Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

mandipropamid

EC number: -
CAS number: 374726-62-2

CLH-O-0000003601-83-01/F

Adopted
08 March 2013

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CLH-O-0000003601-83-01/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 (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:

Substance name:	**mandipropamid**
EC Number:	**-**
CAS Number:	**374726-62-2**

The proposal was submitted by **Austria** and received by the RAC on **28/02/2012.**

In this opinion, all classifications are given firstly in the form of CLP hazard classes and/or categories, the majority of which are consistent with the Globally Harmonised System (GHS) and secondly, according to the notation of 67/548/EEC, the Dangerous Substances Directive (DSD).

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/harmonised-classification-and-labelling-consultation*** on **28/02/2012.** Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **13/04/2012**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Annick Pichard**
Co-rapporteur, appointed by RAC: **Hans-Christian Stolzenberg**

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

The RAC opinion on the proposed harmonised classification and labelling was adopted on **08 March 2013** and the comments received are compiled in Annex 2.

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

OPINION OF THE RAC

The RAC adopted the opinion that **mandipropamid** should be classified and labelled as follows[1]:

1 Note that not all hazard classes have been evaluated

Classification and labelling in accordance with CLP

	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 state-ment Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry											
Dossier submitters proposal		Mandipropamid (ISO); 2-(4-chlorophenyl)-N-{2-[3-methoxy-4-(prop-2-yn-1-yloxy)phenyl]ethyl}-2-(prop-2-yn-1-yloxy)acetamide		374726-62-2	Aquatic Acute 1 Aquatic Chronic 2	H400 H411	GHS09 Wng	H400 H411		M = 1	
RAC opinion		Mandipropamid (ISO); 2-(4-chlorophenyl)-N-{2-[3-methoxy-4-(prop-2-yn-1-yloxy)phenyl]ethyl}-2-(prop-2-yn-1-yloxy)acetamide		374726-62-2	Aquatic Acute 1 Aquatic Chronic 1	H400 H410	GHS09 Wng	H410		M = 1 M = 1	
Resulting Annex VI entry if agreed by COM	616-213-00-2	Mandipropamid (ISO); 2-(4-chlorophenyl)-N-{2-[3-methoxy-4-(prop-2-yn-1-yloxy)phenyl]ethyl}-2-(prop-2-yn-1-yloxy)acetamide		374726-62-2	Aquatic Acute 1 Aquatic Chronic 1	H400 H410	GHS09 Wng	H410		M = 1 M = 1	

Classification and labelling in accordance with DSD

	Index No	International Chemical Identification	EC No	CAS No	Classification	Labelling	Concentration Limits	Notes
Current Annex VI entry								
Dossier submitters proposal		Mandipropamid (ISO); 2-(4-chlorophenyl)-N-{2-[3-methoxy-4-(prop-2-yn-1-yloxy)phenyl]ethyl}-2-(prop-2-yn-1-yloxy)acetamide		374726-62-2	N; R50-53	N R: 50/53 S: 60-61		
RAC opinion		Mandipropamid (ISO); 2-(4-chlorophenyl)-N-{2-[3-methoxy-4-(prop-2-yn-1-yloxy)phenyl]ethyl}-2-(prop-2-yn-1-yloxy)acetamide		374726-62-2	N; R50-53	N R: 50/53 S: 60-61	N; R50-53: C ≥ 25% N; R51-53: 2,5% ≤ C <25% R52-53: 0,25% ≤ C < 2,5%	
Resulting Annex VI entry if agreed by COM	616-213-00-2	Mandipropamid (ISO); 2-(4-chlorophenyl)-N-{2-[3-methoxy-4-(prop-2-yn-1-yloxy)phenyl]ethyl}-2-(prop-2-yn-1-yloxy)acetamide		374726-62-2	N; R50-53	N R: 50/53 S: 60-61	N; R50-53: C ≥ 25% N; R51-53: 2,5% ≤ C <25% R52-53: 0,25% ≤ C < 2,5%	

SCIENTIFIC GROUNDS FOR THE OPINION

RAC evaluation of acute toxicity

Summary of the Dossier submitter's proposal
The Dossier Submitter (DS) did not propose any acute toxicity classification for mandipropamid.

The DS's assessment and conclusion on acute toxicity was based on three studies (oral, dermal and inhalation) in rats.

In female rats, the acute oral LD_{50} for mandipropamid (technical grade) was greater than 5000 mg/kg/bw. No death was reported. No effect on behaviour was observed nor gross abnormalities after examination *post mortem*. All animals gained bodyweight during the observation period of 14 days. Only an anogenital staining was found in one rat (5 hours post dosing period).

The acute inhalation toxicity exposure was performed as a nose-only exposure for four hours. No death was reported and the LC_{50} was stated to be greater than 5.19 mg/l. No treatment-related effects were observed at necropsy. Signs of respiratory tract irritation were observed during and immediately following exposure (slight to mild: increased breathing depth and abnormal respiratory noise) but animals recovered rapidly (full recovery by day 4).

The acute dermal LD_{50} in rats was greater than 5050 mg/kg/bw. There were no signs of systemic toxicity or dermal irritation. All animals showed normal weight gain (no death reported) and no treatment-related findings were reported at necropsy.

According to the DS, no classification and labelling is warranted regarding acute toxicity.

Comments received during public consultation
Two Member States (MSs) agreed with the DS's proposal that classification is not warranted for acute toxicity.

Assessment and comparison with the classification criteria
In rats, the oral LD_{50} for mandipropamid is greater than 5000 mg/kg/bw, the inhalation LC_{50} is greater than 5.19 mg/l and the dermal LD_{50} is above 5050 mg/kg/bw.
All the reported LD_{50} and LC_{50} are above the CLP criteria value for classification (2000 mg/kg/bw for the oral and dermal route, 5mg/l for the inhalation route). The RAC agrees that classification for acute toxicity is not warranted for mandipropamid according to CLP or DSD.

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

Summary of the Dossier submitter's proposal
The DS did not propose STOT-SE classification for mandipropamid. After a single exposure, no specific non-lethal target organ toxicity was observed in acute toxicity tests. No human data is available in supporting classification for the hazard class.

Comments received during public consultation
Three MS agreed with the DS's proposal that classification is not warranted for STOT-SE.

Assessment and comparison with the classification criteria
No effects or toxicological changes were reported to support classification for specific target organ toxicity after single exposure. The RAC agrees with the DS's proposal that classification is not warranted for specific target organ toxicity after single exposure according to CLP or DSD.

RAC evaluation of skin corrosion/irritation

Summary of the Dossier submitter's proposal
The DS did not propose classification for skin corrosion/irritation. The conclusion was based on one skin irritation study in rabbits in which rabbits were dermally exposed for 4 hours to 500 mg of mandipropamid. Only slight effects were observed in one animal on the fourth day after the exposure and the effects disappeared by the seventh day.

Comments received during public consultation
Two MS agreed with the DS's proposal that classification is not warranted for skin corrosion/irritation.

Assessment and comparison with the classification criteria
Estimated skin irritation scores from the irritation study are below the values set in the criteria for classification and labelling. It can also be mentioned that in a repeated dermal toxicity study, only a slight skin irritation was reported at the application site. The RAC agrees with the DS's proposal that classification and labelling is not warranted for skin corrosion/irritation according to CLP or DSD.

RAC evaluation of eye corrosion/irritation

Summary of the Dossier submitter's proposal
The DS did not propose classification for eye corrosion or irritation based on an eye irritation study in rabbits exposed with 100 mg mandipropamid. No corneal effects were reported; only slight ocular reaction of iris and slight to moderate ocular reaction of conjunctiva. All irritation signs were completely resolved within 7 days. No other sign of toxicity was reported.

Comments received during public consultation
Two MS agreed with the DS's proposal that classification is not warranted for eye corrosion/irritation.

Assessment and comparison with the classification criteria
Estimated eye irritation scores are below the values set in the criteria for classification and labelling and the RAC agrees with the DS's proposal that classification and labelling for eye corrosion/irritation is not warranted according to CLP or DSD.

RAC evaluation of skin sensitisation

Summary of the Dossier submitter's proposal
Mandipropamid was tested in an LLNA study at concentrations of 10, 25 or 50% w/v in DMF. At all the concentrations tested, the stimulation index was less than 3 and it was so concluded that mandipropamid is not a skin sensitizer.

Comments received during public consultation
Two MS agreed with the DS's proposal that classification is not warranted for skin sensitisation.

Assessment and comparison with the classification criteria
The results of the reported study are considered negative since the stimulation index was less than 3 at all tested concentrations when compared to the control. Thus, the RAC agrees with the DS's proposal that mandipropamid does not fulfil the criteria for classification according to CLP or DSD as skin sensitizer.

RAC evaluation of repeated dose toxicity (DSD) and specific target organ toxicity (CLP) – repeated exposure (STOT RE)

Summary of the Dossier submitter's proposal

The DS did not propose any classification for repeated dose toxicity (DSD) or specific target organ toxicity after repeated exposure (CLP).

Short-terms oral studies (90-days in rat and dog, 1 year in dog)

Short term toxicity of mandipropamid was tested in a 90-day oral toxicity study in rats exposed via diet at 100, 500, 3000 and 5000 ppm, e.g. 0, 8.2/8.9, 41.1/44.7, 260/260, 435/443 mg/kg bw M/F, respectively (Pinto, 2005a).

Liver was identified as the main target organ with:

- Increased relative liver weight from 3000 ppm in both sexes (24.6 and 33.5% in males and 15.2 and 29.5% in females at 3000 and 5000 ppm, respectively) and also slightly in males at 500 ppm (8.0%).
- Clinical chemistry from 3000 ppm:
  - in both sexes: plasma albumin (up to 7.6%), protein (up to 5.4%, statistically significant in females only at 5000 ppm) and
  - in females: cholesterol (up to 15.7%) and γ-glutamyl transferase.
- Histopathological changes from 3000 ppm with an increased incidence of portal hypertrophy, eosinophilia (only at 5000 ppm in males);

Other treatment-related effects also included:

- Decrease in bodyweight and bodyweight gain in males: at 3000 ppm (11% and 16%, respectively) and 5000 ppm (8% and 11%, respectively)
- Haematological effects at 3000 and 5000 ppm with: decrease in red blood cells parameters with haemoglobin (max 7%), haematocrit (max 5.9%), mean cell volume or MCV (max 4.9%), mean cell haemoglobin (max 6.1%) and mean cell haemoglobin concentration (max 1.6%); MCV was also very slightly lowered (1.9%) in females at 500 ppm;
- Kidney in males: decrease in relative weight from 3000 ppm (6 and 9%) and a tubular basophilia from 500 ppm (higher incidence with historical control groups only significant at 5000 ppm – no detailed data).

The dose of 500 ppm (41.1 mg/kg bw in males and 44.7 mg/kg bw in females) is then considered as NOAEL in this 90-day rat study, the LOAEL being 3000 ppm (260 mg/kg bw in males and females).

Mandipropamid was tested in a 90-day oral toxicity in groups of 4 dogs exposed via gelatine capsules at 5, 25, 100 and 400 mg/kg bw (Brammer, 2005).

Liver was identified as the main target organ with:

- Increased relative liver weight at 400 mg/kg bw in both sexes (16% M -17% F) and also in males at 100 mg/kg bw (19.0%).
- Clinical chemistry in both sexes:
  - Marked elevation of ALT at 400 mg/kg bw (up to 132.9 vs 39.3 IU/l in F, week 13) and AP from 100 mg/kg bw (up to 560 vs 263 IU/l in M at 400 mg/kg, week 13) with increasing value with time
  - Increased cholesterol in both sexes from 100 mg/kg bw (up to 42% in F at 400 mg/kg bw)
- Histopathological changes with a brown pigmentation of hepatocytes and Kupffer cells: all animals of both sexes at 400 mg/kg bw and 1/4 M and 2/4 F at 100 mg/kg bw.

Other treatment related effects included haematological effects in females at 400 mg/kg with decreases in white blood cells and neutrophil count. No change in red blood cell parameters was identified.

The NOAEL for this 90-day dog study was 25 mg/kg bw, with a LOAEL at 100 mg/kg bw.

Mandipropamid was tested in a 1 year oral toxicity in groups of four dogs exposed via gelatine capsules at 5, 40 and 400 mg/kg bw (Brammer, 2005).
Liver was identified as the main target organ with:

- Increased relative liver weight at 400 mg/kg bw in males (20%).
- Clinical chemistry in both sexes:
  - Marked elevation of ALT at 400 mg/kg bw (209.3 vs. 38.4 IU/l in M, week 52) and AP from 40 mg/kg bw (up to 590 vs 158 IU/l in F at 400 mg/kg bw, week 52)
- Histopathological changes with a pigmentation in both sexes: 3/4 M and 3/4 F at 400 mg/kg bw and 2/4 M and 1/4 F at 40 mg/kg bw.

Other treatment related effects included:

- Decreases in bodyweight and bodyweight gain at 400 mg/kg bw in both sexes at some points of the study (week 4-12 for males with max of 6% and week 11-18 for females, max of 8%).
- Haematological effects: decrease in mean cell volume or MCV (max 4.6%), mean cell haemoglobin or MCH (max 5.5%) in both sexes at 400 mg/kg, increase in platelets (males from 40 mg/kg bw), decreased partial thromboplastin time (males at 400 mg/kg bw).

The NOAEL for mandipropamid in this 1 year dog study was 5 mg/kg with a LOAEL of 40 mg/kg bw.

Long-term oral studies (rat, mice)
Mandipropamid was tested in a combined chronic/carcinogenic study in groups of 64 rats exposed for 2 years at doses of 50, 250 and 1000 ppm in diet for 2 years (eq. to 3/3.5, 15.2/17.6 and 61.3/69.7 mg/kg bw in males and females, respectively). Interim sacrifice kill was scheduled after week 52 for 12M and 12F of each group.

Liver effects observed, at the top dose of 1000 ppm, were similar to the effects in the 90-day studies:

- Increase in liver weight at interim kill (week 53): in both sexes at 1000 ppm (10% in M, 14% in F) and in females at 250 ppm (10%). Liver weight was also increased at week 105 in females at 1000 ppm (12%);
- Clinical chemistry at 1000 mg/kg bw: plasma albumin increased (7%) in males up to week 53; γ-glutamyl transferase increased in males from week 53 (16.7 IU/l vs 10.1 IU/l at week 105).
- Histopathological changes at week 53: increase in the incidence periportal eosinophilia in both sexes at 1000 ppm and at 250 ppm in females. This change was not seen at week 105.

Effects on kidney were also reported in males at 1000 ppm:

- Macroscopic findings (enlargement, discoloration, roughened surface and combination) with incidences as follows

Macroscopic kidneys findings

	Mandipropamid			
Findings	**0**	**50**	**250**	**1000**
Enlarged	2	4	4	6
Pale	4	5	5	5
Roughened surface	5	4	8	13
Pale/roughened surface+/-cysts	9	12	9	14
Cyst/s (single or multiple within organ)	3	3	4	7
TOTAL	23	28	30	45
Animals on Study	64	64	64	64

- Histological changes: increase in the severity of chronic progressive nephropathy (CPN) associated with an increased incidence of an osteo-renal syndrome.

Microscopic findings in kidney of males

Microscopic findings in kidney of males	Dose group level (ppm)			
	0	**50**	**250**	**1000**
Total number of animals with marked chronic progressive nephropathy (CPN)	15	17	18	24
Number of individual animals with the full osteo-renal syndrome (CPN plus bone changes plus parathyroid hyperplasia)	3	3	1	11

A slight increase in kidney weights in females at 250 and 1000 ppm was also observed (7% max) but at week 53 only.

Other treatment related effects included:

- Decrease in bodyweight and in bodyweight gain in males during the first 3 months (4%) and on most occasions between weeks 67 and 103 (max 7%),
- Haematological findings in both sexes: decrease in mean cell volume (max 3.9%) and mean cell haemoglobin (up to 5.1%)

The NOAEL in this long-term study in rats is set at 250 ppm (15.2 mg/kg bw in males, 17.6 mg/kg bw in females), with a LOAEL of 1000 ppm (61.3 mg/kg bw in males and 69.7 mg/kg bw in females)

Mandipropamid was tested in a carcinogenic study in mice exposed by diet at doses of 100, 500 and 2000 ppm for 80 weeks (10.6/13.2, 55.2/67.8 and 222.7/284.6 mg/kg bw in males and females, respectively). Liver as a target organ is confirmed in this study with an increase in the liver weight observed at the top dose of 2000 ppm in both sexes (15% in males, 8.9% in females) and slight in males at 500 ppm (11.7%). A slight decrease in bodyweight and bodyweight gain were reported in both sexes (max 6%, not statistically significant) at 2000 ppm. Other treatment related effects at the top dose of 2000 ppm were a decrease in spleen weights in both sexes (17% in M, 10% in F) as well as an increase in kidney weights in females (7.7%). These were not considered as significant since not supported by microscopic findings.

The NOAEL in this long-term study in mice was identified at 500 ppm (55.2 mg/kg bw M, 67.8 mg/kg bw F) with a LOAEL at 2000 ppm (222.7/284.6 mg/kg bw).

Short-term dermal study

No toxicity was reported in the 28-day study in rats exposed to mandipropamid by dermal route up to 1000 mg/kg bw. Only slight irritation was observed at the application site.

Other studies (neurotoxicity)

Mandipropamid was assessed for potential neurotoxicity in an acute and a subchronic neurotoxicity study in the rat and no neurotoxicpotential was observed. No effect on functional observation battery test was reported in the 2 year chronic/carcinogenicity study in rats.

Conclusion of DS

According to the DS, no classification and labelling is proposed regarding repeated toxicity.

Comments received during public consultation

Two MS agreed with the DS's proposal that classification is not warranted for STOT-RE/repeated dose toxicity.

Assessment and comparison with the classification criteria

The RAC agreed with the DS that no classification for STOT-RE/repeated dose toxicity is needed but assessed in more detail the effects on liver and kidneys in coming to this conclusion.

Some liver effects were reported in the different repeated oral toxicity studies conducted in several species and several exposure durations (90-day study in rats and dogs, 1 year study in

dogs, 2 years in rats and mice). The effects were observed mostly above or close to the guidance value ranges (10 < CLP value ≤ 100 mg/kg bw in a 90-day oral study).

- LOAEL of 260 mg/kg bw in 90-day study in rats
- LOAEL of 100 mg/kg in 90-day study in dogs
- LOAEL of 40 mg/kg bw in 1 year study in dogs
- LOAEL of 61.3 mg/kg bw in long-term study in rats
- LOAEL of 222.7 mg/kg bw in long-term study in mice

Moreover, the observed effects consisted of: a slight increase in liver weight, increased metabolic activity, and some histopathological changes mainly considered as adaptative (periportal hypertrophy, eosinophilia).

For the dermal route, the NOAEL and LOAEL (28-days rat study) were > 1000 mg/kg bw, i.e. above the criteria for classification (60 < CLP criteria values for category 2 ≤ 600 mg/kg bw).

According to the CLP Regulation, classification in Category 2 for STOT-RE is applicable, when significant toxic effects observed in repeated-dose study conducted in experimental animals are seen to occur within the guidance value ranges.

The RAC agreed with the DS that the reported effects of mandipropamid in liver, because of their nature and the dose at which they occurred, do not warrant a classification as STOT-RE 2 according to CLP or Xn;R48 according to DSD.

The RAC also assessed the kidney effects because of the chronic progressive nephropathy (CPN) observed in the long-term study in rat. An increase of macroscopic findings in the kidneys was reported at the top dose of 61.3 mg/kg/bw in males (e.g. enlarged, pale, cysts) with an incidence of 45/64 vs 23/64 in the controls. An increase in the incidence and severity of CPN is mentioned (no details), associated with an increase in the number of animals with a marked CPN (24/64 vs 15/64 e.g. 38% vs 23%), as well as an increase in the number of animals with full osteo-renal syndrome (CPN associated with bone changes and parathyroid hyperplasia: 11/64 vs 3/64 in controls). The increase is however above the cut-off value (12.5 mg/kg/bw for a Category 2). CPN is a common pathology in aging rats although no historical control data was provided. Moreover, the majority of animals remained unaffected and no change in chemistry that could be related to renal function impairment was reported (e.g, no change in proteinuria). The CPN pathology seems to occur in male but was not observed in either female rats, or in the long-term study in mice.

The available supporting studies do not provide enough background to consider the kidney as a target organ. In the 2-generation study in rats, kidney weights were increased in the F0 and F1 males and females but only at the top dose of 1500 ppm (120 mg/kg bw), with a maximal change of 10% and no associated histological changes. t can also be mentioned that no effects were reported in dogs (90-days and 1 year studies) and in developmental studies in rats or rabbits (only macroscopic examination in parents was available following the protocol of such studies), bearing in mind that these are all rather short-term studies. Therefore, the RAC concludes that the observed effects in kidneys are not enough to justify classification.

In conclusion, the RAC agrees with the DS that the reported effects of mandipropamid in liver and kidney do not warrant a classification as STOT-RE 2 according to CLP or Xn;R48 according to DSD.

RAC evaluation of germ cell mutagenicity

Summary of the Dossier submitter's proposal

In vitro, mandipropamid was negative for gene mutation in bacterial (Ames test) and mammalian cells (L5178 mouse lymphoma cells, TK). The *in vitro* cytogenetic assay on human lymphocytes was also negative. *In vivo*, mandipopamid did not show evidence of clastogenic properties in a bone marrow micronucleus assay and no induction of DNA damage or repair in a UDS assay.

Comments received during public consultation

Two MS agreed with the DS's proposal that classification is not warranted.

Assessment and comparison with the classification criteria
Mandipropamid was negative in genotoxicity assays *in vitro* and *in vivo*. The RAC agrees that classification is not justified according to CLP or DSD.

RAC evaluation of carcinogenicity

Summary of the Dossier submitter's proposal
Mandipropamid was investigated for carcinogenicity in rats exposed orally in the diet for 105 weeks at doses up to 1000 ppm (eg. 61.3 mg/kg bw males and 69.7 mg/kg bw females). Carcinogenicity was also investigated in orally exposed mice for 80 weeks at doses up to 2000 ppm (eg. 222.7 mg/kg bw males and 284.6 mg/kg bw females). There were no treatment related increases in the incidence of tumours and no trends towards increased numbers of tumours in both studies.

Comments received during public consultation
Two MS agreed with the DS's proposal that classification is not warranted.

Assessment and comparison with the classification criteria
No carcinogenic effect was observed in the rat oral study nor in the mice oral study. However, some non-neoplasic effects were observed in the rat chronic/carcinogenicity study, reported in STOT-RE section.

The RAC agrees with the DS's proposal that carcinogenicity classification for mandipropamid is not warranted according to CLP or DSD.

RAC evaluation of reproductive toxicity

Summary of the Dossier submitter's proposal
The DS did not propose any reproductive toxicity classification for mandipropamid, based on a two-generations study in rats and two developmental studies, one in rabbits and one in rats.

Two-generations study
Mandipropamid was tested in a two generation study in rats at doses in the diet of 50, 250 and 1500 ppm.
At 1500 ppm, effects on bodyweight were observed:

- Decrease in F1 males during pre-mating period: from week 1 (8.4%) and for the majority of the period (until week 9) and increase in F1 females from week 4 (up to 6%).
- Slightly lower (around 3.5%) in F0 and F1 females on days 15 and/or day 22 post-partum but no longer evident on day 29
- Decrease in the pup weight in both sexes in F1A and F2B from day 15 and up to 14%, but no effects were reported in F2A pups.

At 1500 ppm, an increase in liver weight (up to 19%) was observed in both sexes and in both generations (parents and pups).

There were no effects on implantation data or reproductive performance and no microscopic changes related to treatment. The NOAEL for systemic parental toxicity and development was determined at 250 ppm (20 mg/kg bw). The NOAEL for reproduction was identified at the top dose of 1500 ppm in the diet (120 mg/kg bw).

Developmental toxicity in rats
Mandipropamid was tested for teratogenicity in groups of 24 female rats at doses of 50, 200 or 1000 mg/kg bw on days 5-21 of gestation (Moxon, 2005). No effect on clinical condition, maternal bodyweight or food consumption and no treatment related findings were reported at post-mortem examination. At 1000 mg/kg bw, plasma total protein (48.1 vs 52.4) and total bilirubin (2.66 vs 3.46 e.g 23%) were lower and albumin/globulin ratio was higher (1.28 vs 1.19). Total bilirubin was also slightly lower at 200 mg/kg (2.94 vs 3.46 mg/kg e.g 15%).

The maternal NOAEL is considered to be 200 mg/kg bw.

No effects were reported on number, growth, survival or development of foetuses *in utero*.
At foetal examination, major skeletal observations on sternum in foetuses treated with mandipropamid were reported as cleft sternebrae, cleft sternal cartilage and cleft xiphoid cartilage.

Summary of skeletal sternal observations and associated effects

	Mandipropamid (mg/kg bw) (Moxon ME, 2005)			
	0	**50**	**200**	**1000**
Total litters (viable)	23	24	23	24
Live fetuses / dam	12.0	10.8	11.9	12.3
Live fetuses -total	275	259	274	294
number of fetuses (litters) affected	0 (0)	3 (3)	2 (2)	3(3)
% per fetuses - calculated	0,0	1,2	0,7	1,0
% (data)	0 - 1.2%			

Detailed available information on major sternal observations: number of foetuses (%) and number of litters (%)

	Mandipropamid (mg/kg bw) (Moxon ME, 2005)				**HCD data (10 studies between 1996-2003)**
	0	50	200	1000	%
Total litters (viable)	23	24	23	24	
Live fetuses / dam	12.0	10.8	11.9	12.3	
Live fetuses - total	275	259	274	294	
Cleft sternebrae					
sternebra 5 – fetuses (%)	0	2 (0.8)	0	0	0.0 - 0.6
litters (%)	0	2 (8.3)	0	0	
sternebra 6 – fetuses (%)	0	3 (1.2)	0	0	0.0 - 0.4
litters (%)	0	3 (12.5)	0	0	
all sternebrae – fetuses (%)	0	0	0	1 (0,3)	0.0
litters (%)	0	0	0	1 (4,2)	
Cleft sternal cartilage					
between 2 and 1 – fetuses (%)	0	0	1 (0.4)	1(0.3)	0.0 - 0.4
litters (%)	0	0	1 (4.3)	1 (4.3)	
between 3 and 2 – fetuses (%)	0	0	1 (0.4)	0	0.0
litters (%)	0	0	1 (4.3)	0	
between 4 and 3 – fetuses (%)	0	3 (1.2)	1 (0.4)	0	0.0 - 0.4

litters (%)	0	3 (12.5)	1 (4.3)	0	
between 5 and 4 – fetuses (%)	0	2 (0.8)	1 (0.4)	0	0.0 - 0.4
litters (%)	0	2 (8.3)	1 (4.3)	0	
between 6 and 5 – fetuses (%)	0	1 (0.4)	1 (0.4)	0	0.0
litters (%)		1 (4.2)	1 (4.3)	0	
Xiphoid cartilage cleft					
Fetuses (%)	0	2 (0.8)	2 (0.7)	2 (0.7)	0.0
litters (%)	0	2 (8.3)	2 (8.7)	2 (8.3)	

However, the incidence of foetuses affected was very small and not dose related. Also, no effect was observed in the appearance or ossification of sternebrae, which would indicate that mandipropamid adversely affects this area of the skeleton while there was no evidence for an effect on other areas of the skeleton. The low incidence of the major observations affecting the sternum is considered to be incidental.

Some minor skeletal observations (rib 13 shortened, odontoid bipartite ossification) were observed with statistically significance in the 200 mg/kg bw (incidence of 64.9% vs 55.1%, e.g 177/274 vs 150/275) but not in the 1000 mg/kg bw group (48.7%, e.g. 154/294). Some minor external and visceral observations were statistically significantly higher in the 1000 mg/kg bw group (liver cysts, slightly reduced kidneys, slightly dilated ureters, kinked ureters).

Detailed information on minor external and visceral observations: number of foetuses (%) and number of litters (%)

	Mandipropamid (mg/kg bw) (Moxon ME, 2005)			
	0	**50**	**200**	**1000**
Liver cysts - fetuses (%)	1 (0.4)	1 (0.4)	0	4 (1.4)
Litters (%)	1 (4.3)	1 (4.2)	0	2 (8.3)
Kidney reduced slight - fetuses (%)	0	0	0	1 (0.3)
Litters (%)	0	0	0	1 (4.2)
Ureter dilated slight - fetuses (%)	1 (0.4)	2 (0.8)	1 (0.4)	5 (1.7)
Litters (%)	1 (4.3)	2 (8.3)	1 (4.3)	4 (16.7)
Ureter kinked - fetuses (%)	4 (1.5)	4 (1.5)	9 (3.3)	11 (3.7)
Litters (%)	4 (17.4)	3 (12.5)	5 (21.7)	8 (33.3)

The NOAEL for development is 1000 mg/kg bw.

Developmental toxicity in rabbits

Mandipropamid was tested for teratogenicity in groups of 4 female rabbits exposed at 50, 250, 1000 mg/kg bw on days 5-29 of gestation (Moxon, 2005). No effects were observed on parental generation: clinical observations, bodyweight or food consumption. The NOAEL for maternal toxicity is 1000 mg/kg bw. In relation to development, there were no effects on number, growth, survival or development of foetuses *in utero*. Upon foetal skeletal examination, no major effect of the treatment was observed (type or incidence). The frequency of minor observations was increased in all treated groups but with no dose-relation. The frequency of variant was increased at the high dose of 1000 mg/kg bw.

Percentages of skeletal observations

	Mandipropamid (mg/kg bw) (Moxon ME, 2005)			
	0	**50**	**200**	**1000**
Total litters (viable)	22	22	22	24
Live fetuses / dam	7,95	8,23	8,27	8
Live fetuses - total calculated	174,9	181,06	181,94	192
skeletal major observations – fetuses (%) litters	(1.1) 2/22	(1.9) 4/22	(0.9) 2/22	(1.4) 3/24
skeletal minor observations – fetuses (%) litters	(27.3) 19/22	**(47.0) 20/22**	**(45.5) 21/22**	**(41.5) 23/24**
skeletal variant – fetuses (%) litters	(61.7) 22/22	(72.9) 22/22	(67.3) 22/22	**(79.7) 24/24**

Note : Figures in bold with statistical significance

Consideration of the specific observations reveals some minor skeletal effects or variations in particular:

- Increased incidence of incomplete ossification of odontoid (4.4% and 5.7% foetuses affected at 250 and 1000 mg/kg bw, respectively vs 0.6% for control). A dose relationship is reported and the % of litters affected at 1000 mg/kg bw is also higher (33.3% vs 4.5% for controls) but the frequency of affected foetuses is within the historical control values (0.0% - 8.0 % foetuses in 10 studies between 1995-2003)
- Increased incidence of incomplete ossification observed for 5th sternebrae at 250 and 1000 mg/kg bw (22.0 and 20.8 respectively vs 12.6% for control) within the historical control means (9.3% - 38% in 10 studies between 1995 and 2003).
- Some other minor/variant skeletal effects were reported with no dose relation and within historical range, e.g increased unossified 5th sternebrae in all treated groups (17.7%, 13.7% and 15.6% at 50, 250 and 1000 mg/kg bw, respectively, vs 10% in control) and within historical range (5.7-16.9%).
- All effects are reported in the table below.

Detailed on specific skeletal observations

	Mandipropamid (mg/kg bw) (Moxon ME, 2005)				HCD
	0	**50**	**200**	**1000**	**%**
Total litters (viable)	22	22	22	24	
Live fetuses / dam	7,95	8,23	8,27	8	
Live fetuses - total calculated	174,9	181,06	181,94	192	
skeletal minor observations					
Ondontoid incompletly ossified - fetuses (%)	1 (0.6)	4 (2.2)	**8 (4.4)**	**11 (5.7)**	0.0 - 8.0
litters (%)	1 (4.5)	4 (18.2)	6 (27.3)	**8 (33.3)**	
Sternebra 5 not ossified - fetuses (%)	10 (5.7)	**32 (17.7)**	**25 (13.7)**	**30 (15.6)**	5.7 - 16.9
litters (%)	6 (27.3)	12 (54.5)	12 (54.5)	**13 (54.2)**	
skeletal variant					
Sternebra 5 incompletly ossified - fetuses	22	29	**40**	**40**	9.3 -

(%)	(12.6)	(16.0)	**(22.0)**	**(20.8)**	38.0
litters (%)	11 (50.0)	15 (68.2)	**15 (68.2)**	**14 (58.3)**	
Rib 7 costal cartilage shortened - fetuses (%)	7 (4.0)	**33 (18.2)**	**18 (9.9)**	**31 (16.1)**	0.0 - 14.0
litters (%)	6 (27.3)	**15 (68.2)**	9 (40.9)	11 (45.8)	
Rib 13 attached to vertebral column - long length - fetuses (%)	35 (20.0)	**53 (29.3)**	43 (23.6)	52 (27.1)	20.0 - 54.5
litters (%)	14 (63.6)	16 (72.7)	19 (86.4)	18 (75.0)	
27 Pre-pelvic vertebrae bilateral - fetuses (%)	4 (2.3)	**25 (13.8)**	**15 (8.2)**	12 (6.3)	2.3 - 34.4
litters (%)	4 (18.2)	**12 (54.5)**	9 (40.9)	7 (29.2)	

Note : Figures in bold are statistically significant

The skeletal effects were minor or variants, within historical control,without dose-relation and are not considered as treatment related. The NOAEL for development is set at the high dose of 1000 mg/kg bw.

According to DS's proposal, no classification is justified.

Comments received during public consultation
Two MS agreed on the DS's proposal that classification is not warranted for reproductive toxicity.

Assessment and comparison with the classification criteria
No significant effects were observed on fertility or on development in the multigeneration and developmental studies in rats and rabbits. For developmental studies, no effects on number, growth, survival or development of foetuses *in utero* were observed.

In the rat developmental study, some skeletal major observations were observed on sternum. However, the incidence of affected foetuses was very small (up to 3 foetuses – 1.2%) and not dose related. Also, there was no evidence for a specific effect on other areas of the skeleton. Therefore, the NOAEL can be considered as corresponding to the highest dose tested of (1000 mg/kg bw).

In the developmental study in rabbits, no effect of treatment on skeleton was observed. Only some minor observations or variant were reported, within historical control and without dose-relation. Then, the NOAEL was identified at the highest dose of 1000 mg/kg bw.

The observed effects are not considered adverse and therefore, the RAC agrees with the DS's proposal that classification for reproductive toxicity is not justified according to CLP or DSD.

RAC evaluation of environmental hazards

Summary of the Dossier submitter's proposal
The DS proposes to classify mandipropamid for aquatic environment hazards in acute category 1 with M = 1, and in chronic category 2. The proposal is mainly based on the information presented in the draft assessment report (DAR) of mandipropamid under Directive 91/414/EEC.

Mandipropamid shows limited solubility in water with a measured value of 4.2 mg/l in pure water (substance purity = 990 g/kg, 25°C, OECD TG 105), while some reported maximum test concentrations in ecotoxicity studies were lower (2.0 mg/l) or higher (up to 28 mg/l). The purity of mandipropamid batches in ecotoxicity tests ranged from 96.1 to 99 %.

Degradation
Mandipropamid was hydrolytically stable in a study conducted in sterile buffer solutions at pH values of 4, 5, 7, and 9 (50°C over 7 days, 25°C over 32 days).

Biodegradation was studied in a ready biodegradability test. After 28 days less than 5% was degraded (measured as chemical oxygen demand, COD).

Several water/sediment degradation studies indicated primary degradation with mean half-lives of ca 14 days, but mineralisation after 100 days under aerobic conditions was limited to around 4% or 30-35%, depending on the radio-labelled moiety. Due to missing data on aquatic toxicity of several degradants, it was not possible to show that the metabolites are not classifiable. In conclusion the DS proposes to consider mandipropamid as not rapidly degradable.

Bioaccumulation
The measured log Kow of mandipropamid was 3.2 at 25°C and showed no pH-dependency. A fish bioaccumulation study (OECD TG 305, *Pimephales promelas*) was performed with test concentrations of 32 µg/l and 3.2 µg/l, using dimethylformamide as a dispersing agent. The flow-through test was conducted with 190 hrs exposure and 195 hrs depuration phases. Plateau concentrations were reached after 48 hrs, and the test resulted in BCF values of 35 (low conc.) and 48 (high conc.) for the whole body (overall mean lipid content of 11% used for normalisation). In conclusion the DS suggested that mandipropamid shows low potential for bioaccumulation.

Acute aquatic toxicity
Several acute and chronic aquatic toxicity data were available. The toxicity studies followed guideline standards and were throughout marked as GLP studies and reliable by the dossier submitter.

In relation to short-term aquatic hazards, while no effects were observed in three tests with algae and aquatic plants (duckweed), mortalities in two out of five short-term fish tests (with carp and sheephead minnow) were observed at concentrations starting from ca. 7 and 4 mg/l, with calculated LC_{50} values of 8.6 and 4.5 mg/l, respectively.

Three short-term tests with invertebrates were reported: a 48hrs water flea test according to OECD TG 202 resulted in a calculated LC_{50} of 7.1 mg/l (nominal, mean measured concentrations were 96 to 110%). In a 96hrs flow-through test with saltwater mysid the calculated LC50 based on measured concentrations was 1.7 mg/l (NOEC 0.58 mg/l). Another acute toxicity test was available for the Eastern oyster, following the US EPA test guideline OPPTS 850.1025, with 96 hrs test duration resulting in an EC_{50} (shell deposition) of 0.97 mg/l.

In conclusion, the DS proposed to classify mandipropamid for short-term aquatic hazards as Aquatic Acute with M = 1.

Chronic aquatic toxicity
One 28d early life stage test with fathead minnow was reported, with a NOEC of 0.5 mg/l and a LOEC of 1.0 mg/l (nominal, mean measured concentrations were 87 to 100%) for growth (weight and length) as well as for mortality of hatched fish larvae. Moreover, the DS reported one semi-static 21d reproduction test with water fleas according to OECD TG 202, Part II (now TG 211), with NOECs of 0.28 (growth, length), 0.87 (reproduction), and ≥ 2.64 mg/l (mortality), reported as mean measured concentrations.

In conclusion, considering the long-term data and the the lack of rapid degradation, the DS proposed to classify mandipropamid for long-term aquatic hazards as Aquatic Chronic 2.

Comments received during public consultation
Five comments were received from four MSs and one manufacturing company. All MSs supported the classification proposed by the DS, either in general or by specifying agreement with no classification for human health hazard classes or with specific reference to the justification for the proposed environmental classification. Industry informed about another Daphnia reproduction

study (Minderhout et al. 2009, report no. 528A-181B) which had not been considered in the submitted dossier. In contrast to the MS comments, industry disagrees with the proposed classification based on the acute toxicity study with Eastern oyster, arguing that shell deposition in oyster cannot be considered as an endpoint equivalent to the crustacean 48 hour EC_{50}.
The company suggests the acute fish (*Oncorhynchus mykiss*) test result of LC_{50} > 2.9 mg/l (without further specification for this selection from the five available fish tests) as "the most sensitive and appropriate" value resulting in a R51 (DSD) classification.

After public consultation the DS agreed that the provided additional chronic study on daphnids justifies classification as Aquatic Chronic 1.

Assessment and comparison with the classification criteria

Degradation
The RAC agrees with the DS's proposal to consider mandipropamid as not rapidly degradable. The substance is hydrolytically stable at all pH from 4 to 9. In a ready biodegradability test the measured biodegradation was < 5%. Moreover, several water/sediment studies showed primary degradation but mineralisation was well below 70% within 28d (4 or 30-35% after 100d). In addition, insufficient information is available regarding classification of several relevant degradation products.

Bioaccumulation
A log Kow of 3.2 at 25°C without pH-dependency was measured, i.e. below the CLP cut-off criterion of 4 Likewise, measured BCFs of 35 for the low and 48 for the high concentration) were also well below the CLP cut-off criterion of 500. The RAC therefore agrees with the DS's conclusion that mandipropamid shows no potential for bioaccumulation according to the classification criteria.

Aquatic Toxicity
Studies are available for both acute and chronic aquatic toxicity.

Acute toxicity
Most of the reported acute toxicity test results, i.e. for fish and crustaceans, are above the 1 mg/l cut-off value for CLP Category Acute 1. Some values, e.g. 8.7 mg/l even exceed the limit of water solubility determined with a test conducted according to the OECD TG 105 in pure water (4.2 mg/l).

However, another test, i.e. an oyster acute toxicity test (shell deposition), resulted in an EC_{50} consistently lining up at the lower end of the other acute test results, with a value of 0.97 mg/l just under the 1 mg/l cut-off value. While this 96hrs acute test with Eastern Oyster is rather rarely available in Europe for regulatory decisions on classification, the RAC notes that it has been conducted according to the US-EPA Ecological Effects Test Guideline OPPTS 850.1025, which is validated as a standardised test method and designed for measuring acute toxicity using the shell deposition endpoint. In principle, classification is based on the principle of using results from adequately designed and conducted standard tests with organisms from only a few taxonomic groups and with selected measurements (endpoints), provided that they can be considered as relevant surrogates for all aquatic organisms. The RAC considers that this prerequisite is fulfilled for the acute oyster test.

The corresponding acute M-factor for 0.1 < 0.97 ≤ 1.0 mg/l is 1.

Chronic toxicity
Three conclusive results from chronic toxicity tests are available, two of them meeting the NOEC ≤ 1 mg/l criterion for CLP Category Chronic 2 (non-rapidly degradable substances), i.e. the NOEC of 0.5 mg/l in a fish early life stage test, and the NOECs of 0.87 and 0.27 mg/l for reproduction and growth (length), respectively, in a water flea reproduction test.

Conclusive results from the additional *Daphnia* reproduction test, i.e. the NOEC of 0.076 mg/l for growth (length) and reproduction, do however meet the NOEC ≤ 0.1 mg/l criterion for CLP Aquatic Chronic 1 (non-rapidly degradable substances). The corresponding chronic M-factor for 0.01 < 0.076 ≤ 0.1 mg/l is 1.

Conclusion on classification
Mandipropamid is considered as **non-rapidly degradable**. Its bioaccumulation potential is low and does not meet the criteria for classification.

Overall, the available acute and chronic toxicity test data allow a complete evaluation for short- and long-term environmental hazards.

For both acute and chronic data, the relevant toxicity range is within just one order of magnitude. The lowest values, however, meet the respective cut-off criteria for acute and chronic categories 1.

Acute toxicity to fish and crustaceans were in the same range as the acute mollusc test that had the lowest acute toxicity value and was used as the decisive study for short-term hazard classification. Algae and other aquatic plants were not affected at the applied test concentrations of mandipropamid.

The *Daphnia* reproduction test provided during the PC, the RAC concludes that the DS's original proposal for chronic toxicity is not justified. However, the RAC agrees with the DS's response to the public consultation comment that Aquatic Chronic 1 is justified based on the new chronic toxicity data.

In summary, the RAC concludes that the environmental hazard classification of mandipropamid is Aquatic **Acute 1 (H400) with M = 1** and Aquatic **Chronic 1 (H410) with M = 1** according to CLP.

The RAC agrees with the dossier submitter's proposal that mandipropamid should be classified as N; R50-53 according to DSD since its acute aquatic toxicity is below 1 mg/l (oyster) and it is not readily degradable. The corresponding specific concentration limits are:

N; R50-53: C ≥ 25%
N; R51-53: 2.5% ≤ C <25%
R52-53: 0.25% ≤ C < 2.5%

[1] **Reference:** Minderhout T, Kendall TZ, Krueger HO 2009. Mandipropamid – A Static-Renewal Life-Cycle Toxicity Test with the Cladoceran (*Daphnia magna*). Wildlife International, Ltd., MD, USA. Report No 528A-181B. 78 p.

ANNEXES:

Annex 1 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 (excl. confidential information)