Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the Opinion proposing harmonised classification and labelling at EU level of

metribuzin (ISO); 4-amino-6-tert-butyl-3-methylthio-1,2,4-triazin-5(4*H*)-one; 4-amino-4,5-dihydro-6-(1,1-dimethylethyl)-3-methylthio-1,2,4-triazin-5-one

EC Number: 244-209-7
CAS Number: 21087-64-9

CLH-O-0000007008-77-01/F

Adopted

10 June 2021

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON METRIBUZIN (ISO); 4-AMINO-6-TERT-BUTYL-3-METHYLTHIO-1,2,4-TRIAZIN-5(4H)-ONE; 4-AMINO-4,5-DIHYDRO-6-(1,1-DIMETHYLETHYL)-3-METHYLTHIO-1,2,4-TRIAZIN-5-ONE

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties. Journal articles are not confidential; however they are not published on the website due to Intellectual Property Rights.

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Substance name: metribuzin (ISO); 4-amino-6-tert-butyl-3-methylthio-1,2,4-triazin-5(4H)-one; 4-amino-4,5-dihydro-6-(1,1-dimethylethyl)-3-methylthio-1,2,4-triazin-5-one
EC number: 244-209-7
CAS number: 21087-64-9
Dossier submitter: Estonia

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
28.09.2020	Germany		MemberState	1
Comment received				
DE-CA supports the CLH proposal for Metribuzin.				
Dossier Submitter's Response				
Thank you for your supporting comment.				
RAC's response				
Thank you, noted.				

Date	Country	Organisation	Type of Organisation	Comment number
01.10.2020	Germany	Bayer AG	Company-Importer	2
Comment received				
During the Clock Stop of the 1107/2009 process for metribuzin, documents have been provided to EFSA and the Rapporteur Member State. To allow availability of this information for both - 1107/2009 and CLH harmonization - this information submitted during public commenting for metribuzin as well. The documents are as follows: - Metribuzin Task Force response documents and reference list - public.zip - Metribuzin Task Force response documents and reference list - confidential.zip - Studies and documents submitted during STC - public.zip - Studies and documents submitted during STC - confidential.zip				

Due to the size of the files, these will be submitted via the web form for large files. ECHA note – Four attachments were submitted with the comment above. Refer to public attachments: - Comments and additional information to the CLH for metribuzin – public.zip - Metribuzin Task Force response documents and reference list – public.zip - Studies and documents submitted during STC - public part 1.zip - Studies and documents submitted during STC - public part 2.zip ECHA note – Four attachments were submitted with the comment above. Refer to confidential attachments: - Comments and additional information to the CLH for metribuzin – confidential.zip - Metribuzin Task Force response documents and reference list – confidential.zip - Studies and documents submitted during STC - confidential part 1.zip - Studies and documents submitted during STC - confidential part 2.zip
Dossier Submitter's Response
Thank you for the provided information.
RAC's response
Thank you for the documents.

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
01.10.2020	Germany	Bayer AG	Company-Importer	3
Comment received				
Bayer AG agrees with the rapporteur. ECHA note – Four attachments were submitted with the comment above. Refer to public attachments: - Comments and additional information to the CLH for metribuzin – public.zip - Metribuzin Task Force response documents and reference list – public.zip - Studies and documents submitted during STC - public part 1.zip - Studies and documents submitted during STC - public part 2.zip ECHA note – Four attachments were submitted with the comment above. Refer to confidential attachments: - Comments and additional information to the CLH for metribuzin – confidential.zip - Metribuzin Task Force response documents and reference list – confidential.zip - Studies and documents submitted during STC - confidential part 1.zip - Studies and documents submitted during STC - confidential part 2.zip				
Dossier Submitter's Response				
Thank you for your supporting comment.				
RAC's response				
Thank you, noted.				

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
01.10.2020	Germany	Bayer AG	Company-Importer	4
Comment received				
Bayer AG agrees with the rapporteur. ECHA note – Four attachments were submitted with the comment above. Refer to public attachments: - Comments and additional information to the CLH for metribuzin – public.zip - Metribuzin Task Force response documents and reference list – public.zip - Studies and documents submitted during STC - public part 1.zip - Studies and documents submitted during STC - public part 2.zip ECHA note – Four attachments were submitted with the comment above. Refer to confidential attachments: - Comments and additional information to the CLH for metribuzin – confidential.zip - Metribuzin Task Force response documents and reference list – confidential.zip - Studies and documents submitted during STC - confidential part 1.zip - Studies and documents submitted during STC - confidential part 2.zip				
Dossier Submitter's Response				
Thank you for your supporting comment.				
RAC's response				
Thank you, noted.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
01.10.2020	Germany	Bayer AG	Company-Importer	5
Comment received				
Bayer AG agrees with the rapporteur. ECHA note – Four attachments were submitted with the comment above. Refer to public attachments: - Comments and additional information to the CLH for metribuzin – public.zip - Metribuzin Task Force response documents and reference list – public.zip - Studies and documents submitted during STC - public part 1.zip - Studies and documents submitted during STC - public part 2.zip ECHA note – Four attachments were submitted with the comment above. Refer to confidential attachments: - Comments and additional information to the CLH for metribuzin – confidential.zip - Metribuzin Task Force response documents and reference list – confidential.zip - Studies and documents submitted during STC - confidential part 1.zip - Studies and documents submitted during STC - confidential part 2.zip				
Dossier Submitter's Response				
Thank you for your supporting comment.				
RAC's response				
Thank you, noted.				

RESPIRATORY SENSITISATION

Date	Country	Organisation	Type of Organisation	Comment number
01.10.2020	Germany	Bayer AG	Company-Importer	6
Comment received				
Bayer AG agrees with the rapporteur. ECHA note – Four attachments were submitted with the comment above. Refer to public attachments: - Comments and additional information to the CLH for metribuzin – public.zip - Metribuzin Task Force response documents and reference list – public.zip - Studies and documents submitted during STC - public part 1.zip - Studies and documents submitted during STC - public part 2.zip ECHA note – Four attachments were submitted with the comment above. Refer to confidential attachments: - Comments and additional information to the CLH for metribuzin – confidential.zip - Metribuzin Task Force response documents and reference list – confidential.zip - Studies and documents submitted during STC - confidential part 1.zip - Studies and documents submitted during STC - confidential part 2.zip				
Dossier Submitter's Response				
Thank you for your supporting comment.				
RAC's response				
Thank you, noted.				

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
24.09.2020	Finland		MemberState	7
Comment received				
Metribuzin currently has a harmonised classification as Acute Tox. 4*, H302 for the oral route. In the available acute oral toxicity studies in different species, the LD50 values ranged from 322 mg/kg bw up to 2162 mg/kg bw. The lowest LD50 value, 322 mg/kg bw, was based on mortality in female rats. An ATE of 322 mg/kg bw is therefore warranted. According to the CLP Regulation, a substance shall be classified as Acute Tox. 4, H302 if the ATE value is > 300 and ≤ 2000 mg/kg bw. There is sufficient evidence to remove the asterisk from the classification. FI CA supports the proposed classification of Acute Tox. 4; H302 for metribuzin.				
Dossier Submitter's Response				
Thank you for your supporting comment. EE CA has followed the same principles as presented in the comment and has applied the Acute Tox. 4 criteria for classification as described in the CLP Regulation.				
RAC's response				
Thank you, noted.				

Date	Country	Organisation	Type of Organisation	Comment number
01.10.2020	Germany	Bayer AG	Company-Importer	8
Comment received				
Bayer AG agrees with the rapporteur. ECHA note – Four attachments were submitted with the comment above. Refer to public attachments: - Comments and additional information to the CLH for metribuzin – public.zip - Metribuzin Task Force response documents and reference list – public.zip - Studies and documents submitted during STC - public part 1.zip - Studies and documents submitted during STC - public part 2.zip ECHA note – Four attachments were submitted with the comment above. Refer to confidential attachments: - Comments and additional information to the CLH for metribuzin – confidential.zip - Metribuzin Task Force response documents and reference list – confidential.zip - Studies and documents submitted during STC - confidential part 1.zip - Studies and documents submitted during STC - confidential part 2.zip				
Dossier Submitter's Response				
Thank you for your supporting comment.				
RAC's response				
Thank you, noted.				

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
01.10.2020	Germany	Bayer AG	Company-Importer	9
Comment received				
Bayer AG agrees with the rapporteur. ECHA note – Four attachments were submitted with the comment above. Refer to public attachments: - Comments and additional information to the CLH for metribuzin – public.zip - Metribuzin Task Force response documents and reference list – public.zip - Studies and documents submitted during STC - public part 1.zip - Studies and documents submitted during STC - public part 2.zip ECHA note – Four attachments were submitted with the comment above. Refer to confidential attachments: - Comments and additional information to the CLH for metribuzin – confidential.zip - Metribuzin Task Force response documents and reference list – confidential.zip - Studies and documents submitted during STC - confidential part 1.zip - Studies and documents submitted during STC - confidential part 2.zip				
Dossier Submitter's Response				
Thank you for your supporting comment.				
RAC's response				
Thank you, noted.				

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
01.10.2020	Germany	Bayer AG	Company-Importer	10
Comment received				
Bayer AG agrees with the rapporteur. ECHA note – Four attachments were submitted with the comment above. Refer to public attachments: - Comments and additional information to the CLH for metribuzin – public.zip - Metribuzin Task Force response documents and reference list – public.zip - Studies and documents submitted during STC - public part 1.zip - Studies and documents submitted during STC - public part 2.zip ECHA note – Four attachments were submitted with the comment above. Refer to confidential attachments: - Comments and additional information to the CLH for metribuzin – confidential.zip - Metribuzin Task Force response documents and reference list – confidential.zip - Studies and documents submitted during STC - confidential part 1.zip - Studies and documents submitted during STC - confidential part 2.zip				
Dossier Submitter's Response				
Thank you for your supporting comment.				
RAC's response				
Thank you, noted.				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
01.10.2020	Germany	Bayer AG	Company-Importer	11
Comment received				
Bayer AG agrees with the rapporteur. ECHA note – Four attachments were submitted with the comment above. Refer to public attachments: - Comments and additional information to the CLH for metribuzin – public.zip - Metribuzin Task Force response documents and reference list – public.zip - Studies and documents submitted during STC - public part 1.zip - Studies and documents submitted during STC - public part 2.zip ECHA note – Four attachments were submitted with the comment above. Refer to confidential attachments: - Comments and additional information to the CLH for metribuzin – confidential.zip - Metribuzin Task Force response documents and reference list – confidential.zip - Studies and documents submitted during STC - confidential part 1.zip - Studies and documents submitted during STC - confidential part 2.zip				
Dossier Submitter's Response				
Thank you for your supporting comment.				
RAC's response				
Thank you, noted.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
01.10.2020	Germany	Bayer AG	Company-Importer	12
Comment received				
Bayer AG agrees with the rapporteur. ECHA note – Four attachments were submitted with the comment above. Refer to public attachments: - Comments and additional information to the CLH for metribuzin – public.zip - Metribuzin Task Force response documents and reference list – public.zip - Studies and documents submitted during STC - public part 1.zip - Studies and documents submitted during STC - public part 2.zip ECHA note – Four attachments were submitted with the comment above. Refer to confidential attachments: - Comments and additional information to the CLH for metribuzin – confidential.zip - Metribuzin Task Force response documents and reference list – confidential.zip - Studies and documents submitted during STC - confidential part 1.zip - Studies and documents submitted during STC - confidential part 2.zip				
Dossier Submitter's Response				
Thank you for your supporting comment.				
RAC's response				
Thank you, noted.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
24.09.2020	Finland		MemberState	13
Comment received				
Long-term toxic effects of metribuzin have been investigated in a number of in vivo studies in different species. Main effects observed in dogs after oral administration were decreased red blood cell parameters (decreased RBC, Hb and Hct) and severe anemia in two animals which were sacrificed moribund. Decreased red blood cell parameters were also observed in another subchronic study in dogs. In rats, thyroid effects (changes in thyroid hormone levels, increased thyroid weights and/or enlarged thyroid) were observed in five long-term oral studies and in one 15-day inhalation study. Changes in thyroid hormone levels also occurred after subacute dermal exposure in rabbits. The adverse effects on thyroid were in general accompanied by increased activity of liver enzymes, increased liver weights and/or histopathological changes of the liver. A liver enzyme-related thyroid mode of action is therefore possible. Although rodents are known to be more sensitive to this type of mode of action, the effect of metribuzin on thyroid in humans via other mechanisms cannot be excluded. Both the hematological effects in dogs and the thyroid effects in rats and rabbits occurred at dose levels above the guidance values for STOT RE classification (with extrapolation of values for studies of greater or lesser duration; Table 3.9.3, Annex I to the CLP Regulation). FI CA supports the proposed classification of STOT RE 2; H373 (blood,				

thyroid) for metribuzin.
Dossier Submitter's Response
Thank you for the supporting comment. New information regarding mode of action on thyroid has been submitted during the public consultation, which is taken into consideration accordingly. Please see EE CA response to the comment No. 14 below.
RAC's response
Thank you for your comments. Please see the response to comment 14.

Date	Country	Organisation	Type of Organisation	Comment number
01.10.2020	Germany	Bayer AG	Company-Importer	14

Comment received

Comments for the hazard class "Specific target organ toxicity - repeated exposure" are enclosed as attachments:
- Comments and additional information to the CLH for metribuzin - public.zip
- Comments and additional information to the CLH for metribuzin - confidential.zip

Due to the size of the files, these will be submitted via the web form for large files.

ECHA note – Four attachments were submitted with the comment above. Refer to public attachments:
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ECHA note – Four attachments were submitted with the comment above. Refer to confidential attachments:
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Dossier Submitter's Response

STOT RE 2 (target organ: thyroid)

Several studies are presented in the current CLH dossier on Metribuzin, two of them are considered as non-GLP and as supportive. Effects on thyroid and TSH were seen in rats and effects on T4, T3 were also reported in rats and rabbits but not in dogs.
Table below represents a summary of *in vivo* data referring to findings in thyroid and hormone levels.

Study	**Dose (mg/kg bw/d)**	**Haematological effects**	**Thyroid effects**
Guidance value STOT-RE 1 Oral 28-day: ≤ 30 mg/kg bw/d; Guidance value STOT-RE 2 Oral 28-day: ≤ 300 mg/kg bw/d			
28-day Rat oral (M-018443-01-1) Acceptable GLP	150	↓ Hct (males -5%), ↓ Hb (males -5%)	↑ rel. thyroid wt. (females +33%); ↑ incidence and severity of colloidal vacuoles in the thyroid gland (average grades of tissues in dose groups 0/5/30/150 mg/kg bw/d were 1.0/1.0/2.0/2.8 for males and 0/0/0/2.0 for

			females) and severely altered colloidal staining (average grades of tissues in dose groups 0/5/30/150 mg/kg bw/d were 1.6/2.2/2.4/4.8 for males and 1.3/1.0/2.3/4.2 for females) in both sexes. ↓ T4 (males -55% and females -67%), ↑ TBC (males +15% and females +11%) and ↑ TSH conc. (males ~8-fold and females ~5-fold)
28-day Rat oral (M-513577-01-1) Acceptable GLP	89.5	↑ Hct (+12%, combined sex), ↓ MCH (-11%, combined sex), ↓ MCHC (-12%, combined sex);	
Pubertal development 21-31 days Rat (US EPA, 2011) Acceptable GLP	60		↓ serum T4 (males 43%); ↑ TSH (changes were marked and statistically significant in males 109%; in females non-significant decrease by 29%);
	120		↓ T4 (males 72%; females 44%), ↑ TSH (changes were marked and statistically significant in males 236%; in females non-significant decrease by 33%); ↑ thyroid wt. (45-46% in males; 15% in females); enlarged thyroids (6/15 males; 1/15 females); minimal to slight follicular cell hyprtrophy, colloid alteration, and an increased number of mitoses in thyroid (2/15 males);
Guidance value STOT-RE 1 Oral 9-week: ≤ 14 mg/kg bw/d; Guidance value STOT-RE 2 Oral 9-week: ≤ 140 mg/kg bw/d			
9-week Rat (male) dietary (M-018468-01-1) Supplementary Non-GLP	2.41		Day 7: ↑ T4 (+22%); ↓ T3 (-19%); Day 21: ↑ T4 (+45%); ↑ iodine concentration (+33%) Day 63: ↑ T4 (+50%); ↑ iodine quantity (+64%); ↑ iodine concentration (+46%); ↓ rel. thyroid wt. (-11%, day 7); Change in stainability of thyroid colloid in 10/10 animals (on day 63) (0/10 in controls).
	7.43		↑ T4 (+30%); ↓ T3 (-15%); ↑ iodine quantity (+38%), ↑ iodine concentration (+60%) Day 21: ↑ T4 (+58%); ↑ iodine concentration (+19%) Day 63: ↑ T4 (+60%); ↑ iodine quantity (+37%), ↑ iodine concentration (+24%) Change in stainability of thyroid colloid in 10/10 animals (on day 63) (0/10 in controls).
	21.69		↑ T4 (+34%); ↓ T3 (-19%); ↑ iodine quantity (+40%), ↑ iodine concentration (+93%) Day 21: ↑ T4 (+51%); Day 63: ↑ T4 (+55%); ↑ iodine quantity (+51%); ↓ rel. thyroid wt. (-22%, day 7); Change in stainability of thyroid colloid in 10/10 animals (on day 63) (0/10 in controls).
	65.06		↓ T3 (-20%); ↑ iodine quantity (+31%), ↑ iodine concentration (+83%); Day 21: ↑ T3 (+39%); Day 63: ↑ T4 (+24%); ↓ T3 (-13%); ↑ iodine quantity (+37%); ↓ rel. thyroid wt. (-11%, day 7); Change in stainability of thyroid colloid in 10/10 animals (on day 63) (0/10 in controls).

Guidance value STOT-RE 1 Oral 2-year: ≤ 1.25 mg/kg bw/d; Guidance value STOT-RE 2 Oral 2-year: ≤ 12.5 mg/kg bw/d			
2-year Rat combined chronic toxicity / carcinogenicity (M-017948-02-1) Acceptable GLP	1.3/1.6 (m/f)		↓ T3 (males -17% at day 91; -19% at day 182; -15% at day 364; females -16% at day 91; -23% at day 182; -26% at day 546); ↑ T4 (males +57% at day 91; +48% at day 182; +41% at day 364; +21% at day 546; females +28% at day 91; +27% at day 182; +93% at day 364; +22% at day 546; +42% at day 728);
	13.8/17.7 (m/f)		↓ T3 (males -37% at day 182; -24% at day 364; -16% at day 546; -22% at day 728; females -16% at day 182; -13% at day 546; -16% at day 728); ↑ T4 (males +25% at day 91; +41% at day 182; +43% at day 364; females +30% at day 91; +31% at day 182; +84% at day 364; +32% at day 546; +57% at day 728); Enlarged thyroid (males 7/50, females 1/50 animals); ↑ absolute thyroid wt. (females +19%);
	42.2/53.6 (m/f)		↓ T3 (males -17% at day 182; -27% at day 728; females -11% at day 182); ↑ T4 (males +7% at day 182, +27% at day 364; +29% at day 546; females +47% at day 364; +36% at day 728); Enlarged thyroid (males 8/50, females 3/50 animals); ↑ absolute thyroid wt. (males +24% and females +14%); thyroid follicular cell hyperplasia (males 11/20 animals, 1-yr; 38/50 animals, 2-yr).
Guidance value STOT-RE 1 Oral 15 days: ≤ 60 mg/kg bw/d; Guidance value STOT-RE 2 Oral 15 days: ≤ 600 mg/kg bw/d			
Developmental Rat oral (M-018676-01-1) Supplementary GLP	70		Maternal toxicity: ↓ T4 (-52% on day 16)
	200		Maternal toxicity: ↓ T4 (-85% on day 16); ↑ absolute thyroid wt. (+57% on day 16; +33% on day 20)
Guidance value STOT-RE 1 Dermal 15 days: ≤ 120 mg/kg bw/d; Guidance value STOT-RE 2 Dermal 15 days: ≤ 1200 mg/kg bw/d			
Dermal repeated-dose 15 days Rabbit (M-018488-01-1) Acceptable GLP	200		↑ T4 (females +45%)
	1000		↑ T4 (males +33%, females +53%); ↓ T3 (males -23%);
Guidance value STOT-RE 1 Inhalation 15 days: ≤ 0.12 mg/L/6h/day=120 mg/m^3/6h/day; Guidance value STOT-RE 2 Inhalation 15 days: ≤ 1.2 mg/L/6h/day=1200 mg/m^3/6h/day			
Inhalation repeated-dose 15 days Rat (M-018391-01-1) Supplementary Non-GLP	Fist study: 93 mg/m^3		↑ T4 (males 63%, females 39%); ↑ re. thyroid wt. (females 25%);
	Fist study: 219 mg/m^3		↑ T4 (males 24%, females 24%); ↑ rel. thyroid wt. (males and females 25%);
	Fist study: 720 mg/m^3		↓ T4 (females 9%); ↑ rel. thyroid wt. (males 25% and females 50%);

	Second study: 31 mg/m³		↑ T4 (males 50%, females 23%);
	Second study: 93 mg/m³		↑ T4 (males 56%, females 37%) ↑ rel. thyroid wt. (males 25%, females 20%);

New *in vitro* studies with Metribuzin were provided by Industry during public consultation to show the Phenobarbital-like mode of action in rats and the non-relevance of effects to humans.

In one study potential of Metribuzin to induce human and rat cytochrome P450 isoenzymes CYP2B and CYP3A, UDP glucuronosyltransferases UGT1A and UGT2B and thyroxine (T4) glucuronidation in the liver was evaluated. The results of the study show that Metribuzin is a CYP2B inducer, from 15 µM in human hepatocytes and from 5 µM in rat hepatocytes, and to a lesser extent a CYP3A1 inducer in rat hepatocytes. Metribuzin from 5 µM also shows the potential to induce UGT2B1 expression and to increase T4-UGT activity in Wistar rat hepatocytes, while no such effect is seen in human hepatocytes.

In the second study the potential of Metribuzin to inhibit Thyroid Peroxidase (TPO) enzyme was investigated in rat thyroid microsomes, using the Amplex UltraRed® thyroperoxidase inhibition assay with some modifications. TPO was completely inhibited by positive control 6-N-Propyl-2-Thiouracil (PTU) with an IC50 of 3.05µM. Metribuzin did not show any inhibition of TPO activity up to 1000µM.
The inhibition of hormone synthesis in the thyroid due to the inhibition of TPO has been considered the main cause of the T4 depression. Even though Metribusin seems not to inhibit TPO activity in rats, as indicated by *in vitro* data on rat cells, other Metribuzin-dependent interferences could lead to unbalanced thyroid hormone levels and hence to the observed changes in the thyroid gland.

In the third study the potential of Metribuzin to inhibit rat or human deiodinase 1-3 (DIO1-3) activity was investigated. It was concluded that Metribuzin at concentrations up to 300 µM, is not an inhibitor of rat or human DIO1, DIO2 or DIO3.
New data provided by Industry during public consultation is summarized in the table below.

M-753595-01-1
In vitro CYP and UGT induction in human and Wistar rat hepatocytes by Metribuzin

No guideline for this special study exists

Reference Inducer compound	Induced CYPs	Final concentration in dosing solution
Phenobarbital (PB) sodium salt	CYP2B6 (Human) CYP2B1 (Rat)	1000µM
5-pregnen-3β-ol-20-one-16α-carbonitrile (PCN)	CYP3A1 (Rat)	6µM
Rifampicin (RIF)	CYP3A4 (Human)	15µM
Metribuzin, 99,09%		5µM; 15µM; 50µM

A preliminary cytotoxicity study was performed. The effect of Metribuzin on CYP2B and CYP3A activities as well as on T4-glucuronoconjugation was assessed in human and Wistar rat hepatocytes
on Day 3 and Day 7 after daily treatment.

Based on the results Metribuzin is a CYP2B inducer, from
15 µM on in human hepatocytes and from 5 µM on in rat hepatocytes, and to a lesser extent a CYP3A1 inducer in rat hepatocytes. Metribuzin from 5 µM also shows the potential to induce UGT2B1 expression and to increase T4-UGT activity in Wistar rat hepatocytes, while no such effect is seen in human hepatocytes.

CYP2B and CYP3A results in rat and human hepatocytes

Concen-tration (µM)	Rat				Human			
	CYP2B1 fold express*	CYP3A1 fold express*	CYP2B1 fold express*	CYP3A1 fold express*	CYP2B6 fold express*	CYP3A4 fold express*	CYP2B6 fold express*	CYP3A4 fold express*
Day 3								
5	3.60	1.43	0.93	1.03	1.20	1.10	0.87	1.27
15	14.37	1.83	1.37	1.07	1.43	1.23	0.70	1.27
50	61.37	3.60	3.30	1.33	2.00	1.47	0.50	1.33
Day 7								
5	4.30	1.53	2.13	1.53	1.37	1.07	1.43	1.20
15	15.93	2.47	4.17	1.90	2.30	1.37	1.60	1.13
50	19.67	2.20	5.17	1.70	5.67	1.97	1.80	1.40

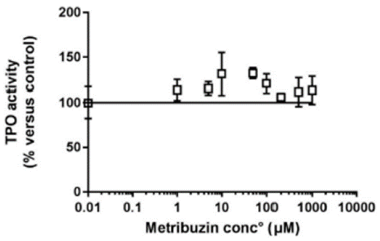
* Fold values are averages of 3 cultures for human and rat cells each

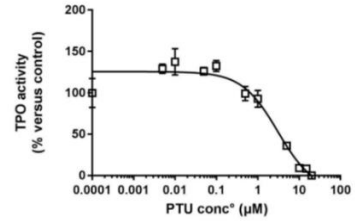
UGT1A1, UGT1A6, UGT1A5/6, UGT2B and UGT-T4 results in rat and human hepatocytes

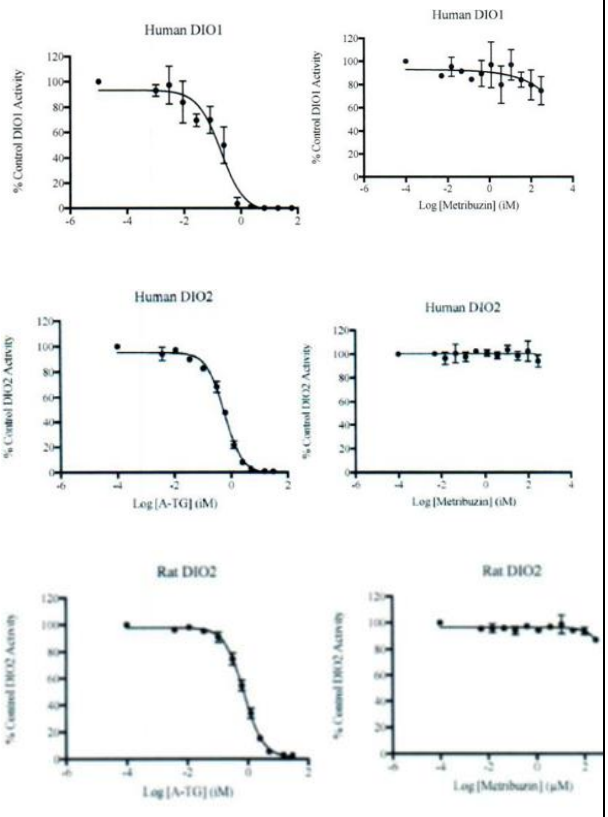
Concen-tration (µM)	Rat					Human			
	UGT1A1 fold express*	UGT1A5/6 fold express*	UGT2B1 fold express*	UGT-T4 fold activity*	UGT-T4 (R17G27 culture)**	UGT1A1 fold express*	UGT1A6 fold express*	UGT2B7 fold express*	UGT-T fold activity
Day 3									
5	1.17	1.07	1.70	0.97	1.2	0.97	1.00	0.93	1.07
15	1.10	1.17	2.27	0.83	1.0	0.97	1.00	1.00	0.97
50	0.97	0.93	3.27	0.83	0.0	1.03	0.97	0.97	1.03
Day 7									
5	1.10	1.20	1.83	1.37	2.2	0.97	1.07	1.13	1.13
15	1.20	1.27	2.87	1.37	2.1	1.13	1.17	1.20	1.20
50	0.93	0.53	3.13	2.03	3.5	1.37	1.30	1.27	1.30

* Fold values are averages of 3 cultures for human (S1555T, S1376T, B1528T) and rat cells (R17G27, R17G28, GZY) each
** Rat culture with highest response

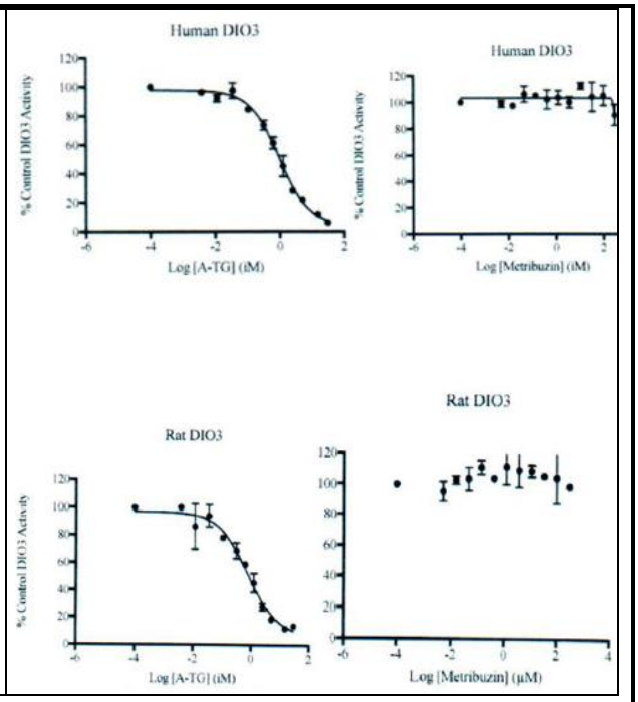
<table>
<tr>
<td>M-680749-01-1
Inhibition of Rat microsomal Thyroid Peroxidase by Metribuzin
No guideline for this special study exists</td>
<td>
<table>
<tr><th>Reference Inducer compound</th><th>Final concentration in dosing solution (µM)</th></tr>
<tr><td>Metribuzin, 99,09%</td><td>1; 5; 10; 50; 100; 200; 500; 1000</td></tr>
<tr><td>6-N-Propyl-2-Thiouracil (PTU)</td><td>0,005; 0,01; 0,05; 0,5; 1; 5; 10; 15; 20</td></tr>
</table>
</td>
<td>Metribuzin did not inhibit Thyroid Peroxidase activity until 1000µM.

Thyroid Peroxidase (TPO) activity in the presence of Metribuzin
 

Inhibition curve of Thyroid Peroxidase (TPO) by PTU
 

</td>
</tr>
<tr>
<td>M-664441-02-1
Evaluate the potential for metribuzin to inhibit recombinant rat and human deiodinases</td>
<td>
<table>
<tr><th></th><th>Final concentratio in dosing solution (µM)</th></tr>
<tr><td>Metribuzin, 99,09% Test material</td><td>0-300 Serial 2-4 fold dilution</td></tr>
<tr><td>Positive control for DIO1 Inhibition: 6-propyl-2-thiouracil (PTU)</td><td>0-60 Serial 2-3 fold dilution</td></tr>
<tr><td>Positive control for DIO2 and DIO3 Inhibition: Aurothioglucose (A-TG) hydrate</td><td>0-60 Serial 2-3 fold dilution</td></tr>
</table>
Deiodinase activity was determined by analyzing the deiodination of thyroxine (T4) to 3,5,3'-triodo-Lthyronine (T3) (DIO 1 and 2) and 3,3'5' triodo-L-thyronine (rT3) (DIO3). T3 or rT3 levels were analyzed by mass spectrometry. Positive deiodinase inhibition was demonstrated using control items, 6-propyl-2-thiouracil (PTU) as an inhibitor of both rat and human DIO1 and, aurothioglucose (A-TG) was used to demonstrate inhibition of rat and human DIO2 and DIO3. Recombinant rat and human DIO1-3 performed as expected showing positive inhibition by PTU (rat and human DIO1) and A-TG (rat and human DIO2 and DIO3).
</td>
<td> 

</td>
</tr>
</table>



The outcomes of the *in vitro* studies give valuable insight into the possible mechanism of action of Metribuzin but can not fully mimic the processes in the living organsms. Altered or elevated levels of thyroid hormones (TSH, T4 and, T3) may be associated with hypothyroidism or hyperthyroidism. Decrease of T4 and T3 or thyroid tumor formation in rats could be explained in some extent by phenobarbital mode of action. However, in case of Metribuzin, increase of T4 and no tumor formation were observed in several *in vivo* studies which leads to some uncertainties whether phenobarbital mode of action and/or other mechanisms may apply. Additionally, in spite of no inhibition of DIO1, DIO2 and DIO3 *in vitro*, the T3 level decreased in several *in vivo* studies. Although, it should be noted that mentioned effects are not observed in dogs.

EE CA considers that the observed effects *in vivo* in rats and rabbits are relevant for humans, regardless the effects are due to direct action on the thyroid peroxidase, or indirectly via other mechanisms. Based on the findings observed *in vivo* in rats and rabbits including thyroid effects (changes in THS, T4 and T3 levels, hypertrophy and increased organ weight) the possibility of Metribuzin to interact the hypothalamic-pituitary-thyroid (HPT) axis can not be excluded. Therefore EE CA considers relevant to classify Metribuzin as STOT RE 2 with target organ thyroid.

STOT RE 2 (target organ: blood)

EE CA considers the subchronic toxicity studies showing anemia in dogs as acceptable.

In two 90-day studies in Beagle dogs, mortalities occurred at the high dose. In the subchronic feeding study with dogs (M-038758-01-1), one male and one female dog were sacrificed on nominal day 59 (male) and on day 58 (female) at the high dose (26.2 mg/kg bw/d in males and 30.2 mg/kg bw/d in females) due to clinical moribund. Also, in the subchronic oral toxicity study with dogs via capsules (M-513582-01-1), the dose level for the high dose group was reduced from 50 to 30 mg/kg bw/d from day 35 onwards, due to occurrence of severe signs of toxicity in dogs of either sex, one high dose male died on

day 33 of treatment. Effects on red blood cell parameters became apparent in dogs from 15 mg/kg bw/d in females (decreased RBC, Hb and Hct in the 90-day study (M-513582-01-1)) and from 26.2 mg/kg bw/d in males (decreased RBC, Hb and Hct in the 90 feeding study (M-038758-01-1)). Two dogs who where sacrificed prior to study termination in the 90-day feeding study, showed severe anemia. In rats generally effects on red blood cells were not observed, only slight decrease in males (-5%) in Hct and Hb were observed at the high dose of 150 mg/kg bw/d in the 28-day oral toxicity study in rats (M-018443-01-1).
In summary, hematologically relevant effects were mainly observed in a 90-day study in dogs observed as lower red blood cell parameters (RBC, Hb, Hct) in males dogs at 26.2 mg/kg bw/d and signs of anaemia in the two dogs which were sacrificed early due to moribundity.

M-038758-01-1 Subchronic Toxicity Feeding Study in the Beagle Dog (4/dose/sex) OECD 409 Additional parameters measured/performed: Intraocular pressure and corneal thickness, electrocardiogram and blood pressure assessments, T3, T4 and TSH. GLP Acceptable	Metribuzin technical (94.3 %), Via diet at 0, 75, 300 and 1200 ppm (equivalent to 0, 2.0, 8.4 and 26.2 mg/kg bw/day (males), and to 0, 1.9, 8.6 and 30.2 mg/kg bw/day (females) for 3 months.	**75 ppm (**2.0/1.9 mg/kg bw/day m/f)**:** ↓ bodyweight by day 84 (males -3%); ↓ bodyweight gain by day 84 (males -6%, females -39%) (no statistics performed on bw gain data) **300 ppm (**8.4/8.6 mg/kg bw/d m/f)**:** ↓ bw by day 84 (males -13%, females -15%); ↓ bw gain by day 84 (males -46%, females -66%) Clinical chemistry: ↑ UDP-GT (females +29%); Pathology: Macroscopic findings: discolored zone in spleen (1/4 males; 0/4 in controls); Microscopic findings: chronic inflammation of the liver (1/4 males; 0/4 in controls); Kupffer cell aggregates in liver (1/4 males; 0/4 in controls); **1200 ppm (**26.2/30.2 mg/kg bw/d m/f)**:** Two animals were sacrificed prior to study termination (one female at day 58 and one male at day 59) due to marked body weight decrease, attributed to treatment, animals showed severe anemia and platelet counts were very low in the female dog. ↓ bw by day 84 (females -10%); ↓ bw gain by day 84 (females +44%) Clinical signs: thin, unthrifty appearance and with pale yellow gingiva in two sensitive high-dose animals, one female dog who was sacrificed at day 58 was reluctant to walk and stand which was considered a secondary manifestation of the moribund condition. Clinical chemistry: ↑ UDP-GT (females +43%); **Haematology: ↓ RBC (males -22%); ↓ Hb (males -25%); ↓ Hct (males -24%). There was substantial evidence of anemia in both animals sacrificed on days 58 and 59. The trend toward anemia was not pronounced except in these animals.** Pathology: Macroscopic findings: Enlarged spleen (1/4 males; 0/4 in controls), raised zone in spleen (1/4 males; 0/4 in controls); Microscopic findings: Discoloration of the liver (2/4 males; 0/4 in controls); chronic inflammation of the liver (1/4 males; 0/4 in controls); Kupffer cell aggregates in liver (1/4 males; 0/4 in controls); congestion of the liver (1/4 males; 0/4 in controls); pigmentation of the liver (1/4 males; 2/4 females; 0/4 in controls); lymphocytic infiltrates in the gall bladder (3/4 males, 1/4 in controls; 3/4 females, 2/3 in controls); abnormal spermatozoa in testes (3/4 males; 1/4 in controls); abnormal spermatozoa in epididymides (4/4 males; 2/4 in controls) Lesions specific to the two dogs sacrificed in moribund condition included: bone marrow hypoplasia and hyperplasia, myocardial degeneration and hemorrhage, inflammation of liver, kidney and small intestine, unusual extramedullary hematopoiesis in liver and spleen, unusual pigmentation in the liver, pronounced involution of the thymus, and renal hemorrhage. In addition, at 1200 ppm effects in testes and epididymides were observed.

M-513582-01-1 Subchronic (90 Day) Oral Toxicity Study with Metribuzin Technical in Beagle Dogs (4/dose/sex) OECD 409 Deviations regarding insufficient reporting of results of ophthalmic examinations, water intake, observations for mortality and moribundity not performed with sufficient frequency, insufficient clinical, organ weights and histopathology analysis and urinalysis. GLP Acceptable with reservations	Metribuzin technical (> 91 %), By capsule at doses of 0, 5, 15 and 50/30 mg/kg bw, for 90 days. The dose level for the high dose group was reduced from 50 to 30 mg/kg bw/d from day 35 onwards, due to occurrence of severe signs of toxicity in dogs of either sex.	**5 mg/kg bw/d:** ↓ bodyweight gain (females -36% on weeks 0-13); **Haematology: ↑ WBC (males +25% on day 90); ↓ WBC (females -24% on day 45); ↑ clotting time (females +23% on day 90);** Clinical chemistry: ↓ inorganic phosphorus (males -18% on day 90); ↑ chloride (females +3% on day 45); **15 mg/kg bw/d:** Clinical signs in one female (dullness, weakness, blood tinged faeces); ↓ bodyweight gain (females -64% on weeks 0-13); **Haematology:↑ WBC (males +23% on day 90); ↓ WBC (females -22% on day 45); ↑ MCV (males +13% on day 90); ↑ MCH (males +6% on day 90); ↓ RBC (females -19% on day 45); ↓ Hb (females -17% on day 45); ↓ Hct (females -19% on day 45); ↓ eosinophiles (females -70% on day 90);** **Clinical chemistry: ↑ total bilirubin (males +61% on day 45, +70% on day 90; females +27% on day 90); ↓ inorganic phosphorus (males -22% on day 90); ↑ chloride (males +3% on day 45); ↑ GGT (females +57% on day 45);** **50/30 mg/kg bw/d:** 50 mg/kg bw was reduced to 30 mg/kg bw from day 35 onwards since one male dog died on day 33 and the other males and one female showed toxic signs (dullness, weakness, blood tinged faeces, eye discharge); body weight loss (males and females weeks 1-13; males -12% and females -3% on week 13); lower food intake (males at weeks 1-8, -40% at week 8; females at weeks 1-5, -38% at week 5) **Haematology: ↓ WBC (females -25% on day 45); ↑ RBC (males 16% on day 90); ↓ RBC (males -24% on day 45; females -17% on day 45); ↑ Hb (males +21% on day 90); ↓ Hb (males -26% on day 45; females -17% on day 45, -14% on day 90); ↓ Hct (males -28% on day 45; females -16% on day 45, -10% on day 90); ↑ MCHC (males +3% on day 45); ↓ neutrophils (males -34% on day 45); ↑ reticulocytes (females ~5-fold on day 90); ↑ clotting time (females +34% on day 90); ↓ eosinophiles (females -65% on day 90);** Clinical chemistry: ↓ ASAT (males -20% on day 90); ↑ total bilirubin (males +93% on day 90; females +52% on day 90); ↓ creatinine (males -36% on day 45, -19% on day 90); ↓ inorganic phosphorus (males -22% on day 90); ↑ GGT (females +57% on day 45); ↓ albumine (males -11% on day 45); ↑ chloride (males +4% on day 45; females +3% on day 45); ↓ Calcium (females -9% on day 90); Relative organ weights: ↑ liver (males +42%; females +26%); ↑ kidneys (males +30%); ↑ adrenal glands (males +27%); ↑ thyroid gland (females +43%); Emaciation and enlarged spleen was seen in high dose animals (in one high dose male and three females)

According to the CLP Regulation Annex I: 3.9.1.1. *Specific target organ toxicity (repeated exposure) means specific, target organ toxicity arising from a repeated exposure to a substance or mixture. All significant health effects that can impair function, both reversible and irreversible, immediate and/or delayed are included*.

The EE CA considers Metribuzin STOT RE 2 classification for target organ blood based on the findings on red blood cell parameters (evidence of anemia and effects on RBC, Hct, and Hb) in dogs at ≥ 15 mg/kg bw/d after 90-days oral exposure classified still relevant.
RAC's response
Thank you for your comments. RAC concluded that the data indicating thyroid-related findings in the rat, rabbit and dog studies with metribuzin are not sufficient to conclude on a STOT RE classification. Still, a concern remains about the unresolved MoA and toxicological significance of the T4 increases at low doses, as well as the possible contribution of this potential second MoA (besides the MoA via UGT induction) to the hypothyroidism at higher doses in the rat studies. For more details please see the RAC opinion. Regarding haematotoxicity, the pattern of effects is rather unusual, with some animals severely affected and others not at all in the two dog dietary studies. It is possible that pneumonia could have played some role in the etiology of anaemia the 2-year dietary study (1974). On the other hand, it does not seem plausible that an infection could cause haemoglobin reduction by 40-80%. In addition, one top dose survivor in the 90-day dietary study (2002) showed a Hb reduction by ca. 35% at the end of the study without showing signs of infection. Further support for classification comes from the 90-day gavage study (1998) where the animals showed less pronounced haematotoxicity but the effect was relatively evenly distributed across animals. Given that haematotoxicity was observed in all 3 available dog studies, RAC considers that the effects are wholly or largely a consequence of treatment with metribuzin. Classification in Category 2 is met based on a haemoglobin reduction of ≥20% and premature deaths in moribund animals.

Date	Country	Organisation	Type of Organisation	Comment number
29.09.2020	France		Individual	15
Comment received				
CLH report – Proposal for Harmonised Classification and Labelling Metribuzin EC# 244-209 Independent Opinion by Dr <confidential>, Toxicologist The CLH report and proposal for harmonised classification and labelling for Metribuzin, submitted by the Health Board, Estonia in July 2020 includes a proposal for STOT-RE Category 2, based in part on the finding of thyroid changes in the rat, and supported by findings in the rabbit, but not by findings in the dog or in mice. The proposal argues that these effects are in animals are adverse and can be presumed to have the potential to produce significant toxicity in humans or have the potential to be harmful to human health following repeated exposure, and consequently metribuzin should be classified as a specific organ toxicant. In my opinion, as a toxicologist with many years of experience, the proposal is not correct for two reasons. 1. The effects in animals are not adverse, and 2. The effects in animals are not relevant to humans. My opinion that the effects are not relevant to humans is not unique to myself, indeed the majority of toxicologists and regulatory agencies, both European and International, have the same opinion (EU Commission, 1999; IARC, 1999; ECHA, 2017). The effects in animals are not adverse				

The effects on thyroid hormone levels (T4, T3, TSH) and thyroid organ histopathology seen in several studies are clearly typical of the rat-specific UDPGT glucuronidation metabolic pathway which is not a significant route of metabolism in humans (Choksi et al., 2003). The levels of UDPGT enzyme activity in the liver are typically induced in the rodent after exposure to many xenobiotic chemicals, the classic example being phenobarbitone. In the rat, increased UDPGT activity results in secondary effects on T4 levels, TSH levels, and potentially on T3 levels. Such effects do not normally occur in humans. Furthermore, the effects in rodents are reversible, and in the case of metribuzin the effects at low dose levels are highly variable and transient, in fact the effects diminish with duration of dosing, which is hardly a characteristic of STOT-RE toxicity.
The effects in animals are not relevant to humans
The ECHA CLP guidance document states that:
"In general, valid data from animal experiments are considered relevant for humans and are used for hazard assessment/classification. However, it is acknowledged that there are cases where animal data are not relevant for humans and should not be used for that purpose."
And (my bold)
"Certain chemicals cause induction of liver enzymes and are interfering with the regulation of thyroid hormones. An increase in the activity of hepatic UDPG-transferase results in increased glucuronidation of thyroid hormones and increased excretion. It is known that rodents are highly sensitive to a reduction in thyroid hormone levels (T4), resulting in thyroid toxicity (e.g. hypertrophy, hyperplasia) after repeated stimulation / exposure of this organ. This in turn is related to an increase in the activity of hepatic UDPG-transferase. Humans, unlike rodents, possess a T4 binding protein that greatly reduces susceptibility to plasma T4 depletion and thyroid stimulation. Thus, such a mechanism/effect cannot be directly extrapolated to humans, i.e. these thyroid effects observed in rodents caused by an increase in hepatic UDPG-transferase are therefore considered of insufficient concern for classification (see ECBI/22/98 Add1, EU Commission Meeting of the Commission Working Group on C&L of Dangerous Substances ECBI/27/98 Rev.2)."
Thus, the ECHA CLP guidance specifically identifies such effects as not relevant to humans and that they cannot be directly extrapolated to humans or used for classification.
Conclusion
The proposal for classification of metribuzin as STOT-RE Category 2 on the basis of the effects on thyroid hormone levels is wrong, both in terms of scientific validity and according to regulatory guidance.
Classification should not be made on the basis of extreme precautionary principles because to do so will undermine the confidence and trust of the very people that CLP is primarily designed to protect, the worker. If substances are over-classified, then the classification system loses credibility and functionality. Over-classification is just as bad as under-classification and should be avoided. There is no justification for classification of metribuzin as STOT-RE Category 2 for thyroid effects.

References
EU Commission Group of Specialised Experts in the fields of carcinogenicity, mutagenicity and reprotoxicity: Non genotoxic thyroid carcinogens in the rodent bioassay, ECBI/49/99 Add. 1 Rev. 2 excerpt of agenda point 3.1, 1999.
IARC (1999) Scientific Publications No. 147 Species Differences in Thyroid, Kidney and Urinary Bladder Carcinogenesis.
ECHA Guidance on the Application of the CLP Criteria Version 5.0-July 2017, page 473.

Choksi, N, Jahnke, G, St.Hilaire, C, and Shelby M. (2003) Role of thyroid hormones in human and laboratory reproductive health. Birth Defects Research (Part B) 68, 479-491.

Note. <confidential> is an independent toxicologist working for a regulatory consultancy company. The time expended reviewing the relevant documents and preparing this opinion were compensated by Adama Agan Ltd. However, the opinion expressed in this document is mine alone and is based on my toxicological experience and knowledge. Adama Agan Ltd. had no influence on the expression of my opinion.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Public comment on CLP PJ-28-09-2020-redacted.docx
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Public comment on CLP PJ-28-09-2020.docx

Dossier Submitter's Response

Thank you for your comment.
Please see EE CA response to the comment No. 14 above.

RAC's response

Thank you for your comments, please see the response to comment 14.

Date	Country	Organisation	Type of Organisation	Comment number
02.10.2020	France		Individual	16

Comment received

CLH report – Proposal for Harmonised Classification and Labelling
Metribuzin EC# 244-209-7
Independent Opinion No. 2 by Dr <confidential>, Toxicologist

The CLH report and proposal for harmonised classification and labelling for Metribuzin, submitted by the Health Board, Estonia in July 2020 includes a proposal for STOT-RE Category 2, based in part on the finding of haematological changes in the dog.
The proposal argues that these effects are in animals are adverse and can be presumed to have the potential to produce significant toxicity in humans or have the potential to be harmful to human health following repeated exposure, and consequently metribuzin should be classified as a specific organ toxicant. In my opinion, as a toxicologist with many years of experience, the proposal is not correct for two reasons.
1. The effects in animals (dogs) are not specific to the target organ, and
2. The effects in animals (dogs) are not relevant to humans.
The effects on haematology (primarily red blood cell and haemoglobin changes) in dogs, considered to be adverse by the Estonia RMS, do not meet the accepted criteria for adverse toxicological effects specific to a target organ.
In one study in which dogs were dosed with 25, 100, or 1500 ppm metribuzin in the diet, equivalent to approximately 0.8, 3.5, and 55 mg/kg respectively. The haematology endpoints were investigated at 0, 2, 4, 6, 12, 23 and 24 months. Reductions in red blood cell counts, haemoglobin levels, haematocrit, thrombocyte counts, and sedimentation rates were observed after 2, 4, 6, and 12 months. But, at 23 and 24 months these parameters had returned to normal. The study was compromised by a high mortality rate, of the four animals of each sex that started the study only 1 male and 1 female dog survived the 2 year treatment period. Both animals showed normal haematological parameters at termination. No effects were observed in animals exposed to 25 or 100

ppm. Whilst the study is considered to be seriously flawed, it seems difficult to accept that the high mortality rate was caused by specific toxicity to the haematological system when the surviving animals showed no evidence of adverse effects on this target organ.
In two other studies in the dog, one used dosing by capsule at 0, 5, 15, and 50/30 (reduced after 35 days because of excessive toxicity) mg/kg/day for 56 days, and the other used dietary administration at 0, 75, 300, and 1200 ppm (equivalent to approximately 0, 2, 8.5, and 28 mg/kg/day) for 90 days. Generalised toxicity was evident in the high dose groups but severe effects on haematological parameters was not a group effect, but rather limited to specific animals that were terminated prematurely. There was no evident dose response relationship, which may be expected in the case of a specific target organ toxicity.
It can be argued for in all of these studies, that the high dose level was greater than the maximum tolerated dose level because of the high mortality rate and low tolerance of the dose level, and therefore any effects observed at the high dose level should not be considered in isolation.
The ECHA guidance on the application of the CLP criteria indicates that animal data which are of acceptable quality should be used in a weight of evidence approach based on a comparison with the classification criteria. Also, if the effects observed in animals are not considered relevant to humans then these should not be used to support classification. Furthermore, the decision on classification should be based on reliable evidence associating repeated exposure to the substance with a consistent and identifiable toxic effect that demonstrates support for the classification. In this case the effects on the haematological system are not consistent in that there was no evidence of a dose response relationship and were associated only with excessive and generalised toxicity. There was also evidence that the effects were reversible and did not affect all animals in a group. Furthermore, the effects were only observed at highly toxic dose levels in one species, so the relevance to humans is marginal.
In conclusion, the data do not support classification because, on a weight of evidence basis, the data are not conclusive for STOT-RE category 2 for haematological toxicity.

References
ECHA Guidance on the Application of the CLP Criteria Version 5.0-July 2017.

Note. <confidential> is an independent toxicologist working for a regulatory consultancy company. The time expended reviewing the relevant documents and preparing this opinion were compensated by Adama Agan Ltd. on behalf of the Metribuzin Task Force. However, the opinion expressed in this document is mine alone and is based on my toxicological experience and knowledge. Neither Adama Agan Ltd. nor the Metribuzin task Force had any influence on the expression of my opinion.

The attached documents are Word versions of the comment shown above, without any additional content. Note that this comment is different to a previous comment that I made a few days ago.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Public comment 2 on CLP PJ-28-09-2020-redacted.docx
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Public comment 2 on CLP PJ-28-09-2020.docx

Dossier Submitter's Response
Thank you for your comment. Please see EE CA response to the comment No. 14 above.
RAC's response
Thank you for your comments, please see the response to comment 14.

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
02.10.2020	France		MemberState	17
Comment received				
FR agrees with the classification for environmental hazards and with the acute and chronic M factor values proposed in the CLH report.				
Dossier Submitter's Response				
Thank you for your supporting comment.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
02.10.2020	United Kingdom	HSE	National Authority	18
Comment received				
metribuzin (CAS; 21087-64-9) The CLH report refers to both an M-factor of 10 and an M-factor of 100 for the Aquatic Chronic 1 classification. We consider that the most reliable endpoints for chronic classification are in the range from 0.001-0.01 mg/L: Lemna gibba 7-d ErC10 = 0.0059 mg a.s./L based on frond number 0.00678 mg a.s./L based on frond area & 0.0056 mg a.s./L based on biomass; Desmodesmus subspicatus 72-h ErC10 = 0.00516 mg a.s./L; and Myriophyllum spicatum 14-d ErC10 = 0.00507 mg a.s./L based on dry weight, 0.00713 mg a.s./L based on fresh weight & 0.00764 mg a.s./L based on total shoot length. These endpoints support an M-factor of 10.				
Dossier Submitter's Response				
Thank you for your comment. EE CA in principle agrees that chronic classification could be based on the lowest E_rC_{10} values from the above metioned studies since E_rC_{10} value has been used preferentially over the NOE_rC to determine the chronic hazard classification. However, EE CA has taken the worst case approach and proposed *Lemna gibba* 7-d NOE_rC = 0.000205 mg a.s./L as the lowest endpoint for aquatic chronic classification. Therefore, Metribuzin should be classified as 'Aquatic Chronic Category 1' with a chronic M-factor of 100 since the lowest aquatic NOE_rC value is one order of magnitude lower than E_rC_{10}. Please see EE CA response to comment No. 20 below for further information on the key study for classification.				
RAC's response				
RAC is of the opinion that the ErC10 of the *Lemna gibba* study takes precedence. According to recent scientific developments EC10 values are preferred as these are				

statistically derived from the entire dataset, and less dependent on test design considerations than the NOEC.

Date	Country	Organisation	Type of Organisation	Comment number
01.10.2020	Germany	Bayer AG	Company-Importer	19

Comment received

Comments for the category "Hazardous to the aquatic environment" are enclosed as attachments:
- Comments and additional information to the CLH for metribuzin - public.zip
- Comments and additional information to the CLH for metribuzin - confidential.zip
Due to the size of the files, these will be submitted via the web form for large files.

ECHA note – Four attachments were submitted with the comment above. Refer to public attachments:
- Comments and additional information to the CLH for metribuzin – public.zip
- Metribuzin Task Force response documents and reference list – public.zip
- Studies and documents submitted during STC - public part 1.zip
- Studies and documents submitted during STC - public part 2.zip

ECHA note – Four attachments were submitted with the comment above. Refer to confidential attachments:
- Comments and additional information to the CLH for metribuzin – confidential.zip
- Metribuzin Task Force response documents and reference list – confidential.zip
- Studies and documents submitted during STC - confidential part 1.zip
- Studies and documents submitted during STC - confidential part 2.zip

Dossier Submitter's Response

The following comment has been received from Industry:

11.5 Acute aquatic hazard, Table 63 (Summary of acute aquatic studies)
For the freshwater diatom species Navicula pelliculosa for which the existing study (M-013747-02-1 and M-431222-01-1) was considered to be only supplementary, a new study has been performed in context of the EU approval renewal of metribuzin. This new and fully valid study (M-663179-03-1) was submitted in response to the EFSA request for additional information in June 2020 and may be added to the CLH report for Metribuzin. The results of this new study (72h-ErC50 = 34 µg a.s./L, 72h-NOErC = 1.0 µg a.s./L) do not change the overall conclusion on classification and labelling for environmental hazards as described under point 11.8 of the CLH report for Metribuzin.

11.7.1 Acute aquatic hazard
The following is stated in the CLH report: 'The lowest ErC50 value of 0.0265 mg a.s./L was obtained in Pseudokirchneriella subcapitata Growth Inhibition Test.' The applicants would like to clarify that the overall lowest ErC50 in the acute dataset was obtained for Lemna gibba (study M-455636-01-1): ErC50 dry weight = 0.0161 mg a.s./L. In Table 63 (Summary of acute aquatic studies), for this Lemna study only the ErC50 = 0.0385 mg a.s./L for frond number is given which is higher than the P. subcapitata endpoint. The applicants assume that the reason for preferring the P. subcapitata endpoint for classification and labelling can be found in the ECHA CLP Guidance from 2015: 'The observational endpoint is based on change in the number

of fronds produced' and 'Under the REACH Regulation growth inhibition study on aquatic plants, algae are the preferred species.'

11.5 Acute aquatic hazard / 11.6 Longterm aquatic hazard
The two tables summarizing acute and chronic aquatic toxicity studies (Table 63, Table 64) include the macrophyte study performed with Myriophyllum spicatum (M-663178-01-1). With regard to the selection of taxa considered in hazard classification, the ECHA CLP Guidance (2015) states the following under point I.3 (Aquatic toxicity concepts):
'Acute aquatic toxicity is normally determined using a fish 96 hour LC50, a crustacea species 48 hour EC50, an algal species 72 or 96 hour EC50 and/or aquatic plants 7 days EC50. These species cover a range of trophic levels and taxa and are considered as surrogate for all aquatic organisms. Data on other species shall also be considered if the test methodology is suitable.' The fact that Myriophyllum studies in accordance with OECD guideline 239 (2014) are water-sediment studies leads to the question if such studies should really be taken into account for hazard classification. Their methodology significantly differs from normal aquatic (water only) lab studies and the study design is closer to higher tier than to Tier 1. With regard to macrophyte species, the CLP Guidance further states under point I.2.3.2 (Tests with aquatic macrophytes):
'The most commonly used vascular plants for aquatic toxicity tests are duckweeds (Lemna gibba and L. minor). The tests last for up to 14 days and are performed in nutrient enriched media similar to that used for algae, but may be increased in strength. The observational endpoint is based on change in the number of fronds produced. Tests consistent with OECD Test Guideline on Lemna (2006) and US-EPA 850.4400 (aquatic plant toxicity, Lemna) should be used.'
To conclude and to ensure a harmonized approach, if macrophyte data is considered in hazard classification, it should focus on the standard species Lemna.

EE CA thanks for the provided information on the new study.

For acute aquatic hazards classification the lowest E_rC_{50} value of 0.0265 mg a.s./L obtained in *Pseudokirchneriella subcapitata* Growth Inhibition Test was used for the same reason as stated in the comment. In *Lemna gibba* study (M-455636-01-1) the E_rC_{50} = 0.0385 mg a.s./L for frond number was reported. The CLP guidance says: "The observational endpoint is based on change in the number of fronds produced". ECHA Guidance on Information Requirements and Chemical Safety Assessment, Chapter R.7b (2017) explains further that frond number is the primary measurement variable used for aquatic toxicity tests with vascular plants. Other additional measurement parameters are total frond area, dry weight/fresh weight. The EC_x/NOEC should be related to growth rate, thus biomass endpoints although reported should not be used.

EE CA proposal for aquatic chronic classification is based on the *Lemna Gibba* study (M-455636-01-1) with NOE_rC = 0.000205 mg a.s./L which is the lowest chronic endpoint obtained in relevant studies. The macrophyte study performed with *Myriophyllum spicatum* (M-663178-01-1) was added to aquatic acute/chronic data because it is well perfomed study conducted according to the guideline with no deviations and could be considered as supplementary information.

RAC's response
Thank you for informing about new study results on *Navicula pelliculosa*. The test report also gives a 72-hour EC_{10} value of 0.00655 mg/L in addition to a 72-hour NOEC of 0.001 mg/L. In RAC's opinion the EC_{10} value should be used for classification because according to recent scientific developments EC10 values are preferred as these are statistically derived from the entire dataset, and less dependent on test design considerations than the NOEC. RAC agrees that the lowest acute toxicity value is for *Lemna gibba* (study M-455636-01-1): ErC50 dry weight = 0.0161 mg a.s./L. This is a relevant endpoint for growth rate as stated in the OECD TG 221 "Toxicity estimates should be based on frond number and one additional measurement variable (total frond area, dry weight or fresh weight), because some substances may affect other measurement variables more than the frond number. This effect would not be detected by calculating frond number only." RAC considers the water-sediment *Myriophyllum* study as supportive evidence in this case. Although the concentrations of metribuzin in overlaying water in aged media ranged between 88.7 and 110%, the pore water concentrations ranged between 22.7 and 47.5%. A sediment-rooted aquatic macrophyte as *Myriophyllum* takes up contaminants from pore water directly through the roots and it is not possible to conclude that the effect is solely based on metribuzin in overlaying water.

Date	Country	Organisation	Type of Organisation	Comment number
28.09.2020	Germany		MemberState	20

Comment received
DE-CA agrees with the dossier submitter's overall conclusions on aquatic toxicity. Based on the presented data on the key study on Lemna gibba (M-455636-01-1), DE-CA agrees that it is justified to use the NOErC instead of the ErC10 as endpoint relevant for classi-fication. NOErC as well as LOErC values are both below 0.001 mg/L, indicating that it seems appropriate to use this more sensitive endpoint instead of the ErC10, which is higher than 0.001 mg/L. However, it would be helpful to include some further information on this key study (e.g. % inhibition at the respective test concentrations, coefficients of variation) to allow a more informed assessment of the preferred endpoint. In section 11.7 and 11.8 a chronic M-factor of 100 is derived, based on the toxicity to aquatic plants. However, Table 3 in section 2.1 states a chronic M-factor of 10. Please use the chron-ic M-factor of 100 also in your proposal in Table 3.
Dossier Submitter's Response
Thank you for your comments. EE CA has submitted to ECHA CLH proposal with correct Table 3 including aquatic chronic M-factor of 100. It's regrettable that the incorrect version of the proposal is available on

ECHA website. EE CA is unaware of the consequences of such a situation on the outcome of the public consulation.

Please find below more detailed information on the key study on *Lemna gibba* (M-455636-01-1):

Report:	M-455636-01-1
Title:	Lemna gibba G3 - Growth inhibition test with AE F055208 (metribuzin) under semi-static conditions
Guideline(s):	EU Directive 91/414/EEC; Regulation (EC) No. 1107/2009; US EPA OCSPP 850.4100; OECD Guideline 221 (2006)
Guideline deviation(s):	No deviations from OECD 211 guideline. The validity criteria were met.
GLP/GEP:	**yes**

Objective:
The aim of the study was to determine the influence of the test item on exponentially growing Lemna gibba G3 expressed as NOEC, LOEC and ECx for growth rate of the measurement variables frond number, total frond area and biomass of plants.
Dates of experimental work: 2012-12-03 to 2013-03-27
Materials and methods:
Metribuzin, analysed purity: 94.4 %.

3 x 12 fronds of Lemna gibba G3 per test concentration were exposed in a chronic multi-generation test for 7 days under semi-static (renewal on day 2 and day 4) exposure conditions to the nominal concentrations of 0.205, 0.512, 1.28, 3.20, 8.00, 20.0 and 50.0 µg a.s./L in comparison to a water control. Counting of fronds and determination of total frond area on study days 2, 4 and 7 was carried out using a LemnaTec Scanalyzer machine. Plant dry weight (biomass) was determined at termination of the test by weighing.
The pH values ranged from 7.6 to 8.0 in the fresh controls and the incubation temperature ranged from 25.1 to 25.4°C. There was continuous illumination of 7989 - 8014 lux over the whole period of testing.
Quantitative amounts of test substance were measured in all freshly prepared test levels on day 0, 2, and 4 and additionally in all aged test levels on day 2, 4, and 7 of the exposure period.

Results:
Validity of the study
Frond numbers in the control increased by a factor of 22.3 within 7 days which corresponds to a doubling time of about 1.6 days. Hence, the study is considered to be valid.
Analytical results
The analytical findings of metribuzin in all freshly prepared test levels on day 0, 2, and 4 ranged between 100 and 118 % of nominal concentrations. In aged test levels on days 2, 4, and 7, analytical findings ranged between 98 and 114 % of nominal. Thus, all reported results were based on nominal concentrations of the test item metribuzin. No residues of metribuzin were found in the control above the limit of quantification (LOQ = 0.05 µg a.s./L).
Biological results
There were no visual effects observed in any of the test concentrations.

Table 1. Frond counts, doubling time, percent inhibition of average growth rate

nominal concentration [µg a.s./L]	replicate	frond counts				growth rate µ [1/d] (0→7 d)	doubling time [d]	inhibition of µ [%]
		Day 0	Day 2	Day 4	Day 7			
Control	A	12	37	79	266	0.443	1.6	
	B	12	36	78	293	0.456	1.5	
	C	12	38	73	244	0.430	1.6	
	Mean	**12**	**37**	**76.7**	**267.7**	**0.443**	**1.6**	--
	%CV		2.7	4.2	9.2	3.0	2.9	
0.205	A	12	36	76	257	0.438	1.6	
	B	12	34	68	233	0.424	1.6	
	C	12	30	70	235	0.425	1.6	
	Mean	**12**	**33.3**	**71.3**	**241.7**	**0.429**	**1.6**	**3.2**
	%CV		9.2	5.8	5.5	1.8	1.8	
0.512	A	12	27	60	199	0.401	1.7	
	B	12	30	73	214	0.412	1.7	
	C	12	28	54	200	0.402	1.7	
	Mean	**12**	**28.3**	**62.3**	**204.3**	**0.405**	**1.7**	**8.6**
	%CV		5.4	15.6	4.1	1.4	1.5	
1.28	A	12	29	62	213	0.411	1.7	
	B	12	28	58	202	0.403	1.7	
	C	12	25	49	157	0.367	1.9	
	Mean	**12**	**27.3**	**56.3**	**190.7**	**0.394**	**1.8**	**11.1**
	%CV		7.6	11.8	15.6	5.9	6.1	
3.20	A	12	33	71	238	0.427	1.6	
	B	12	32	76	233	0.424	1.6	
	C	12	33	69	243	0.430	1.6	
	Mean	**12**	**32.7**	**72.0**	**238**	**0.427**	**1.6**	**3.7**
	%CV		1.8	5.0	2.1	0.7	0.7	
8.00	A	12	30	59	172	0.380	1.8	
	B	12	24	52	167	0.376	1.8	
	C	12	30	58	164	0.374	1.9	
	Mean	**12**	**28.0**	**56.3**	**167.7**	**0.377**	**1.8**	**15.0**
	%CV		12.4	6.7	2.4	0.9	0.8	
20.0	A	12	24	41	93	0.293	2.4	
	B	12	29	46	121	0.330	2.1	
	C	12	33	55	118	0.327	2.1	
	Mean	**12**	**28.7**	**47.3**	**110.7**	**0.316**	**2.2**	**28.6**
	%CV		15.7	15.0	13.9	6.6	6.7	
50.0	A	12	21	24	41	0.176	3.9	
	B	12	23	32	47	0.195	3.6	
	C	12	21	27	38	0.165	4.2	
	Mean	**12**	**21.7**	**27.7**	**42**	**0.178**	**3.9**	**59.7**
	%CV		5.3	14.6	10.9	8.6	8.3	

Table 2. Total frond area and percent inhibition of their average growth rate

nominal concentration [µg a.s.L]	replicate	total frond area [mm²]				growth rate µ (0→7) [1/d]	inhibition of µ [%]
		Day 0	Day 2	Day 4	Day 7		
	A	115	293	599	2202	0.422	
	B	112	288	610	2299	0.432	
control	C	108	282	593	1914	0.411	
	Mean	**111.7**	**287.7**	**600.7**	**2138.3**	**0.421**	---
	%CV	3.1	1.9	1.4	9.4	2.5	
	A	101	264	597	1890	0.418	
	B	99	255	529	1773	0.412	
0.205	C	98	253	522	1864	0.421	
	Mean	**99.3**	**257.3**	**549.3**	**1842.3**	**0.417**	**1.0**
	%CV	1.5	2.3	7.5	3.3	1.1	
	A	93	218	437	1442	0.392	
	B	98	219	450	1516	0.392	
0.512	C	87	204	415	1431	0.400	
	Mean	**92.7**	**213.7**	**434**	**1463.0**	**0.394**	**6.4**
	%CV	5.9	3.9	4.1	3.2	1.3	
	A	98	213	461	1630	0.402	
	B	92	202	427	1466	0.396	
1.28	C	84	179	364	1129	0.371	
	Mean	**91.3**	**198**	**417.3**	**1408.3**	**0.389**	**7.6**
	%CV	7.7	8.8	11.8	18.1	4.1	
	A	100	261	527	1785	0.412	
	B	103	254	529	1784	0.407	
3.20	C	103	261	563	1885	0.415	
	Mean	**102**	**258.7**	**539.7**	**1818**	**0.411**	**2.3**
	%CV	1.7	1.6	3.7	3.2	1.0	
	A	95	227	428	1165	0.358	
	B	83	202	374	1228	0.385	
8.00	C	97	223	431	1182	0.357	
	Mean	**91.7**	**217.3**	**411**	**1191.7**	**0.367**	**13.0**
	%CV	8.3	6.2	7.8	2.7	4.3	
	A	95	177	265	536	0.247	
	B	107	210	331	734	0.275	
20.0	C	110	225	354	792	0.282	
	Mean	**104**	**204**	**316.7**	**687.3**	**0.268**	**36.4**
	%CV	7.6	12	14.6	19.5	6.9	
	A	99	187	182	248	0.131	
	B	110	176	217	276	0.131	
50.0	C	100	151	183	244	0.127	
	Mean	**103**	**171.3**	**194**	**256**	**0.130**	**69.1**
	%CV	5.9	10.8	10.3	6.8	1.7	

Table 3. Biomass of average growth rate

nominal concentration [µg a.s.L]	replicate	total biomass [mg]		growth rate µ (0→7) [1/d]	inhibition of µ [%]
		Day 0 (mean of 12 replicates from the same culture)	Day 7		
I	A		44.2	0.383	
	B		45.9	0.388	
control	C		33.8	0.344	
	Mean	**3.03**	**41.3**	**0.372**	**-**
	%CV		15.9	6.4	
	A		36.7	0.356	
	B		32.6	0.339	
0.205	C		36.2	0.354	
	Mean	**3.03**	**35.2**	**0.350**	**5.89**
	%CV		6.4	2.6	
	A		28.4	0.320	
	B		28.2	0.319	
0.512	C		28.6	0.321	
	Mean	**3.03**	**28.4**	**0.320**	**14.1**
	%CV		0.7	0.3	
	A		31.9	0.336	
	B		28.7	0.321	
1.28	C		21.1	0.277	
	Mean	**3.03**	**27.2**	**0.311**	**16.2**
	%CV		20.4	9.8	
	A		31.7	0.335	
	B		34.2	0.346	
3.20	C		33.8	0.344	
	Mean	**3.03**	**33.2**	**0.342**	**8.03**
	%CV		4.0	1.7	
	A		20.2	0.276	
	B		20.9	0.276	
8.00	C		22.8	0.288	
	Mean	**3.03**	**21.5**	**0.280**	**24.7**
	%CV		5.1	2.6	
	A		8.5	0.147	
	B		11.7	0.193	
20.0	C		12.8	0.206	
	Mean	**3.03**	**11.0**	**0.182**	**51.1**
	%CV		20.3	16.9	
	A		2.2	-0.046	
	B		3.6	0.024	
50.0	C		2.8	-0.011	
	Mean	**3.03**	**2.87**	**-0.011**	**100**
	%CV		24.5	-	

Toxicity of metribuzin to aquatic plants (based on nominal concentrations of the test item):

Endpoint (0-7 day)	Effect on mean growth rate of frond no. [µg a.s./L]	Effect on mean growth rate of total frond area of plants [µg a.s./L]	Effect on mean growth rate of biomass [µg a.s./L]
E_rC_{10} (CI 95%)	5.9 (0.85-10.99)	6.78 (3.28-9.97)	5.06 (0.02-9.8)
E_rC_{20} (CI 95%)	11.2 (3.43-17.8)	11.2 (6.79-14.87)	7.54 (0.17-13.03)
E_rC_{50} (CI 95%)	**38.5** (25.4 – 86.5)	**29.0** (23.0 – 37.9)	**16.1** (6.49 – 41.2)
LOE_rC	0.512	0.512	0.512
NOE_rC	0.205	0.205	0.205

RAC's response

RAC is of the opinion that the ErC10 of 0.00506 mg/L of the *Lemna gibba* study takes precedence. According to recent scientific developments EC10 values are preferred as these are statistically derived from the entire dataset, and less dependent on test design considerations than the NOEC.

ECHA note – A typographical error was present in the version of the CLH dossier published during the standard consultation. An ad hoc consultation was held from 15/03/2021 to 29/03/2021 in order to ensure that all comments are framed based on correct information in relation to the classification proposed.

PUBLIC ATTACHMENTS
1. Public comment 2 on CLP PJ-28-09-2020-redacted.docx [Please refer to comment No. 16]
2. Comments and additional information to the CLH for metribuzin – public.zip [Please refer to comment No. 2, 3, 4, 5, 6, 8, 9, 10, 11, 12, 14, 19]
3. Metribuzin Task Force response documents and reference list – public.zip [Please refer to comment No. 2, 3, 4, 5, 6, 8, 9, 10, 11, 12, 14, 19]
4. Studies and documents submitted during STC – pubic part 1.zip [Please refer to comment No. 2, 3, 4, 5, 6, 8, 9, 10, 11, 12, 14, 19]
5. Studies and documents submitted during STC – pubic part 2.zip [Please refer to comment No. 2, 3, 4, 5, 6, 8, 9, 10, 11, 12, 14, 19]
6. Public comment on CLP PJ-28-09-2020-redacted.docx [Please refer to comment No. 15]

CONFIDENTIAL ATTACHMENTS
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4. Studies and documents submitted during STC - confidential part 1.zip [Please refer to comment No. 2, 3, 4, 5, 6, 8, 9, 10, 11, 12, 14, 19]
5. Studies and documents submitted during STC - confidential part 2.zip [Please refer to comment No. 2, 3, 4, 5, 6, 8, 9, 10, 11, 12, 14, 19]
6. Public comment on CLP PJ-28-09-2020.docx [Please refer to comment No. 15]