Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

mesosulfuron-methyl (ISO); methyl 2-[(4,6-dimethoxypyrimidin-2-ylcarbamoyl)sulfamoyl]-α-(methanesulfonamido)-*p*-toluate

EC Number: -
CAS Number: 208465-21-8

CLH-O-0000001412-86-131/F

Adopted

9 December 2016

9 December 2016

CLH-O-0000001412-86-131/F

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 Regulation (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling (CLH) of:

Chemical name: **mesosulfuron-methyl (ISO); methyl 2-[(4,6-dimethoxypyrimidin-2-ylcarbamoyl)sulfamoyl]-α-(methanesulfonamido)-*p*-toluate**

EC Number: **-**

CAS Number: **208465-21-8**

The proposal was submitted by **France** and received by RAC on **27 November 2015.**

In this opinion, all classification and labelling elements are given in accordance with the CLP Regulation.

PROCESS FOR ADOPTION OF THE OPINION

France 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/harmonised-classification-and-labelling-consultation/*** on **22 December 2015**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **5 February 2016**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Žilvinas UŽOMECKAS**

Co-Rapporteur, appointed by RAC: **Christine HÖLZL**

Advisor: **Annemarie LOSERT**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation and the comments received are compiled in Annex 2.

The RAC opinion on the proposed harmonised classification and labelling was adopted on **9 December 2016** by **consensus**.

No current Annex VI entry (CLP, Table 3.1)

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 statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	No current Annex VI entry										
Dossier submitters proposal		mesosulfuron-methyl (ISO); methyl 2-[(4,6-dimethoxypyrimidin-2-ylcarbamoyl)sulfamoyl]-α-(methanesulfonamido)-*p*-toluate	-	208465-21-8	Aquatic Acute 1 Aquatic Chronic 1	H400 H410	GHS09 Wng	H410		M=100 M=100	
RAC opinion		mesosulfuron-methyl (ISO); methyl 2-[(4,6-dimethoxypyrimidin-2-ylcarbamoyl)sulfamoyl]-α-(methanesulfonamido)-*p*-toluate	-	208465-21-8	Aquatic Acute 1 Aquatic Chronic 1	H400 H410	GHS09 Wng	H410		M=100 M=100	
Resulting Annex VI entry if agreed by COM	607-729-00-9	mesosulfuron-methyl (ISO); methyl 2-[(4,6-dimethoxypyrimidin-2-ylcarbamoyl)sulfamoyl]-α-(methanesulfonamido)-*p*-toluate	-	208465-21-8	Aquatic Acute 1 Aquatic Chronic 1	H400 H410	GHS09 Wng	H410		M=100 M=100	

GROUNDS FOR ADOPTION OF THE OPINION

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of acute toxicity

Summary of the Dossier Submitter's proposal

One oral, one dermal and one inhalation acute toxicity study, all in rats, were summarised in the CLH report.

After oral exposure of 10 Wistar rats (5 / sex) to 2,000 and 5,000 mg/kg bw, no deaths occurred and no effects on weight gain or gross pathological findings were seen. For both sexes, clinical signs were observed from 10 min and persisted in some cases up to 6 h after administration and comprised of decreased spontaneous activity, squatting posture, stilted gait and also irregular respiration, uncoordinated gait and increased fright reaction. The oral LD_{50} was > 5,000 mg/kg bw for both sexes.

No deaths also occurred after dermal exposure to 5,000 mg/kg bw (Wistar rat, 5 / sex, occlusive) and there were no effects on weight gain or gross pathological findings and there were no clinical signs of toxicity. The dermal LD_{50} was > 5,000 mg/kg bw for both sexes.

In the acute inhalation toxicity study, no deaths occurred among 10 Sprague-Dawley rats (5 / sex) exposed for 4 h to the highest technical achievable concentration of 1.33 mg/L (nominal concentration of 0.76 – 1.09 mg/L). During exposure, rats exhibited irregular respiration. No clinical signs of toxicity or body weight impairment were recorded up to the study termination. Gross pathological examination did not reveal any macroscopic changes. The LC_{50} was > 1.33 mg/L for both sexes.

The Dossier Submitter (DS) therefore proposed no classification for acute toxicity.

Comments received during public consultation

One Member State supported the proposal for no classification. No further comments for this endpoint were received during public consultation.

Assessment and comparison with the classification criteria

The substance induced no mortalities after oral or dermal exposure at or above the doses defining the categories for classification or inhalation exposure at concentrations at the highest technically achievable concentration. RAC thus agrees with the DS that **no classification for acute toxicity is warranted for any of the exposure routes**.

RAC evaluation of specific target organ toxicity – single exposure (STOT SE)

Summary of the Dossier Submitter's proposal

No toxicity to a specific organ was observed in acute oral, inhalation or dermal toxicity studies in animals. Clinical signs of toxicity were observed after single oral exposure to mesosulfuron-methyl, but these were transient in nature and considered to be unspecific signs of general acute toxicity (see section on acute toxicity). Additionally, no acute organ toxicity was observed in short-term nor long-term studies.

The Dossier Submitter (DS) therefore proposed no classification for specific target organ toxicity after repeated exposure (STOT-SE).

Comments received during public consultation

In the only comment received addressing this endpoint, one Member State supported the proposal for no classification.

Assessment and comparison with the classification criteria

No effects that could lead to classification as STOT SE were reported. RAC thus agrees with the DS that **no classification for STOT SE is warranted**.

RAC evaluation of skin corrosion/irritation

Summary of the Dossier Submitter's proposal

The skin irritation potential of mesosulfuron-methyl was tested in a standard guideline compliant study (OECD TG 404) in rabbits using the Draize scores for erythema and oedema formation. The overall mean erythema and oedema scores from the 1-, 24-, 48-, and 72-h observations were in all cases 0. No signs of toxicity occurred during the 3-day observation period. Furthermore, there were no human data demonstrating skin irritation potential.

The DS proposed no classification for this endpoint.

Comments received during public consultation

One Member State supported the proposal for no classification. No further comments for this endpoint were received during public consultation.

Assessment and comparison with the classification criteria

In the reported skin irritation study, there were no indications of irritation or corrosion. RAC thus agrees with the DS that **no classification for skin corrosion/irritation is warranted**.

RAC evaluation of serious eye damage/irritation

Summary of the Dossier Submitter's proposal

The eye irritation potential of mesosulfuron-methyl was tested in a standard guideline compliant study (OECD TG 405). Mesosulforon-methyl was applied to the eye of three female rabbits. After 24-h exposure period, treated eyes were rinsed and examined after 1-, 24-, 48- and 72-h post exposure. At 1 h up to 24 h post installation, evidence of hyperaemia of the blood vessels up to a diffuse deeper crimson reddening was observed. Furthermore, at 1 h post-installation swelling with partial eversion of the lids and a clear colourless discharge were observed. The irritation signs disappeared after two days and no signs of other signs of clinical toxicity occurred during the study.

According to the DS the overall mean scores for the 24-, 48-, and 72-h observations were 0, 0 and 0.33 for corneal opacity, iris and conjunctival redness, respectively. The DS concluded that mesosulfuron-methyl was slightly irritating to the rabbit eye. However, these slight effects seen in the *in vivo* eye irritation study did not meet the CLP classification criteria.

Comments received during public consultation

One Member State supported the proposal for no classification. No further comments for this endpoint were received during public consultation.

Assessment and comparison with the classification criteria

According to the CLP criteria, a substance needs to be classified as "Irritating to eyes" (Category 2) if a substance produces, in at least 2 of 3 tested animals, a positive response of corneal opacity ≥ 1 and/or iritis ≥ 1 and/or conjunctival redness ≥ 2 and/or conjunctival oedema (chemosis) ≥ 2, calculated as mean scores, following grading at 24, 48 and 72 h after installation of the test material and which fully reverses after 21 days.

The overall mean scores from the 24-, 48- and 72-h observations were 0, 0 and 0.33 for corneal opacity, iris and conjunctival redness, respectively. Thus, the criteria for classification were not met. RAC thus agrees with the DS that **no classification for serious eye damage/ irritation is warranted**.

RAC evaluation of respiratory sensitisation

Summary of the Dossier Submitter's proposal

No studies were available which specifically investigated respiratory sensitisation and no human data were present. Thus, no comparison with the criteria could be made. The DS therefore proposed no classification for this endpoint.

Comments received during public consultation

One Member State supported the proposal for no classification. No further comments for this endpoint were received during public consultation.

Assessment and comparison with the classification criteria

RAC concludes that no comparison with the classification criteria can be made since there were no human or animal data available and therefore **no classification for respiratory sensitisation** is warranted.

RAC evaluation of skin sensitisation

Summary of the Dossier Submitter's proposal

An *in vivo* Magnusson & Kligman (M&K) skin sensitisation study in guinea pigs, conducted according to OECD TG 406, was negative for skin sensitisation. There were no reports that mesosulfuron-methyl caused dermal allergic reactions in humans after dermal contact. The DS concluded that mesosulfuron-methyl did not meet the CLP criteria for classification as a skin sensitizer.

Comments received during public consultation

One Member State supported the proposal for no classification. No further comments for this endpoint were received during public consultation.

Assessment and comparison with the classification criteria

In an M&K test, 20 female guinea pigs were treated with intradermal injections of 0.1 mL mesosulfuron-methyl at 5% in deionized water and 50% Freund's Complete Adjuvant (FCA), by topical induction (0.5 mL) at 25% in deionised water, and challenged with 25% in deionised water. No signs of toxicity were observed throughout the study and no sensitisation symptoms were observed.

According to the DS, the concentrations for induction and challenge were determined in pre-screening range finding studies. As stated in the OECD TG 406, in the guinea pig maximization test method, "the concentration of test substance used for each induction exposure should be well-tolerated systemically and should be the highest to cause mild-to-moderate skin irritation. The concentration used for the challenge exposure should be the highest non-irritant dose." Based on the presented data it cannot be determined whether appropriate dosages were applied.

RAC takes into consideration that no explicit evaluation of the applied dose could be made since no details of the dose range finding tests were provided.

In conclusion, since no signs of sensitisation were detected in the M&K test, the criteria for classification were not met and **no classification for skin sensitisation is warranted**.

RAC evaluation of specific target organ toxicity– repeated exposure (STOT RE)

Summary of the Dossier Submitter's proposal

Mesosulfuron-methyl has been extensively studied in standard GLP/OECD-compliant studies involving repeated oral treatments of rats and mice for 90 days, and for up to 1 year in dogs.

Due to the low intrinsic toxicity observed in these studies, repeated dose studies via dermal and inhalation routes were deemed unnecessary.

No adverse effects or signs of serious damage ('clear functional disturbance or morphological change which has toxicological significance') were seen at any dose levels up to the highest dose tested in rats, mice and dogs. The highest tested dose was 1,238 mg/kg bw/d in male mice and 1,603 mg/kg bw/d in female mice. In all of the studies the NOAEL was the highest dose administered. This can be explained by the low toxicity of the test substance in combination with a non-linear resorption from the gastrointestinal tract, i.e., up to 23% after oral low doses of 10 mg/kg bw/d and only 2% or slightly above at the limit dose of 1,000 mg/kg bw/d after oral exposure.

Slight changes in some biochemical parameters (bilirubin, lipids, calcium, inorganic phosphate) were seen in the sub-chronic toxicity study in rats. Slightly reduced values for leukocytes were observed in male mice after 90 days. These findings, which occurred in the mid and high dose groups without showing a clear dose-response pattern, were not consistently seen in both sexes and were therefore, in the absence of any histopathological findings, considered as non-adverse effects. Slightly reduced values for leukocytes in male mice after 90 days were not reproduced with the same strain in the respective oncogenicity study, which in contrast showed slightly increased leukocytes in the high dose group only after 18 months. This minimal shift in leukocyte counts within the biological range over the time may reflect the bioavailability of mesosulfuron-methyl, in particular in the blood of male animals (as indicated by the toxicokinetic investigations). However, in the absence of any clinical and histopathological correlation, it was not considered to be toxicologically relevant.

The DS concluded that no classification for STOT RE was supported based on the absence of relevant toxicological findings up to the highest dose tested.

Comments received during public consultation

One Member State supported the proposal for no classification. No further comments for this endpoint were received during the public consultation.

Assessment and comparison with the classification criteria

Mesosulfuron-methyl did not induce any adverse toxicological effects to support a classification as STOT RE in any of the available repeated dose studies (28 days to 1 year) in rats, mice and dogs, up to doses far above the relevant guidance values (up to 1,238 mg/kg bw/d in males and 1,603 mg/kg bw/d in females in a 90-day mouse study).

In the 90-day dog study, some statistically significant changes of absolute and relative organ weights were described. It was mentioned that some of these changes (absolute uterus, ovary and testes weights) were due to differences in the status of menstrual cycle and / or maturity, which appears plausible. Also the relative pituitary and adrenal weights were changed, with a decrease in males and an increase in females, sometimes reaching statistical significance. Except for the testis weight, no dose-response relationship was obvious, no changes were observed in the recovery group and in the absence of histopathological findings in these organs, these changes were not considered toxicologically relevant.

In the 90-day mouse study, statistically significantly decreased leukocyte counts (in males at mid and high doses, in females at the high dose) exhibited some dose-dependency. However, since there were no histopathological or clinical corroborates and considering that mouse leukocyte counts were increased in the mouse carcinogenicity study (see section on carcinogenicity) this finding was not considered supportive for a STOT RE classification.

A minimal to slight increase in foveolar mucous secretion in the cardiac and fundic sections of the stomach in 3/6 high dose males, accompanied by a chronic superficial gastritis in 1 dog, seen in the 1 year dog study was considered to be due to local irritation in the stomach following treatment with a very high concentration of test substance in the diet. The dose leading to this effect (646 mg/kg bw/d) was also far above the relevant guidance value for STOT RE 2, when adjusted to a 1 year study (25 mg/kg bw/d) using Haber's rule.

Also in the two carcinogenicity studies in rats and mice and the reproductive toxicity studies (all conducted according to GLP and OECD guidelines) no evidence for repeated dose toxicity could be identified (see sections on carcinogenicity and reproductive toxicity).

In conclusion, RAC agrees with the DS that **no classification for STOT RE is warranted**.

RAC evaluation of germ cell mutagenicity

Summary of the Dossier Submitter's proposal

The *in vitro* test battery compromised of the following tests: bacterial gene mutation assay (according to OECD TG 471 and 472), mammalian chromosome aberration test (according to OECD TG 473), mammalian cell gene mutation (HPGRT test, according to OECD TG 476) and DNA damage and repair (UDS test, according to OECD TG 482). Furthermore, an *in vivo* mouse micronucleus assay in bone marrow according to OECD TG 474 was carried out.

None of the five tests, which were all considered as reliable showed any indication of germ cell mutagenicity due to the test substance.

The DS concluded that mesosulfuron-methyl is not genotoxic and proposed no classification for this endpoint.

Comments received during public consultation

One Member State supported the proposal for no classification. No further comments were received during public consultation.

Assessment and comparison with the classification criteria

No germ cell mutagenicity potential was identified in an acceptable battery of tests conducted in accordance with the applicable TG.

RAC agrees that **no classification for germ cell mutagenicity** is warranted.

RAC evaluation of carcinogenicity

Summary of the Dossier Submitter's proposal

Carcinogenicity was investigated in two GLP carcinogenicity studies, one dietary combined chronic and oncogenicity study in the rat conducted in accordance with OECD TG 453 and one dietary mouse oncogenicity study conducted according to OECD TG 451.

Rat

In the rat study, continuous dietary treatment for 106 weeks with dose levels of up to 16,000 ppm, which approximated to the international regulatory limit dose of 1,000 mg/kg bw/d did not produce any evidence of toxicity or oncogenicity during the natural life span of the animals.

A few statistically significant changes in absolute and/or relative organ weights were noted mostly for one sex, with relatively strong effects on adrenal and lung weights.

At the interim sacrifice, the relative lung weight was statistically significantly decreased in all dosed females, ranging between 10.4% to 12.5%, but not in a dose-manner. At the end of the study, a statistically significant decrease in lung weight was only seen in high dose females (-13.8%).

Absolute and relative adrenal weight loss was observed at the interim sacrifice only in females. Statistical significance was reached at the highest dose level for the absolute weight and at all doses for the relative weight. The decreases ranged between 15% and 21.6%; no dose-response relationship was observed.

As there was no clear dose-response relationship and no corroborating histopathological findings the organ weight effects were considered not adverse.

Mouse

Dietary treatment with up to 8,000 ppm (ca. 1,000 mg/kg bw/d) for 80 weeks did not produce any evidence for an oncogenic potential. Survival rates were equal in all groups, only body weight gain was slightly reduced in the high dose females. As a result resulting the NOAEL was set at 103 and 130 mg/kg bw/d in males and females, respectively.

Slight but statistically significant increases in the mean RBC count and Hb, and a decrease in mean MCV, were observed in high dose males only. A statistically significant increase in WBC counts in high dose males and females and in mid dose males at 18 months (not seen at 12 months) could be treatment related, since some dose dependence was seen in males. However, this change was slight and not corroborated by any clinical or histopathological changes and was therefore regarded as of limited toxicological significance. Moreover, it should be noted that leukocyte counts were decreased in the mouse 90-day toxicity study for dose levels ≥ 176 mg/kg bw/d in males and at 1,603 mg/kg bw/d in females.

No other relevant toxicological findings were reported and there was no evidence for an oncogenic potential of mesosulfuron-methyl.

The available studies in mouse and rat gave no indication that mesosulfuron-methyl is carcinogenic.

The lack of oncogenic potential of mesosulfuron-methyl is supported by the absence of genotoxic activity, as determined by results from a battery of four *in vitro* and one *in vivo* genotoxicity tests.

Comments received during public consultation

One Member State supported the proposal for no classification. No further comments for this endpoint were received during public consultation.

Assessment and comparison with the classification criteria

In TG compliant studies in 2 species no evidence of carcinogenicity or pre-neoplastic lesions was observed. Based on the available data, RAC agrees with the DS that **no classification for carcinogenicity** is warranted.

RAC evaluation of reproductive toxicity

Summary of the Dossier Submitter's proposal

Effects on fertility

Reproductive toxicity was tested in a two-generation dietary study in rats, which was conducted according to OECD TG 416.

There were no treatment-related effects on mortality of the parental P and F1 generations. Also no clinical findings could be attributed to treatment in any of the P1 and F1 parental animals. No effects on food consumption (except slightly higher food consumption in high dose P males) and body weight gain were observed.

No test substance related effect on sperm motility in any of the treated groups of P and F1 parental males were recorded. However, there was some indication of test substance related effects on reproductive performance in the P and F1 generations, due to lower initial pregnancy rates, but following a second cohabitation using the same parental pairs, pregnancy rates were comparable with controls in all dose groups.

All pups selected to become the F1 parental generation exhibited a normal development of genitalia and there was no statistically significant difference in the meantime interval for preputial separation or vaginal opening.

Mating indices for both males and females, pregnancy rates, male fertility indices, gestation indices and parturition indices were unaffected by treatment (see table 4.11.1.1-4 in the background document). For both generations, pregnancies and deliveries were not impaired by the test substance; the mean gestation duration for the treated and control groups were comparable. There were no treatment related gross macroscopic organ changes nor histological alterations of the reproductive organs in either the P or F1 generation parental rats.

No treatment related effects were detected in the F1a, F1b, F2a and F2b offspring. The mean number of live and dead pups at birth were comparable in all groups from all litters and they were all normally developed and had normal body weight. No test substance related effects was seen on sex ratio and on external abnormalities in any of the litters. During lactation, mortality was comparable in all groups, including controls.

No treatment related macroscopic findings were observed in F1a, F1b, F2a and F2b pups sacrificed on day 4 (culling) and on postnatal day 21. No test substance related microscopic findings were seen in F2b pups.

Overall, it can be concluded that no adverse effects were indicated from the evaluation of parental or neonatal parameters and no treatment related effects on reproductive performance were noted at dietary levels up to and including 16,000 ppm (1,175 and 1,288 mg/kg bw/d in males and females, respectively).

Developmental toxicity

Developmental toxicity was tested in single rat and rabbit gavage developmental toxicity studies conducted according to OECD TG 414.

Oral administration of daily doses up to 1,000 mg/kg bw/d in pregnant rats did not induce maternal or developmental toxicity. All females became pregnant except one in the control group, three in the low dose group and one in the high dose group. One low dose foetus exhibited multiple major defects which were considered to be an isolated event and not substance related.

For the rabbit study a preliminary range finding study was performed, in which no deaths or signs of toxicity were observed in dams and pups at doses up to 1,000 mg/kg bw/d.

In the main study there were no treatment related deaths, no clinical signs of toxicity and no effects on body weight gain reported. A slight but statistically significant reduction in food consumption was seen between day 8 and day 10 in the high dose group and between day 13 and day 26 in all treated groups. There was no dose-response relationship for this effect (equal among the different treated groups) and it was stated to be within the historical control range.

Apart from one female in each of the low and high dose groups of the main study, all females became pregnant. One foetus in the high dose group displayed effects, which were reported to be related to strangulation with the umbilical cord and thus not considered treatment related. There were no increased incidences for skeletal and organ findings when compared to the control group, all findings being within historical control ranges and not dose dependent.

Oral administration of mesosulfuron-methyl up to a dose of 1,000 mg/kg bw/d did not induce maternal or embryo/foetal toxicity nor teratogenicity.

Summary

In the two-generation study in rats, administration of mesosulfuron-methyl at dietary concentrations of up to and including 16,000 ppm (equivalent to approximately 800 mg/kg bw/d up to 3,000 mg/kg bw/d) did not cause any substance related adverse effects on reproduction, fertility, mating behaviour or malformations in the offspring in a multigeneration study in rats. This lack of substance related findings was in line with the results of the developmental toxicity studies in rats and rabbits, performed at the same laboratory, which clearly showed no substance related adverse findings up to and including the limit dose level of 1,000 mg/kg bw/d.

It is concluded that mesosulfuron-methyl is not a developmental toxicant and is devoid of any teratogenic potential. There is no indication of reproductive toxicity even at extremely high test substance doses, which during certain phases of dietary treatment by far exceeded the internationally accepted limit dose of 1,000 mg/kg bw/d.

Comments received during public consultation

One Member State supported the proposal for no classification. No further comments for this endpoint were received during public consultation.

Assessment and comparison with the classification criteria

No findings indicating effects on fertility were seen in a 2-generation TG compliant study in rats even at high doses. In TG compliant studies in rats and rabbits, no evidence of developmental toxicity was observed.

Based on the available data, RAC agrees with the DS that **no classification for reproductive toxicity (effects on fertility or developmental toxicity)** is warranted.

ENVIRONMENTAL HAZARD EVALUATION

RAC evaluation of aquatic hazards (acute and chronic)

Summary of the Dossier Submitter's proposal

Mesosulfuron-methyl is an herbicide that has been reviewed as a new active substance. All data presented are derived from the methyl ester mesosulfuron-methyl and the proposed classification is for mesosulfuron-methyl.

The dossier submitter (DS) indicated aquatic plants to be the most sensitive trophic level. Based on the available data, the DS proposed environmental hazard classification as Aquatic Acute 1 (H400) with an M-factor of 100 based on acute aquatic toxicity for *Lemna gibba* (7d E_rC_{50} = 0.00129 mg/L), and Aquatic Chronic 1 (H410) with an M-factor of 100, based on chronic aquatic toxicity for *Lemna gibba* (7d NOE_rC = 0.00038 mg/L) and being not rapidly degradable.

Degradation

There are no available data on biodegradation as well as no available ready biodegradability screening tests. The results of a hydrolysis study (OECD TG 111) showed that mesosulfuron-methyl is rapidly hydrolysed at pH 4 (DT_{50} 3.5 days) but was not rapidly hydrolysed at pH 7 and pH 9 (respectively DT_{50} 253 and 318 days). Based on the two water/sediment degradation studies (SETAC, GLP) mesosulfuron-methyl was microbially degraded in the tested aerobic sediment/water systems. The water phase geometric mean DT_{50} at 20°C was 33.9 days and sediment phase geometric mean DT_{50} at 20°C was 55.2 days. The total system geometric mean DT_{50} at 20°C was 45.7 days. Based on the aerobic mineralisation in a surface water study (OECD TG 309, GLP), mesosulfuron-methyl did not mineralise to any relevant extent in dark laboratory conditions. The formation of carbon dioxide was insignificant throughout the study (< 0.1% AR at study end). Therefore, the DS concluded that mesosulfuron-methyl does not meet the assessment criteria for ready biodegradability and should be considered as not rapidly degradable in the aquatic environment.

Bioaccumulation

The estimated log P_{ow} for mesosulfuron–methyl was -0.48 at pH 7. This value is below the CLP trigger value of 4 intended to identify substances with a potential to bioaccumulate. As the log P_{ow} value indicates a low potential to bioaccumulate, no study has been conducted to determine the BCF of mesosulfuron-methyl. Therefore, the DS proposed considering the substance as having a low potential for bioaccumulation.

Aquatic Toxicity

The ecotoxicological tests results from available acute and chronic studies for all trophic levels of mesosulfuron–methyl are summarised in the following table and sections.

Test organism / guideline, test method	Short-term result (endpoint)	Long-term result (endpoint)	Reference
Toxicity to fish			
Rainbow trout (*Oncorhynchus mykiss*) / OECD TG 203, GLP	96h LC_{50} > 100 mg/L	-	M-186666-01-1, 1999

Test organism / guideline, test method	Short-term result (endpoint)	Long-term result (endpoint)	Reference
Toxicity to fish			
Bluegill sunfish (*L. macrochirus*) / OECD TG 203, GLP	96h LC_{50} > 100 mg/L	-	M-186597-01-1, 1999
Sheepshead minnow (*C. variegatus*)	96h LC_{50} > 100 mg/L	-	M-238810-01-1; 2001
Rainbow trout (*Oncorhynchus mykiss*) / OECD TG 204, GLP	-	28d NOEC = 32 mg/L	M-187567-01-1, 2000
Fathead minnow (*P. promelas*) / OPPTS 850.1400, EPA OPP 72-4, GLP	-	32d NOEC = 95 mg/L	M-241475-01-1; 2003
Toxicity to aquatic invertebrates			
Daphnia magna / OECD TG 202, GLP	48h EC_{50} > 100 mg/L	-	M-186707-01-1, 1999
Mysid shrimp (*Mysidopsis bahia*) / US-EPA OPP 72-3, GLP	96h LC_{50} > 100 mg/L	-	M-238811-01-1 ; 2001
Daphnia magna / OECD TG 202, GLP	-	21d NOEC = 1.8 mg/L	M-197785-02-2, 2000
Toxicity to algae			
Selenastrum capricornutum (*Pseudokirchneriella subcapitata*) / OECD TG 201, GLP	72/96h E_rC_{50} > 0.29 mg/L	NOE_rC = 0.018 mg/L	M-143500-01-1, 1998
Selenastrum capricornutum (*Pseudokirchneriella subcapitata*) / OECD TG 201, GLP	72h E_rC_{50} = 3.99 mg/L	NOE_rC = 0.143 mg/L	M-516540-01, 2015
Navicula pelliculosa / OECD TG 201, GLP	96h E_rC_{50} > 74.9 mg/L	NOE_rC = 74.9 mg/L	M-187975-01-1, 2000
Anabaena flos-aquae / OECD TG 201, GLP	96h E_rC_{50} = 4.1 mg/L	NOE_rC = 1 mg/L	M-238869-01-1 ; 2001
Skeletonema costatum / OECD TG 201, GLP	72h E_rC_{50} > 100 mg/L	NOE_rC = 60 mg/L	M-238809-01-1; 2001
Toxicity to aquatic plants			
Lemna gibba / Draft OECD guideline, US-EPA J§123-2, ASTM 1415-91, GLP	7d E_rC_{50} > 0.001 mg/L	7d NOE_rC = 0.00018 mg/L	M-195390-01-1; 2000

Test organism / guideline, test method	Short-term result (endpoint)	Long-term result (endpoint)	Reference
Toxicity to fish			
Lemna gibba / Draft OECD guideline, US-EPA J§123-2, ASTM 1415-91, GLP	7d E_rC_{50} = 0.001717 mg/L	7d NOE_rC < 0.00077 mg/L	M-206814-01; 2002
Lemna gibba / OECD TG 221, GLP	**7d E_rC_{50} = 0.00129 mg/L** 7d E_rC_{50} = 0.00161 mg/L	**7d NOE_rC = 0.000388 mg/L**	M-445139-01-1; 2013

The DS confirmed that all the provided studies are reliable and proposed classification of mesosulfuron-methyl based on aquatic toxicity studies using *Lemna gibba* (2013). The study of *Lemna gibba* (2013) was considered as fully valid without any restrictions.

Acute toxicity

The DS proposed classification of mesosulfuron-methyl as Aquatic Acute 1 (H400), M-factor = 100, based on acute toxicity in aquatic plants (*Lemna gibba*): 7d E_rC_{50} = 0.00129 mg/L (growth inhibition for total frond area).

Chronic toxicity

The DS proposed classification of mesosulfuron-methyl as Aquatic Chronic 1 (H410), M-factor = 100, based on chronic toxicity in aquatic plants (*Lemna gibba*): 7d NOE_rC = 0.000388 mg/L (growth inhibition and no changes in plant appearance and development).

Comments received during public consultation

Three Member State Competent Authorities (MSCA) submitted comments on the environmental part of the DS's proposal. All of them support the proposed classification as Aquatic Acute 1 and Aquatic Chronic 1, as well as the corresponding M-factors of 100.

However, one MSCA asked for clarification on the substance identity as three substances identities are given in CLH report (mesosulfuron-methyl, mesosulfuron and mesosulfuron-methyl-sodium). It not was clear why the other two substances were mentioned in this dossier as the IUCLID Dossier and the cover page of the CLH report indicate that the substance is known only as mesosulfuron-methyl. In answer, the DS clarified that Mesosulfuron is the ISO common name. The active substance manufactured is the variant mesosulfuron-methyl. All data are related to this variant. The DS agreed that for better clarity, only mesosulfuron-methyl shall be considered in the CLH report proposal.

One MSCA pointed out that it would be helpful if, in the assessment, key and supportive studies were identified, and also if the reliability of the studies were indicated. Another MSCA noted that with the exception of the more detailed description for the study on *Lemna gibba*, little information is given for the other reported studies on aquatic toxicity. This makes it difficult to make an objective evaluation of the environmental hazards and to decide which studies should be regarded as key studies. Nevertheless, they agree that aquatic plants (*Lemna gibba*) are the most sensitive trophic level. In answer, the DS confirmed that all studies reported in the CLH report are reliable. The key study was described as follows: "This study is considered to be relevant and reliable and is carried forward for classification purposes with a 7 day E_rC_{50} of 1.29

µg/L and 7 day NOE_rC of 0.388 µg/L" with a detailed summary of the study included in the CLH report. A detailed description of the rest of the study was reported in the RAR volume CA-B9.

Assessment and comparison with the classification criteria

Degradation

RAC notes that there are no available data on biodegradation estimation as well as no available ready biodegradability screening tests and therefore the substance must be considered to be not readily biodegradable. RAC agrees that mesosulfuron-methyl does not fulfil the criteria necessary to be considered ultimately degraded in a surface water simulation test (DT_{50} < 16 days, corresponding to 70% degradation after 28 days). RAC agrees that mesosulfuron-methyl does not fulfil the criteria for primarily degradation, biotically or abiotically, in the aquatic environment (DT_{50} < 16 days corresponding to 70% degradation after 28 days), when it can be demonstrated that the primary degradation products do not fulfil the criteria for classification as hazardous to the aquatic environment. RAC notes that mesosulfuron-methyl degraded in water/sediment systems, however with a DT_{50} > 16 days. In conclusion, RAC agrees that mesosulfuron-methyl does not meet any of the assessment criteria and should be considered as not rapidly degradable in the aquatic environment.

Bioaccumulation

RAC agrees that the estimated log P_{ow} for mesosulfuron–methyl is -0.48 (at pH 7) which is below the CLP log P_{ow} trigger value of 4. As this value shows a low potential to bioaccumulate no study to determine the BCF of the mesosulfuron-methyl was required.

Aquatic toxicity

RAC agrees that there are adequate acute and chronic aquatic toxicity data for all trophic levels (fish, invertebrates, algae/aquatic plants). RAC agrees that aquatic plants (*Lemna gibba*) are the most sensitive trophic level for the purpose of aquatic acute and chronic classification.

Acute toxicity

RAC agrees that the aquatic plant (*Lemna gibba*) 7 day E_rC_{50} = 0.00129 mg/L (based on growth inhibition for total frond area) is the lowest reliable acute/short-term endpoint for aquatic acute classification purposes.

Chronic toxicity

RAC agrees that the aquatic plant (*Lemna gibba*) 7 day NOE_rC = 0.000388 mg/L (based on growth inhibition no changes in plant appearance and development) is the lowest reliable long-term endpoint for aquatic chronic classification purposes.

Conclusion on classification

Mesosulfuron-methyl is considered as not rapidly degradable and does not fulfil the criteria for having a high potential for bioaccumulation. Based on the available and most reliable information, RAC is of the opinion that mesosulfuron-methyl should be classified as:

Aquatic Acute 1 based on E_rC_{50} = 0.00129 mg/L for *Lemna gibba*. As this acute toxicity value falls within the 0.001 < $L(E)C_{50}$ ≤ 0.01 mg/L range, the **acute M-factor is 100**.

Aquatic Chronic 1 based on NOE_rC = 0.000388 mg/L for *Lemna gibba*. As this chronic toxicity value falls within the 0.0001 < NOEC ≤ 0.001 mg/L range, the **chronic M-factor is 100**.

ANNEXES:

Annex 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'.

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and RAC (excluding confidential information).