Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

etofenprox

EC number: 407-980-2

CAS number: 80844-07-1

CLH-O-0000003158-74-01/F

Adopted

28 November 2012

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CLH-O-0000003158-74-01/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:

Chemical names: Etofenprox (2-(4-ethoxyphenyl)-2-methylpropyl 3-phenoxybenzyl ether)

EC number: 407-980-2

CAS number: 80844-07-1

The proposal was submitted by **Austria** and received by the RAC on **25/01/2012.**

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).

The proposed harmonised classification

	CLP	**DSD**
Current entry in Annex VI of CLP Regulation (EC) No 1272/2008	Not currently in Annex VI, table 3.1 of the CLP Regulation	Not currently in Annex VI, table 3.2 of the CLP Regulation
Original proposal by dossier submitter for consideration by RAC	STOT RE 2; H373 - May cause damage to organs (liver, kidney) H362 – May cause harm to breast-fed children Aquatic acute 1; H400 – Very toxic to aquatic life (M=100) Aquatic chronic 1; H410 – Very toxic to aquatic life with long lasting effects (M=1000)	N; Dangerous for the environment R50-53 SCL: N; R50-53: C ≥ 0.25%; N; R51-53: 0.025% ≤ C < 0.25%; R52-53: 0.0025% ≤ C < 0.025%
Amended proposal by dossier submitter for consideration by RAC following public consultation	None	None
Resulting harmonised	STOT RE 2; H373 - May	N; Dangerous for the

classification (future entry in Annex VI of CLP Regulation) as proposed by dossier submitter	cause damage to organs (liver, kidney) H362 – May cause harm to breast-fed children Aquatic acute 1; H400 – Very toxic to aquatic life (M=100) Aquatic chronic 1; H410 – Very toxic to aquatic life with long lasting effects (M=1000)	environment R50-53 SCL: N; R50-53: C ≥ 0.25%; N, R51-53: 0.025% ≤ C <0.25%; R52-53: 0.0025% ≤ C < 0.025%

PROCESS FOR ADOPTION OF THE OPINION

Austria has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation*** on **25/01/2012.** Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **12/03/2012**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Marja Pronk**
Co-rapporteur, appointed by RAC: **Marian Rucki**

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 reached on **28 November 2012** 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 **etofenprox** should be classified and labelled as follows:

Classification & 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)		
604-091-00-3	Etofenprox (ISO); 2-(4-ethoxyphenyl)-2-methylpropyl 3-phenoxybenzyl ether	407-980-2	80844-07-1	Lact. Aquatic Acute 1 Aquatic Chronic 1	H362 H400 H410	GHS09 Wng	H362 H410		Acute: M=100 Chronic: M= 1000	

Classification & Labelling in accordance with DSD:

Index No	International Chemical Identification	EC No	CAS No	Classification	Labelling	Concentration Limits	Notes
604-091-00-3	Etofenprox (ISO); 2-(4-ethoxyphenyl)-2-methylpropyl 3-phenoxybenzyl ether	407-980-2	80844-07-1	R64 N; R50-53	N R: 50/53-64 S: 60-61	N; R50-53: C ≥ 0.25% N; R51-53: 0.025% ≤ C < 0.25% R52-53: 0.0025% ≤ C < 0.025%	

SCIENTIFIC GROUNDS FOR THE OPINION

The opinion relates only to those hazard classes that have been reviewed in the proposal for harmonised classification and labelling, as submitted by Austria.

Physical hazards

Summary of the Dossier submitter's proposal
No classification is proposed based on available data.

Comments received during public consultation
No comments were received during public consultation.

RAC assessment and comparison with the classification criteria

RAC supported the non-classification for physico-chemical properties, as proposed by the dossier submitter.

Acute toxicity

Summary of the Dossier submitter's proposal
Acute toxicity studies in rat and mouse are available by the oral, dermal, subcutaneous and intra-peritoneal route. In addition, one acute inhalation study in rat and one acute oral study in dog are available. The latest acute oral and dermal study in rat (Oda 2003a, b) and the inhalation study in rat (Jackson *et al.*, 1983) are considered to be the key studies by the dossier submitter. In these key studies, oral and dermal LD_{50}-values were both above 2000 mg/kg bw, and the inhalation 4-hour LC_{50} value was above 5.88 mg/l. All these values are above the acute toxicity estimates (ATE) that would lead to classification according to Regulation (EC) 1272/2008 (CLP) or Directive 67/548/EEC (DSD). Hence, no classification for acute toxicity is proposed.

Comments received during public consultation
One MSCA supported the proposal not to classify for acute toxicity. No comments opposing the proposal were received.

RAC assessment and comparison with the classification criteria
Following a comparison of the LD_{50} and LC_{50} values in the key studies with the criteria, RAC supported the conclusion of the dossier submitter that these values (as well as the LD_{50} values in the additional studies) are above the cut-off values for classification (2000 mg/kg bw for the oral and dermal route and 5 mg/l for inhalation of dust/mist/aerosol, under both CLP and DSD) and RAC therefore supported the conclusion of the dossier submitter that etofenprox should not be classified for acute toxicity.

Specific target organ toxicity – single exposure (STOT SE)

Summary of the Dossier submitter's proposal
No specific target organ toxicity after single exposure was identified in any of the relevant acute toxicity studies, and no classification is proposed.

Comments received during public consultation
No comments were received during public consultation.

RAC assessment and comparison with the classification criteria
According to the DAR (Public version of August 2007, volume 3, section B.6.2.1-3), no clinical signs were observed in the key acute oral and dermal studies at the limit dose level. In the key acute inhalation study, etofenprox treated animals showed abnormal body posture accompanied

in some rats by partially or fully closed eyelids and abnormal respiratory movements, lethargy (approximately one hour post exposure) and oily appearance of the fur. Additionally, some female rats showed hair loss and transient hyperactivity. These signs are indicative of non-specific, general acute toxicity.
Further to this, no functional or histopathological evidence of neurotoxicity was observed in an acute oral neurotoxicity study in rats (Smith, 2002).

As there was no clear evidence of specific toxic effects on a target organ or tissue, and no signs of respiratory tract irritation or narcotic effects, and RAC therefore supported the conclusion of the dossier submitter that etofenprox should not be classified for specific target organ toxicity (single exposure) under CLP.

Skin corrosion/irritation

Summary of the Dossier submitter's proposal
One study in rabbits (Japanese White, 6 males, 4 hour exposure) is available, showing a mean skin irritation index score of 0.1 (24-72 hours). No individual score was greater than or equal to the scores that would justify classification (0 in 5/6 animals; 0.6 in 1/6 animals), and inflammation did not persist until the end of the observation period in more than one animal. The dossier submitter concluded that no classification for skin irritation or corrosion was justified according to CLP or DSD.

Comments received during public consultation
One MSCA supported the proposal not to classify for skin irritation. No comments opposing the proposal were received.

RAC assessment and comparison with the classification criteria
Five of the six test animals scored zero for both erythema and oedema throughout the observation period. The remaining test animal showed very slight erythema (grade 1) at the 48 and 72 hr observation points, and was examined for a further 11 days. The grade 1 erythema persisted up to day 7, after which no signs of skin irritation were apparent. Therefore, only slight, transient irritation was observed, with mean scores for erythema and oedema below the threshold value of 2.3 for Skin Irrit. 2 – H315 (CLP) or 2 for Xi; R38 (DSD) in all six animals, and RAC therefore supported the conclusion of the dossier submitter that etofenprox should not be classified for skin irritation.

Eye corrosion/irritation

Summary of the Dossier submitter's proposal
One study in rabbits (Japanese White, 6 males) is available, showing no corneal opacity or iris lesions. Conjunctival oedema was only seen in one animal (score 1) after 1 hour, but not at the later observation times. Transient, minimal (score 1) conjunctival erythema was seen in 6/6 animals after 1 hour, 5/6 animals after 24 hours, 3/6 animals after 48 hours, and 0/6 animals after 72 hours; mean individual scores over 24-72 hours were 0–0.66, with an overall mean index score of 0.44. It was concluded that the irritation scores did not fulfil the criteria for classification according to the CLP or DSD and no classification was proposed.

Comments received during public consultation
One MSCA supported the proposal not to classify for eye irritation. No comments opposing the proposal were received.

RAC assessment and comparison with the classification criteria
In the rabbit eye irritation study, only slight, transient effects on the conjunctivae were observed. The mean scores for conjuctival redness and chemosis were below the threshold values for classification (2 for Eye Irrit. 2 – H319 (CLP) or 2.5 (redness) and 2 (chemosis) for Xi; R36 (DSD)) in all six animals, and RAC therefore supported the conclusion of the dossier submitter that etofenprox should not be classified for eye irritation.

Respiratory sensitisation

Summary of the Dossier submitter's proposal
No information is available and no classification was proposed.

Comments received during public consultation
No comments were received during public consultation.

RAC assessment and comparison with the classification criteria
In the absence of data, no conclusion can be drawn on the classification for respiratory tract irritation.

Skin sensitisation

Summary of the Dossier submitter's proposal
A Guinea pig maximisation test is available, indicating no skin sensitising properties of etofenprox (0/20 animals scored positive), while all animals showed skin reactions in the positive control group. Hence, no classification for skin sensitisation was proposed.

Comments received during public consultation
No comments were received during public consultation.

RAC assessment and comparison with the classification criteria
A substance is classified as a skin sensitiser if, in a Guinea pig maximisation study, a positive response is observed in at least 30% of treated animals. As 0/20 animals gave a response following treatment with etofenprox, it can be concluded that it does not meet the criteria for classification in accordance with CLP or DSD, and RAC therefore supported the conclusion of the dossier submitter that etofenprox should not be classified for skin sensitisation.

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

Summary of the Dossier submitter's proposal
Four short-term repeated dose studies are available; two 13-week oral studies (one in rat and one in mouse), one 13-week inhalation study in rat, and one 4-week dermal study in rabbit. Further, a 52-week study in dogs and two 2-year studies (one in rat and one in mouse), were considered relevant.

The 4-week dermal study in rabbit was considered negative as only minor local skin irritation occurred (that appeared reversible), but no systemic toxicity was observed at doses up to and including 1000 mg/kg bw/d.
In the 52-week dog study the liver was identified as the target organ (the LOAEL for minimal and reversible hepatic effects was 352/339 mg/kg bw/d), but at higher doses than in the rat. In the rat oral studies, the liver (e.g. hepatocyte enlargement and liver dysfunction) and thyroid gland (increase in thyroid microfollicles and reduced levels of thyroxine) were identified as target organs, with LOAELs of 120/142 and 25.5/34.3 mg/kg bw/day for the 13-week and 2-year study, respectively.
In the 13-week rat inhalation study, effects on the adrenal glands were seen next to effects on liver and thyroid. The effects in the inhalation study were however considered minimal at the LOAEL of 0.21 mg/l, which is around the guidance value for classification (0.2 mg/l under CLP and 0.25 mg/l under DSD).
In the mouse studies, the liver was also identified as a target organ, but at much higher doses than in the rat. Other target organs in the mouse were kidneys and (in 13-week study) haemolymphoreticular system. In the 13-week mouse study the effects were seen only at the highest dose (1975/2192 mg/kg bw/d) but in the 2-year study the LOAEL was determined to be 10.4/11.7 mg/kg bw/d. In deciding on the classification, the dossier submitter multiplied the LOAELs of the 2-year study by a factor of 2 to account for the longer exposure duration.

The dossier submitter concluded that effects relevant for classification were not seen at doses below the guidance values (50 mg/kg bw/day) for classification according to DSD and hence no classification was proposed. Due to the large dosing step in the 13-week oral rat study (20 and 120 mg/kg bw/day), it was argued that the LOAEL could be below the guidance value of 100 mg/kg bw/day for STOT RE 2 according to CLP. Also the effects seen in the 2-year studies (with LOAELs of 25.5/34.3 and 10.4/11.7 mg/kg bw/d for rat and mouse, respectively) were considered relevant, even when multiplied by 2 to account for the longer study duration. Hence, classification with STOT RE 2 – H373 (liver, kidneys) was proposed.

Comments received during public consultation

During the public consultation several MSCAs and one industry representative commented on the classification proposal.

Three MSCAs and one IND representative disagreed with the dossier submitter's proposal for STOT RE 2. Arguments against classification included that effects seen were not severe enough for classification and that effects occurred above the guidance levels for classification. One MSCA commented that the dossier presented insufficient information to reach a decision on the proposed classification. This MSCA further noted that multiplying the LOAELs of the 2-year study by a factor of 2 to account for the longer exposure duration is not a correct application of Haber's rule. A correct way would be to divide the guidance values for a 90-day study by a factor of 8 to obtain guidance values for a 2-year study.

Two MSCAs agreed with STOT RE 2, although one raised doubts about the classification for liver effects.

RAC assessment and comparison with the classification criteria

Dermal: The 4-week dermal study in rabbit showed no systemic toxicity at doses up to and including 1000 mg/kg bw/d. Locally, only minor, reversible skin irritation occurred (from 400 mg/kg bw/d). No severe effects were observed at dose levels relevant for classification, neither under CLP (extrapolated guidance value 600 mg/kg bw/d) nor DSD (extrapolated guidance value 300 mg/kg bw/d).

Inhalation: In the 13-week rat inhalation study, effects observed at the LOAEC of 0.21 mg/l consisted of small increases in liver weight in females and in kidney weights in males and females, and minimally increased adrenal cortical width in 3/20 females. At the highest dose of 1.01 mg/l; weights of liver, kidney and thyroid were increased in males and females. Histopathologically, minimal hepatocyte enlargement (in 4/10 males and 4/10 females), increased number of thyroid microfollicles (in 4/10 males) and increased adrenal cortex thickness in 4/10 females were observed at 1.01 mg/l. RAC concludes that at dose levels relevant for classification (0.2 mg/l under CLP and 0.25 mg/l under DSD) the effects were not severe enough for classification.

Oral: In the available short- and longer term studies the liver (rat, mouse, dog), thyroid (rat), kidney (mouse) and haemolymphoreticular system (mouse) were identified as target organs. As to the liver effects, the rat was the most sensitive species. In the 13-week rat study, the high dose of 743/820 mg/kg bw/d (in males/females, respectively) caused clinical evidence of liver dysfunction in males (affecting fat metabolism and the synthesis of blood clotting factors) and minimal hepatocyte enlargement in 9/20 females. At the dose level of 120/142 mg/kg bw/d relative liver weight was slightly increased (9%) in females, 2/20 males had an enlarged liver but upon histopathology it was only 1/20 females that showed minimal hepatocyte enlargement. Considering the low incidence and severity of the effects at 120/142 mg/kg bw/d, it is not expected that they will occur at a dose level at or just below the cut-off value for classification as STOT RE 2 (100 mg/kg bw/d). In the 13-week mouse study, the 52-week dog study and the 2-year rat and mouse studies, liver effects occurred only at dose levels (1975/2192, 352/339, 25.5/34.3 and 546.9/615.5 mg/kg bw/d, respectively) that are (far) above the (extrapolated) guidance values for classification (25 mg/kg bw/d for a 1-year study, 12.5 mg/kg bw/d for a 2-year study). Hence, the liver effects do not warrant classification under CLP or DSD, where the cut-off values for classification are even lower.

The thyroid effects observed in the 13-week rat study at the two highest doses (120/142 and 734/820 mg/kg bw/d) included a decrease in circulating thyroxine (T4) and an increase in relative thyroid weight in males only, as well as an increased incidence of minimal to moderate number of

thyroid microfollicles in both sexes. In the 2-year study there was also an increase in benign neoplasms of the thyroid, follicular cell adenoma, at the highest dose (186.7/249.1 mg/kg bw/d) in both sexes (see section on Carcinogenicity). A mechanistic study is available providing some evidence that the thyroid effects could be secondary to microsomal enzyme induction in the liver (specifically UDPGT). If so, the thyroid effects would be of less relevance to humans, as it is known that humans are considerably less susceptible for thyroid effects mediated by UDPGT (see also section on Carcinogenicity). A definite conclusion on the exact mode of action is, however, not possible based on the available data. Nevertheless, the thyroid effects occurred at effect levels that are in fact above the (extrapolated) guidance values for classification under both CLP and DSD and thus do not warrant classification.

In mice, kidney effects were observed in the 13-week and the 2-year studies, but in the 13-week study only at a dose (1975/2192 mg/kg bw/d) far above the guidance values for classification (100 and 50 mg/kg bw/d under CLP and DSD, respectively). In the 2-year study, kidney effects were seen at 10.4/11.7 mg/kg bw/d and above. Given the extrapolated guidance values for a 2-year study (12.5 and 6.25 mg/kg bw/day under CLP and DSD, respectively) only the effects at 10.4/11.7 mg/kg bw/d may possibly be relevant for classification. At this dose, the incidences of dilated and basophilic tubules were slightly increased, sometimes accompanied by focal loss of tubules. Although the severity of the tubular lesions was also slightly increased, the majority was still grade 1 or 2, i.e. generally of minimal severity with few tubules affected. RAC considers these effects not severe enough for classification.

The effects on the haemolymphoreticular system in the 13-week mouse study are not relevant for classification, as they were observed at a dose (1975/2192 mg/kg bw/d) far above the guidance values for classification (100 and 50 mg/kg bw/d under CLP and DSD, respectively).

Overall, it can be concluded that in the available short- and longer term studies no biologically relevant effects warranting classification under CLP/DSD have been observed. Etofenprox further provided no functional or histopathological evidence of neurotoxicity in a 13-week dietary neurotoxicity study in rats (Smith, 2003b). RAC therefore concludes that etofenprox should not be classified for toxicity upon repeated exposure. This conclusion was also drawn by EFSA in their peer review of etofenprox in 2008.

Germ cell mutagenicity

Summary of the Dossier submitter's proposal
Etofenprox has been tested in three standard *in vitro* assays and one *in vivo* micronucleus assay which were all clearly negative. The dossier submitter concluded that these tests were enough to assess the mutagenic toxicity of etofenprox, and that no *in vivo* study in germ cells is needed. Based on the negative results it was concluded that no classification is justified.

Comments received during public consultation
One MSCA supported the no classification proposal for mutagenicity. No comments opposing the proposal were received.

RAC assessment and comparison with the classification criteria
Etofenprox tested negative in four *in vitro* assays (a bacterial mutation assay, a mammalian gene mutation assay, a cytogenicity test in human lymphocytes and an unscheduled DNA synthesis assay in cultured human cells) and in one *in vivo* micronucleus assay with mice, and RAC therefore supported the conclusion of the dossier submitter that etofenprox should not be classified for mutagenicity.

Carcinogenicity

Summary of the Dossier submitter's proposal
A 1-year study in dog and 2-year studies in rat and mouse, respectively, are available.
No target organs that had not already been identified in short-term studies were identified in any of the species. Etofenprox did not induce any frank carcinogenic effects in either dog, rat or mouse.

In rat there was an increase in benign neoplasms of the thyroid, follicular cell adenoma, at the highest dose (186.7 and 249.1 mg/kg bw/day in males and females, respectively). A mechanistic study is available investigating the aetiology of the follicular cell adenoma in the thyroid, and the results were consistent with the hypothesis that these effects are secondary to microsomal enzyme induction in the liver. This mode of action is considered to be an indirect, non-genotoxic mechanism, which is further considered of limited relevance to humans due to humans having different T4 plasma kinetics compared to rats. In the mouse study, three males at the highest dose (546.9 mg/kg bw/d) and one male at the next lower dose (75.2 mg/kg bw/d) showed a renal neoplasm. However, two of the neoplasms at the highest dose were benign and the increase was not statistically significant. It was concluded by the dossier submitter that there was insufficient evidence of carcinogenic effects in mice.

Taking all data into consideration it was concluded by the dossier submitter that no classification for carcinogenicity was justified according to either CLP or DSD.

Comments received during public consultation
Two MSCAs supported the conclusion that no classification for carcinogenicity was warranted. No comments opposing the proposal were received.

RAC assessment and comparison with the classification criteria
In the 2-year rat study, an increase in follicular cell adenoma of the thyroid was observed in both males (not statistically significant) and females at the highest dose. A mechanistic study with etofenprox is available providing some evidence that the adenomas are not a primary effect of etofenprox, but could be the result of an increased hepatic microsomal enzyme induction (specifically UDPGT). This would reduce the relevance to humans, as it is known that humans are considerably less susceptible than rodents (especially rats) to the formation of follicular cell adenomas mediated by UDPGT induction, with consequent T4 reduction, TSH increase and finally increased thyroid stimulation (CLP guidance 3.6.2.3.2(k)). A definite conclusion on the exact mode of action is, however, not possible based on the available data. Given that the thyroid tumours induced were only benign in nature and only occurred at a high dose (at which the overall body weight gain was decreased by 24.2 and 34% in males and females, respectively), that the thyroid gland related carcinogenicity is of low potency (with a T25 > 100 mg/kg bw/d), and that etofenprox is not considered genotoxic, RAC concluded that the follicular cell adenomas present insufficient evidence for classification.

In the 2-year mouse study, some renal cortical tumours were observed, three at the high dose (one of which was malignant) and one at the mid dose (malignant). These tumours were only observed in males, not in females, and were not observed rats. Besides, the incidences at the high and mid dose were not statistically significantly increased compared to controls, and etofenprox can be considered a non-genotoxic substance. Overall, the relevance of the observed one sex/one species renal tumours to humans is doubtful, and they present insufficient evidence for classification.

The study in dogs is considered less relevant for carcinogenicity due to the limited exposure and observation duration and the limited number of animals. Yet, no increase in tumours was observed.

Considering the above, RAC supports the conclusion of the dossier submitter that etofenprox should not be classified for carcinogenicity. This conclusion was also drawn by EFSA in their peer review of etofenprox in 2008.

Reproductive toxicity

Summary of the Dossier submitter's proposal

The reproductive toxicity of etofenprox has been investigated in several studies in rats and rabbits. In rabbits there were two developmental toxicity studies (via gavage). In rats, there was a fertility study (gavage), a dietary 2-generation, 2 litters/generation) study, a peri-/post-natal study

(gavage) and a developmental toxicity study (gavage). In the latter study, part of the dams were allowed to litter normally and rear their young. Part of the F1 progeny in this study and in the peri-postnatal study were selected to produce the F2 generation. Further to these studies, there was a dietary developmental neurotoxicity study in rats.

Reference	Test guideline	GLP	Short study description	Main effects / target organs
Cozens *et al*, 1985a	no OECD TG	Yes	**Rat**; 0, 12.5, 125, 250 & 5000 mg/kg bw/d (oral gavage) Exposure time: P0 males: 9 weeks pre-mating until post-mating day 20 P0 females: 2 weeks pre-mating until GD 7 P0 animals sacrificed at GD 20.	*12.5-5000 mg/kg:* minor clinical signs (e.g. increased salivation and brown staining around the mouth) *5000 mg/kg:* Slightly higher pre-implantation loss and slightly lower litter size and weight (n.s.)
Cozens *et al*, 1985b	no OECD TG (in conformity with (88/302/EEC, Part B, with some deviations)	Yes	**Rat**; 0, 12.5, 125, 250 & 5000 mg/kg bw/d (oral gavage) Exposure time: P0 animals: GD 6-17 21-24 P0 females/ group sacrificed on GD 20; 11-14 P0 females/group kept to rear F1 pups until PND 21. F1 animals: treated only *in utero* and via lactation. Part of F1 animals mated to produce an F2 generation, kept until PND 21.	*12.5-5000 mg/kg:* minor clinical signs (e.g. increased salivation and red-brown staining around the mouth) *5000 mg/kg:* Slightly lower maternal gestation weight gain: P0 females: -3.6% bw at GD 20 F1 females: -7% bw at GD 20 (n.s.) F1 offspring: No treatment-related malformations, visceral anomalies or skeletal variations. No effects on physical, behavioural or sexual development in F1 offspring exposed *in utero*.
Cozens *et al*, 1985c	no OECD TG	Yes	**Rat**; 0, 12.5, 125, 250 & 5000 mg/kg bw/d (oral gavage) Exposure time: P0 females: GD 17 – PND 21; kept to rear pups until PND 21. F1 animals: treated only *in utero* and via lactation. Part of F1 animals mated to produce an F2 generation, kept until PND 21.	*250 mg/kg:* P0 animals: Increased salivation and brown staining around mouth. *5000 mg/kg:* P0 animals: Increased salivation and brown staining around mouth, yellow staining of fur in anogenital region, slight decrease in body weight gain during GD17-20 (13.4%). F1 weanlings: During (late) lactation: 3 total litter losses, increased pup mortality, reduced weight gain (6-9.4%), tremors, subcutaneous haemorrhage, general motor incoordination, increased kidney weights and histopathological alterations (cystic collecting ducts, focal fibrosis, cortical scarring, mineral deposits).

				F1 post-weaning: Increased water consumption, same kidney effects as weanlings. F2 offspring: Marginally reduced pup weight (n.s.) due to slightly larger litter size, 1 total litter loss.
Cozens *et al*, 1985d	no OECD TG (in conformity with (88/302/EEC, Part B, with some deviations)	Yes	**Rat**; 0, 100, 700, 4900 ppm (approx. 0, 4.3-14.3, 30-104, 225-753 mg/kg bw/d, depending on sex and age) Exposure time: P0 animals: continuously from 6 weeks of age through mating and gestation until weaning of F1 offspring F1b and F2a & F2b: continuous exposure until at least 13 weeks from weaning.	*30(-104) mg/kg:* Parental animals: 1 F1b pup (f) with cystic collecting ducts extending into renal cortex, increased kidney weight in F2b females. Offspring: 2 F1a pups with ocular defects (at late lactation/ weaning); 1 F1a pup with subcutaneous haemorrhage (PND12); increased liver weight in F1a (m&f), F1b (m), F2b (m&f) *225-753 mg/kg:* Parental animals: Slightly reduced body weight gain (F1b males at wk 14, F0 and F1b females at pre-mating, F1a and F2a females overall); increased water consumption in F1a/b and F2b; increased liver, kidney and thyroid weights; similar kidney lesions as in Cozens *et al.*, 1985c in F1b but not in F0; minimal hepatocyte enlargement in F1b; slightly increased height of columnar epithelium of thyroid in some F1b males. No effects on fertility or reproductive capacity. Offspring: During (late) lactation: 2 total litter losses, increased pup mortality (n.s.); reduced weight gain (5-14%); tremors, distended abdomen, abnormal gate; small number of pups with ocular defects and subcutaneous haemorrhage; increased liver, kidney and heart weights.
Bottomley, 1985	not stated	not stated	**Rabbit**; 0, 10, 50, 250 mg/kg bw/d (oral gavage) Exposure time: P0 animals: GD 6-18 Sacrificed on GD 28.	Not considered valid. Performed on groups of animals from different sources. *50 mg/kg:* Reduced weight gain in P0 animals *250 mg/kg:* Slight increase in post-implantation loss.
Fisher, 2000	OECD TG 414	Yes	**Rabbit**; 0, 30, 100, 300 mg/kg bw/d (oral gavage) Exposure time:	*300 mg/kg:* P0 animals: Increased post-implantation loss (10.1 vs 4.3% in controls) and reduced embryo-fetal weight gain. Abortion/unscheduled death in 4

			Mated females: GD 6–28 Sacrificed on GD 29.	dams (0, 1, 1 in 0, 20 and 100 mg/kg groups). Maternal toxicity seen at the same dose: -10% bw, -2.9% bw loss on GD 6-29; -18.9% reduced food consumption. <u>F1 offspring:</u> Fetal malformations considered not to be related to treatment. Skeletal variations at higher incidence than controls but not considered related to treatment.
Myers, 2003	no OECD TG (developmental neurotoxicity study)	Yes	**Rat**; 28.4, 79.2, 238 mg/kg bw/d (in diet) <u>Exposure time:</u> P0 females: GD 6 – PND 21. F1 animals exposed *in utero*, via lactation and late pre-weaning. Functional investigations at several time points post-natally. CNS/PNS histopathology of F1 animals at 63-67 days of age.	*79 mg/kg:* <u>P0 animals:</u> Slight, transient decrease in weight gain from GD 6-10. <u>F1 offspring:</u> Low incidence of ocular lesions. *238 mg/kg:* <u>P0 animals:</u> Slight, transient decrease in weight gain from GD6-10; increased rearing activity. <u>F1 offspring:</u> Increased pup mortality between PND 14 and 21 (5.7% vs. 0.6% in controls), low incidence of subcutaneous haemorrhage and ocular lesions. No effect on bw or bw gain until PND 63, and no effect on sexual development. Functional neurological effects possibly related to treatment: higher mean auditory startle response amplitudes, reduced habituation (females); clustering of differences in motor activity and latency to peak startle response (males). No selective developmental neurotoxicity at dose levels with slight maternal toxicity. Histo-morphological development of CNS and PNS nerve tissue not affected by treatment.

TG = test guideline
bw = body weight
n.s. = not significant
GD = gestation day
PND = post-natal day (= lactation day)

It was concluded that in rats, effects are seen in offspring exposed *in utero* and during lactation, and that these effects are not evident in adults who have not been exposed during this time period. The effects seen were increase in pup mortality, non-specific haemorrhagic lesions (subcutaneous and ocular), renal toxicity, liver/thyroid/renal histopathological changes as well as functional neurological effects. There are other effects seen in offspring but these are also seen in parental animals. It was concluded that the effects seen only in offspring could indicate a need for classification for developmental toxicity. However, since the effects were only evident at (partly very) high doses and/or were inconsistent with parallel or subsequent cohorts findings and/or marginal in frequency/severity and/or clustered in two litters and/or were observed also in adult animals in other (non-reproductive) repeated dose studies the dossier submitter concluded that they did not justify classification for developmental toxicity.

It was instead argued that the effects were due to a naturally high ratio of milk uptake compared to bodyweight. Thisis also supported by toxicokinetic findings which indicate a potential for accumulation of etofenprox in fat and active secretion into milk, leading to a high concentration ratio between pup stomach content and maternal plasma content. Toxicokinetic studies show that etofenprox is transferred via the placenta to the fetus. Placental and fetal concentrations are however relatively low compared to plasma concentrations in the dams, and etofenprox is rapidly eliminated from these tissues. In general, etofenprox concentration decreases rapidly in all tissues except for fat. Toxicokinetic studies also show that unchanged etofenprox is actively secreted into maternal milk and is ingested by pups at a concentration ratio of over 20 (pup stomach content compared to maternal plasma). Transfer in milk decreases rapidly when dosing stops.

Based on these data, the dossier submitter concluded that classification for fertility or developmental toxicity is not justified, but classification for lactation effects (Lact. – H362 according to CLP) is proposed. The dossier submitter further argued that R64 according to DSD is not possible due to the fact that no other classification for health hazards is proposed according to this directive.

Comments received during public consultation

Several comments were received during public consultation.

Four MSCAs supported the proposed classification with Lact. - H362, three of which said that a corresponding classification with R64 according to DSD should be added to the proposal. They considered the reason given by the dossier submitter not to do this a misinterpretation of DSD as according to this directive, R64 can be added as additional labelling to any other classification, not only to classification in health hazard classes. Consequently, as environmental classification according to DSD has been proposed by the dossier submitter, R64 can be proposed as well. One MSCA also wanted to add labelling with R33 (Danger of cumulative effects) as the substance seems to be accumulating in the body.

Classification for lactation effects was questioned by one MSCA and one IND representative. The IND representative argued that H362 was not justified e.g. since the haemorrhagic effects were of low incidence (and possibly secondary to other effects) and that some of the observations were not necessarily consistent with an effect on lactation. Aside from the low incidence of haemorrhagic effects, the MSCA also questioned whether the reduced body weight development in pups meets the classification criteria.

RAC assessment and comparison with the classification criteria

Fertility

No adverse effects on sexual function and fertility were observed in the fertility and 2-generation study in rats. Also rats that had only been exposed to etofenprox *in utero* or during lactation did not show these adverse effects when allowed to litter. RAC therefore supports the conclusion of the dossier submitter that etofenprox should not be classified for fertility effects. This conclusion was also drawn by EFSA in their peer review of etofenprox in 2008.

Development

No teratogenic effects were observed in either rats or rabbits. In the key study in rabbits (Fisher, 2000), some embryo- and foetotoxicity was observed (slightly increased post-implantation loss and reduced fetal weight) at the highest tested dose of 300 mg/kg bw/d, but this was considered secondary to the maternal toxicity induced at that dose, resulting in reduced food consumption and weight loss over the treatment period. They therefore do not warrant classification.
In rats, no treatment-related embryo- or foetotoxic effects were observed in the fertility study (with maternal dosing from 2 weeks prior to mating up to gestation day 7; Cozens *et al.*, 1985a) or in the developmental toxicity study (with maternal dosing from day 6-17 of gestation; Cozens *et al.*, 1985b). In the latter study, the physical, behavioural and sexual development of the F1 progeny exposed *in utero* was also not affected by treatment with etofenprox.
In contrast, in the rat peri-/post-natal study (with maternal dosing from day 17 of gestation to PND 21; Cozens *et al.*, 1985c), effects on the F1 progeny were observed at the highest tested dose of 5000 mg/kg bw/d, a dose at which no significant maternal toxicity occurred. The effects were not observed at the lower doses. The effects seen included reduced pup weight (up to 9.4%; from PND 8, but only statistically significant at PND 12 and 21), increased pup mortality during PND 12-21 (with cumulative loss of 26.1% at PND 21, compared to 2.7% for controls), pups showing subcutaneous haemorrhage, tremors and general motor incoordination during the 3rd week of lactation. All F1 weanlings, as well as F1 adults, further had increased kidney weights and histopathological renal alterations. The post-weaning physical, behavioural and sexual development of the F1 progeny was not affected.
In the rat 2-generation study (Cozens *et al.*, 1985d), at 4900 ppm (225-753 mg/kg bw/d) the same type of effects on the kidneys as in the peri-/post-natal study were observed in the progeny (but not in the F0 animals), and pups also showed tremors in late lactation, as well as distended abdomen and abnormal gait. Further at 4900 ppm (a dose level that for dams corresponded to an intake of approximately 300-350 mg/kg bw/d), pup weight was slightly decreased in all litters (up to 14%; from PND 4, but only statistically significant at PND 8, 12 and 21), and pup mortality was slightly increased (not statistically significantly), mainly in the first matings due to one total litter loss in the 2nd half of lactation. A few pups also showed ocular lesions or subcutaneous haemorrhage when sacrificed at weaning or when dying during the second half of lactation. Next to the renal lesions also minimal hepatocyte enlargement was seen in the progeny, as well as some thyroid alterations (males only).
The rat developmental neurotoxicity study (Myers, 2003) showed no selective developmental neurotoxicity at dose levels with slight maternal toxicity, but impaired pre-weaning survival was observed in the 3rd week of lactation (5.7% vs 0.6% in controls) at 2100 ppm (238 mg/kg bw/d), as well as an increase in ocular lesions (enlarged/dark/opaque eyes, associated with intraocular haemorrhage) and subcutaneous haemorrhages at 700 ppm (79.2 mg/kg bw/d) and 2100 ppm, and some minor functional neurological effects at 2100 ppm.
The effects seen in rat offspring indicate a need for classification, but given their onset (mainly in the 3rd week of lactation or thereafter), classification for developmental toxicity seems not warranted. A classification for effects via lactation might be more appropriate. According to CLP, classification for effects via lactation can be assigned based on:

- human evidence indicating a hazard to babies during the lactation period; and/or
- results of one or two generation studies in animals which provide clear evidence of adverse effect in the offspring due to transfer in the milk or adverse effect on the quality of the milk; and/or
- absorption, metabolism, distribution and excretion studies that indicate the likelihood that the substance is present in potentially toxic levels in breast milk

Similarly, according to the DSD, R64 may also be applied to substances that are not toxic to reproduction but where

- toxicokinetic studies indicate the likelihood of toxic levels of the substance in breast milk and/or
- the results of one or two generation studies in animals indicate the presence of adverse effects on the offspring due to transfer in the milk and/or
- evidence in humans indicates a risk to babies during the lactational period.

The toxicokinetic study by Hawkins *et al.* (1985a) indicates a slight potential for accumulation in fat (half-life 5-8.5 days) and active secretion into milk, with a pup stomach/maternal plasma

concentration ratio of 20. Etofenprox further has a log P_{ow} of 6.9. In the reproductive toxicity studies, several adverse effects were observed in the progeny during the lactation period, such as renal lesions and ocular defects and subcutaneous haemorrhage (for further details, see table above and background document). In addition, slightly decreased pup weight and increased pup mortality was observed during the lactation period. In the peri-/post-natal study (Cozens *et al.*, 1985c), pup weight was slightly decreased from PND 8 (significantly from PND 12) and pup mortality was increased from PND 12. As this is a gavage study, the effects seen must be due to lactation exposure. They are however only observed at a very high dose of 5000 mg/kg bw/d, not at doses of 250 mg/kg bw/d and below, and such a high dose (or in fact any other effective dose above 1000 mg/kg bw/d) is not considered relevant for classification. In the multi-generation study (Cozens *et al.*, 1985d), which is a diet study, pup weight was slightly decreased from PND 4 (significantly from PND 8). Other adverse effects in this study (such as tremors, haemorrhages and kidney effects) were mainly observed from the 3rd week of lactation. Also in the dietary developmental neurotoxicity study by Myers (2003) increased pup mortality was seen in late lactation; subcutaneous haemorrhage and ocular lesions were also mainly observed in late lactation or pre-weaning, although some bruising was already seen in the first week of lactation. The time of onset of the effects in the latter two studies seems to indicate that the effects occur via lactation, although direct exposure via food intake of the pups cannot be completely ruled out (especially in the multi-generation study). Given, however, the similarity in effects with the gavage study, it seems more likely that they are caused via exposure through lactation. Moreover, the effect on body weight starts at a period during lactation (from PND 4) when pups are only exposed via lactation.

In conclusion, there is high transfer of etofenprox into the milk, with clear effects on or via lactation at a dose level considered too high for classification (5000 mg/kg bw/d). There is still evidence, albeit weak, for effects on or via lactation at the next lower dose levels tested (up to approximately 350 mg/kg bw/d). Although no doses between 350 and 5000 mg/kg bw/d have been tested, RAC considered it not unlikely that more severe lactational effects could have occurred at dose levels higher than 350 mg/kg bw/d that are still relevant for classification (up to 1000 mg/kg bw/d). RAC therefore considers classification with **Lact. – H362** (CLP) and **R64** (DSD) justified. The labelling with R64 is applicable, as the required additional classification for etofenprox under DSD (Annex VI of DSD, 3.2.8) is present (namely for environmental effects). RAC noted that EFSA in their peer review of etofenprox in 2008 also proposed R64, but no classification for developmental toxicity.

Additional labelling with R33 - Danger of cumulative effects (next to R64) was not deemed necessary, as the fairly short half-life of etofenprox in fat does not seem to indicate a high accumulation potential.

Environmental hazards

Summary of the Dossier submitter's proposal

The dossier submitter proposed classification according to the CLP criteria as Aquatic Acute 1 (H400) with an M-factor of 100 and Aquatic Chronic 1 (H410) with an M-factor of 1000. The proposal according to the DSD criteria is N; R50-53 with specific concentration limits of N; R50/53: C ≥ 0.25%; N, R51/53: 0.025% ≤C <0.25%; R52/53: 0.0025% ≤ C< 0.025%.

Rapid degradation

The rate of hydrolysis was tested according to OECD TG111 and this was considered as an insignificant route of degradation.

Direct photo-transformation induced degradation of etofenprox with DT_{50} values of 4.7 and 7.9 days to two main metabolites comprising 75.6% and 52.2% of applied radioactivity in sterile buffer and natural water, respectively. Lack of toxicity data on photolytic metabolites and their relatively low contribution to the removal justified the conclusion that direct photolysis is an insignificant route of degradation (NB: due to problems with extrapolating the data to the aquatic environment, these data are normally difficult to use for concluding on the degradability of etofenprox (Guidance II.2.3.9)).

Two ready biodegradability tests were reported: a closed bottle oxygen consumption test conducted according to OECD TG 301D and a $^{14}CO_2$-evolution test conducted according OECD TG 301B. In the closed bottle test, 17% degradation in 28 days was reported. However, the test was performed at a concentration (2 mg/l) which was above the water solubility limit of etofenprox (i.e. 0.012-0.0225 mg/l). The $^{14}CO_2$-evolution test was performed at a concentration (0.0108 mg/l), which is within the water solubility limits and the resulting ultimate degradation of 32% was measured after 28 days incubation period. A limitation of this study is that no reference substance (positive control) was included. Using the former test as key study, the dossier submitter concluded etofenprox to be not readily biodegradable.

Simulation tests on etofenprox's degradation in soil and water/sediment systems were also reported. In the first water/sediment study, the reported primary degradation DT_{50} values for the whole system were 6.5 days for the pond system and 20.1 days for the lake system. Mineralisation was 28 and 18% after 99 days for the pond and lake system, respectively. The second (repeat) study assessed the degradation of etofenprox in the pond system, resulting in a primary degradation DT_{50} value for the whole system of 6.5 days and a mineralization up to 35% within 100 days. Etofenprox was therefore not considered to undergo degradation to a level > 70% within a 28-day period, or to have fast primary degradation (DT_{50} in aquatic systems is not <16 days).

In the overall conclusion on rapid degradation, the DS used the closed bottle test, water/sediment simulation tests, hydrolytic stability and photolysis test as a basis to conclude that etofenprox is not rapidly degradable.

Bioaccumulation

The octanol-water partition coefficient of etofenprox was reported to be 6.9. One experimental study on bioaccumulation on bluegill sunfish (*Lepomis macrochirus*) was reported (OECDTG 305) with a resulting BCF value of 2565 (whole body, lipid normalized).

Acute aquatic toxicity

Acute studies were reported for all key trophic levels (i.e. fish, crustacean, algae). Two acute studies according to US EPA Section 72-1 guideline on fish (*Oncorhynchus mykiss* and *L. macrochirus*) using technical etofenprox as the test substance gave 96-h LC_{50} values of 0.0027 and 0.013 mg/l both values based on mean measured concentrations, respectively. In an additional acute study (a limit test according to OECD TG 203) *O. mykiss* was exposed to etofenprox's metabolite α-CO but mortality was not observed at the used concentration (0.048 mg/l).

Acute toxicity of etofenprox and its metabolite α-CO were tested (both according to the OECD TG 202) in water flea (*Daphnia magna*). The EC_{50} (48-h) for etofenprox was 0.0012 mg/l based on mean measured concentrations. Metabolite α-CO did not cause any observed effect (i.e. immobilisation) at the applied concentration (i.e. 0.044 mg/l).

Two studies (OECD TG 201, biomass and growth) on acute toxicity of etofenprox and its metabolite to green algae (*Pseudokirchneriella subcapitata*) were reported. No acute toxicity was observed in the study in which the highest exposure concentration was 0.056 mg/l (NB: this is the average measured concentration; nominally 0.150 mg/l was applied, but the recovery was only 37.5% (geometric mean)). Similarly, acute toxicity of metabolite α-CO did not cause any effect at the applied concentration (i.e. 0.053 mg/l) of the limit test.

Chronic aquatic toxicity

Chronic studies were reported for all key trophic levels (i.e. fish, crustacean, algae). In fish a 40 days study (OECD TG 210) on zebra fish (*Brachydanio rerio*) was reported. In addition, the dossier submitter considered a 21 day study (OECD TG 204) on *O. mykiss* juveniles as a chronic study even though it is not normally considered as a chronic study. The NOEC value for mortality

was 0.025 mg/l (mean measured concentration) in the *B. rerio* study and 0.0032 mg/l (nominal concentration) in the *O. mykiss* study. In the latter study, the mean measured concentration were 41-65% of the nominal concentration but still the DS applied nominal values in calculating the NOEC value.

One toxicity study in crustaceans (*D. magna OECD TG 211*) was reported. The measured NOEC for reproduction, i.e. the total number of living offspring produced per parent animal alive at the end of the test, was 0.000054 mg/l (mean measured concentration).

No inhibition of the growth by etofenprox or its metabolite α-CO was observed in the chronic test on algae (the same studies as described for acute toxicity) at the applied test concentrations.

Classification proposals

Aquatic acute classification according to CLP criteria:
The DS's conclusion on acute aquatic hazard, i.e. Aquatic Acute 1, was based on the lowest effective concentration of etofenprox that was observed in *D. magna* (0.0012 mg/l) that also led to acute M-factor of 100.

Aquatic chronic classification according to CLP criteria:
The DS's conclusion on long-term aquatic hazard was based on the not rapid degradation of etofenprox and the NOEC value of 0.000054 mg/l in *D. magna* that justified classification as Aquatic Chronic 1 with an M-factor 1000.

Aquatic hazard classification according to DSD criteria:
The DS's conclusion on aquatic hazard was based on not ready degradation of etofenprox, a BCF value of 2565 and the lowest effective concentration of etofenprox that was observed in *D. magna* (0.0012 mg/l) that led to classification as N; R50-53 with the specific concentration limits of N; R50-53: C ≥ 0.25%; N, R51-53: 0.025% ≤ C <0.25%; R52-53: 0.0025% ≤ C < 0.025%.

Comments received during public consultation
Six MSCA's supported the proposed classification and no comments opposing the proposal were received.

RAC assessment and comparison with the classification criteria
The information provided on degradation shows that etofenprox is hydrolytically stable, is not ready biodegradable in screening studies, does not degrade to a level greater than 70% in 28 days and cannot be considered to have rapid primary degradation. Etofenprox is therefore considered not rapidly/readily degradable.

A BCF value of 2565 in whole fish (lipid normalised) was obtained in a bioaccumulation study. This value is higher than the threshold value of 500 (CLP) and 100 (DSD).

Aquatic acute and chronic toxicity studies are available for all trophic levels. The material tested in these studies is comparable to the specifications provided for etofenprox, so including the (confidential) impurities (none of which have a harmonised or self-classification for aquatic toxicity). For acute toxicity the lowest $L(E)C_{50}$ value obtained was 0.0012 mg/l in *Daphnia magna*. For chronic toxicity the lowest NOEC value obtained was 0.000054 mg/l in *Dapnia magna*.

Aquatic acute classification according to CLP criteria
The lowest $L(E)C_{50}$ value is ≤1 mg/l. Etofenprox therefore fulfils the criteria for classification as Aquatic Acute 1 (H400). As the lowest $L(E)C_{50}$ value is between 0.001 and 0.01, this leads to an M-factor 100.

Aquatic chronic classification according to CLP criteria
Etofenprox is not rapidly degradable. Chronic data are available for all trophic levels. The lowest NOEC is ≤ 0.1 mg/l. Etofenprox therefore fulfils the criteria for classification as Aquatic Chronic 1 (H410). As the lowest NOEC value is between 0.00001 and 0.0001, this leads to an M-factor 1000.

Aquatic hazard classification according to DSD criteria
Etofenprox is not readily degradable and has a BCF > 100. The lowest $L(EC)_{50}$ is ≤1 mg/l. Etofenprox therefore fulfils the criteria for classification as N; R50-53.
The lowest $L(E)C_{50}$ value is $0.001 < L(E)C_{50} \leq 0.01$; this leads to the following SCLs:
N; R50-53: $C_n \geq 0.25\%$
N; R51-53: $0.025\% \leq C_n < 0.25\%$
R52-53 : $0.0025\% \leq C_n < 0.025\%$.

RAC is thus in support of the environmental classification as proposed by the dossier submitter.

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 rapporteurs' comments (excl. confidential information).