.

In the rat developmental toxicity study, there is 1 cleft palate to take into consideration for classification and labelling, as a possible indication of developmental toxicity.

It is proposed to classify abamectin for harm to the unborn child as **Repr. Cat. 3; R63** according to Directive 67/548/EEC, and **Repr. Cat. 2; H361d** according to Regulation (EC) 1272/2008. The

classification is based on an increase in malformations (clubbed fore-foot), considered not secondary to maternal toxicity and relevant to humans.

Acute toxicity

Abamectin is very toxic to rats by oral and inhalation administration, with characteristic signs of abamectin toxicity ranging from tremors and ataxia to mortality. A few human cases seem to indicate a somewhat lower acute oral toxicity of abamectin towards humans than to rats.

Based on the acute oral LD_{50} values (8.7-12.8 mg/kg bw) observed in the rat, which are below the threshold value of 25 mg/kg/day for oral acute toxicity T+; R28, abamectin should be classified as **T+; R28 "very toxic if swallowed"**.

Based on the acute inhalation LC_{50} value (<0.21 mg/l, females 0.034-0.051 mg/l, males 0.051-0.21 mg/l), which is lower than the threshold value of 0.25 mg/l/4h for acute inhalation toxicity (T+; R26) of particulates, abamectin should be classified as **T+; R26 "very toxic by inhalation"**.

According to CLP criteria, and based on the data mentioned above, abamectin/avermectin B_{1a} should be classified in **acute hazard category 2** for oral exposure (threshold values 5-50 mg/kg/day) and in **acute hazard category 1** for inhalation exposure (threshold value $\leq$ 0.05 mg/l for particulates), and labelled with signal word 'Danger' and hazard statements: **H300** and **H330** respectively.

There was full support for this proposal during the public consultation.

Repeated dose toxicity

Repeated dose dietary administration of abamectin reveals that the nervous system is a primary target organ for toxicity. A steep dose response curve exists for this effect. Although clinical signs of neurotoxicity occur in all species evaluated, no histopathological effects are evident in central or peripheral nerves. In addition, histopathological changes in the liver of dogs and extramedullary haematopoiesis in the spleen of mice were observed. With respect to inhalation toxicity, the data in the rat study indicate that the nervous system is the primary target organ for toxicity.

Clear signs of oral neurotoxicity were observed in a 90-day study in rats at a dose of 4 mg/kg bw/day. In an 18-week oral (gavage) study in dogs severe signs of toxicity, including mortality, were observed at 0.5 mg/kg bw/day. In a 2-year dietary study in rats severe signs of toxicity, including mortality, were observed at 2.0 mg/kg bw/day. Clear signs of neurotoxicity were also observed in a 30-day inhalation study (6h/day, 5 days/week) in rats, with a LOAEC of 2.69 µg/L (=0.00269 mg/L).

In view of the effects and effect levels for oral and inhalation (neuro-)toxicity in repeated exposure studies, abamectin/avermectin B_{1a} should according to Directive 67/548/EEC be classified with **R48/23/25: Toxic: danger of serious damage to health by prolonged exposure through inhalation and if swallowed**. There was clear neurotoxicity at 0.00269 mg/L which is below the guidance value for R48/23 in a 30 day inhalation study of 0.075 mg/L. In the oral 18-weeks dog study, neurotoxicity and mortality were observed at 0.5 mg/kg/day, a dose level clearly below the guidance value for R48/25 of 5 mg/kg bw/day in a 13-week study.

According to CLP criteria (Regulation (EC) 1272/2008) abamectin should be classified with **STOT-RE Cat. 1**; **H372**, with the hazard statement "**Causes damage to the nervous system**

through prolonged or repeated exposure". In oral repeated dosing studies in animals abamectin appears to be (neuro-)toxic at doses of 4 and 0.5 mg/kg/day in rats and dogs, respectively, which is lower than the guidance value for STOT-RE Cat. 1 of 10 mg/kg bw/day for oral 13-week studies. In a 30-day repeated exposure inhalation study in rats, abamectin is neurotoxic at concentrations of 0.00269 mg/L and above (range-finding study). This is below the guidance value for STOT-RE Cat. 1 in a 30 day inhalation study of 0.06 mg/L (particulates).

Considering the CLP guidance, specific concentration limits (SCL) of 5% and 0.5% have been calculated for repeated dose toxicity by the inhalation route and will be applied both under Directive 67/548/EEC and Regulation (EC) 1272/2008. There was full support for the classification proposal during the public consultation.

Environment

RAC agrees with the environmental classification proposal (N, R50-53; Aquatic Acute 1 (H400), Aquatic Chronic 1 (H410)) and the associated M-factor of 10,000, for the reasons given below. The few comments made during the public consultation were also broadly supportive of this proposal.

Abamectin is not readily biodegradable, achieving 3% degradation over 28 days in an OECD 301F test, at a test concentration (100 mg/L) that significantly exceeded water solubility (1.21 mg/L at 25°C). Avermectin B_{1a} is hydrolytically stable at pH 4 and 7, and hydrolyses slowly at pH 9, with a calculated half-life of 380 days at 20°C. Although rapid aqueous photolysis has been demonstrated for avermectin B_{1a} in laboratory tests (with a half-life of between 1 and 2 days under light conditions representative of summer at 40°N (southern Europe) under clear skies), this degradation pathway is unlikely to be significant in most natural water bodies since it is influenced by water depth and the presence of dissolved and suspended organic matter (e.g. humic acids). The concentration of these natural components will normally be high compared to the concentration of the substance, and they will consequently absorb the larger portion of the sunlight penetrating the water body. For this reason, DT_{50} values for whole water/sediment systems are considered most appropriate for classification purposes in this case. In two natural aerobic water/sediment systems, the system DT_{50} for avermectin B_{1a} based on radioactivity measurements was 87 – 91 days (in the dark at 20°C). After 100 days the degree of mineralisation was around 3%. In two natural anaerobic water/sediment systems, the system DT_{50} for avermectin B_{1a} based on radioactivity measurements was 230 – 312 days (in the dark at 20°C). Consequently, the substance does not meet the classification criteria for readily biodegradable or rapidly degradable.

The steady state fish bioconcentration factor (BCF) measured for avermectin B_{1a} is 69 L/kg (on a wet weight (ww) basis), in a flow-through test in accordance with a standard test guideline. The kinetic BCF was 52 L/kg (ww). Although it is unlikely that this result has been lipid normalised and corrected for growth dilution, the analytical method (total radioactivity) is likely to include metabolites, and so it is presumed to be a worst case. Based on these data, the substance does not meet the classification criteria for bioaccumulation (i.e. the BCF is below 100/500).

Acute toxicity data are available for several species of fish, aquatic invertebrates and algae, following internationally accepted methods. Due to the potential for photolysis and adsorption, flow-through conditions with analytical confirmation of test concentrations are preferred. With the exception of algae, almost all acute $L(E)C_{50}$ values are below 1 mg/L (in fact in the low µg/L range). Invertebrates are the most sensitive trophic group (about an order of magnitude more sensitive than fish), whereas the algal EC_{50} appears to lie above the water solubility limit. Consequently the substance meets the classification criteria for being very toxic to aquatic organisms.

The most sensitive species is the marine crustacean *Mysidopsis bahia* (now *Americamysis bahia*), with a lowest 96-h LC_{50} of 2×10^{-5} mg/L (i.e. 0.02 µg/L) for abamectin (in accordance with standard test guidelines, using a flow-through system and measured concentrations). Although this result appears to be an order of magnitude lower than those for other invertebrates, it is considered to be reliable (in addition, the other invertebrate studies were all static tests with results based on nominal concentrations, and so the actual exposure concentrations might also have been lower than implied). Given the very low acute LC_{50} value for mysids, an M-factor of 10,000 is appropriate and the following Specific Concentration Limits should apply:

Classification of the preparation/mixture		
N; R50-53 H400, H410	N; R51-53 H411	R52-53 H412
Cn ≥ 0.0025%	0.00025% ≤ Cn <0.0025%	0.000025% ≤ Cn <0.00025%

where Cn is the concentration of abamectin/avermectin B_{1a} in the preparation/mixture.

Acute toxicity data are available for two major degradation products 8a-hydroxy-avermectin B_{1a} and [8,9-Z]-avermectin B_{1a} (formed during oxidation and aqueous photolysis respectively) for one species of fish, invertebrate and algae. These degradation products are not more toxic than the parent compound, with one exception, namely a 48-h immobilisation EC_{50} for *Daphnia magna* of 0.082 µg/L for [8,9-Z]-avermectin B_{1a} (based on mean measured concentrations in a static test). This EC_{50} is higher than the lowest value for mysids for the parent substance, but comparable *Daphnia* values for avermectin B_{1a} are in the range 0.12 – 0.38 µg/L (i.e. it appears that [8,9-Z]-avermectin B_{1a} may be 1.5 to 5 times more toxic to *Daphnia* than the parent). Whilst this degradant could also be more toxic to mysids, it is not possible to conclude on this point in the absence of actual data, and since it only appears to be formed in relatively small amounts (<10% of applied radioactivity in the aqueous photolysis study) the M-factor should not be affected.

Additional information

The Background Document, attached as Annex 1, gives the detailed scientific grounds for the Opinion.

ANNEXES:

Annex 1 Background Document (BD)[2]

Annex 2 Comments received on the CLH report and response to comments provided by the dossier submitter (excl. confidential information)

[2] The Background Document (BD) supporting the opinion contains scientific justifications for the CLH proposal. The BD is based on the CLH report prepared by a dossier submitter. The original CLH report may need to be changed as a result of the comments and contributions received during the public consultation(s) and the comments by and discussions in the Committees.