Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

benfluralin (ISO); *N*-butyl-*N*-ethyl-α,α,α-trifluoro-2,6-dinitro-*p*-toluidine

EC Number: 217-465-2
CAS Number: 1861-40-1

CLH-O-0000006963-64-01/F

Adopted

18 March 2021

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON BENFLURALIN (ISO); N-BUTYL-N-ETHYL-A,A,A-TRIFLUORO-2,6-DINITRO-P-TOLUIDINE

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: benfluralin (ISO); N-butyl-N-ethyl-α,α,α-trifluoro-2,6-dinitro-p-toluidine
EC number: 217-465-2
CAS number: 1861-40-1
Dossier submitter: Norway

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
17.01.2020	Germany	Gowan Crop Protection Ltd.	Company-Manufacturer	1
Comment received				
New relevant mechanistic data on human relevance of rodent liver- and thyroid tumorigenicity was developed since dossier submission for approval renewal and is submitted herewith. The attachments will be uploaded separately due to file size as per guidance of the Helpdesk. ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Benfluralin_comments to carcinogenicity CLH.zip				
Dossier Submitter's Response				
Noted. New available data to be considered by RAC (has not been assessed by DS).				
RAC's response				
Noted. New data was assessed in the RAC opinion document.				

Date	Country	Organisation	Type of Organisation	Comment number
05.02.2020	Germany		MemberState	2
Comment received				
In table 5 in the cell of the dossier submitters proposal / labelling / Pictogram, Signal Word Code(s) as well as in the cell of the "Resulting Annex VI entry agreed by RAC and COM / Labelling / Pictograms, Signal Word Codes(s) the code "Wng" for the signal word				

"warning" has to be supplemented. Usually, systemic absorption is calculated by including the radioactivity that is excreted via bile. Then, it is very likely that, following oral administration, total absorption is higher than suggested in section 9.1 even though it is acknowledged that it was still below 30 % in males and 40 % in females. Accordingly, the systemic doses causing the various adverse effects that trigger the classification proposals were lower than the external oral doses. However, this difference in the approach taken to estimate internal exposure has no direct impact on classification.
Dossier Submitter's Response
Noted, thank you for the comment. Regarding table 5 agreed that "Wng" should be supplemented. During the EFSA Pesticides Peer Review expert meeting 182 it was concluded that the oral absorption of benfluralin is 20 %. The biliary excretion was not added since the critical effect for the AOEL setting was seen in kidneys. In our opinion this was the correct approach.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
04.02.2020	France		MemberState	3
Comment received				
FR: Data reported in CLH report regarding the impurity EBNA is not clear. The maximum content of the relevant impurity ethyl-butyl-nitrosamine according to the LOEP July 2019 in the RAR of the substance is 0.085 mg/kg.				
Dossier Submitter's Response				
Noted, thank you for the comment. The previous technical specification of the relevant impurity ethyl-butyl-nitrosamine (EBNA) was 0.1 mg/kg. Since EBNA has been tested up to 0.085 mg/kg in genotoxicity studies, the technical specification of EBNA has been limited to a level of 0.085 mg/kg (EFSA conclusion 2019).				
RAC's response				
Noted. EBNA was also tested up to 0.3 mg/kg in some older mutagenicity studies and the mouse 2-year dietary study. EBNA was also tested up to 0.18 mg/kg in the new *in vitro* mechanistic studies which were designed to investigate proliferation in mouse, rat, CAR/PXR double knock out rat and human hepatocytes.				

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
05.02.2020	Germany		MemberState	4
Comment received				
Based on the increased incidence of (mostly benign) liver and (benign as well as malignant) thyroid tumours in the long-term study in the rat and some evidence of an increase in liver cell adenoma and carcinoma in female mice, a treatment-related oncogenic effect of benfluralin may be assumed. Mechanistic studies were performed of which the results do not exclude human relevance. Also, they did also not provide convincing evidence that the thyroid tumours in rats were due to a rodent-specific				

mechanism with activation of microsomal liver enzymes, a reduction in circulating T3 and T4 levels and continuing stimulation of the thyroid by TSH. Thus, in principle, there was a multi-site response in two species of which human relevance could not be excluded. However, it must be acknowledged that the increase in tumour frequency in the rat was confined to the two upper dose levels of 2500 and 5000 ppm which were apparently toxic as demonstrated by a number of severe, non-neoplastic pathological findings, organ weight changes, alterations in many haematological and clinical chemistry parameters, lower body weight and food consumption and, at least in males, impaired survival. (On the other hand, a higher mortality rate may mask the frequency of tumour formation. It seems that no respective statistical analysis had been performed to adjust for the lower survival in the high-mid and high dose groups.) In the mouse study, the dose response for the increase in liver tumour incidence was rather flat and, again, the highest dose caused marked toxicity. Because of these considerations, classification of benfluralin for carcinogenicity is justified but category 2 is considered more appropriate than 1B. Accordingly, the proposal for "Carc. 2" (H351) is supported.
Dossier Submitter's Response
Thank you for the comment. DS has still the opinion that the available data when submitting the dossier supports proposal for "Carc. 2" (H351). We have noted that the applicant has submitted new mechanistic data on human relevance of rodent liver- and thyroid tumorigenicity during the consultation of this dossier. This data has not assessed by DS.
RAC's response
Noted. RAC has assessed all the available data and supports the DS' proposal to classify as Carc. 2. RAC did not consider the mouse study reliable because the B6C3F1 hybrid is a specifically susceptible mouse strain for both benign and malignant neoplasms in the liver. In contrast to the above comments, RAC considered sufficient convincing evidence was provided for the thyroid tumour MoA. The new data addressed some of the concerns that both the MSCA and the DS expressed. The final assessment of carcinogenicity was based on the rat liver tumours only. More data was provided via *in vitro* investigations into hepatocyte proliferation under a number of conditions that reinforce the CAR/PXR MoA for liver tumour development. There were still uncertainties and important gaps in information such as a lack of *in vivo* knock out animal data. While the available data package was strongly supportive of a CAR/PXR based mechanism for liver tumours in rats, human relevance of these tumours cannot be excluded.

Date	Country	Organisation	Type of Organisation	Comment number
17.01.2020	Germany	Gowan Crop Protection Ltd.	Company-Manufacturer	5
Comment received				
A set of in vitro hepatocellular proliferation studies in wild type and CAR/PXR knockout rats, mice and humans was developed which supports (together with the previously available data on mechanism, dose- and time concordance of events) a CAR/PXR driven mode of action for liver tumors that is not relevant for humans. A new 90 day thyroid hormone study and a thyroid peroxidase assay were developed to support (together with the previously available data on mechanism, dose- and time concordance of events) the human non-relevance of the rodent-specific UDPGT-driven thyroid tumorigenesis observed in chronic rat study. Furthermore, ToxCast data was included on the sodium-iodide symporter.				

ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Benfluralin_comments to carcinogenicity CLH.zip
Dossier Submitter's Response
Noted, thank you for the comment. New relevant mechanistic data on human relevance of rodent liver and thyroid tumorigenicity to be considered by RAC (has not been assessed by DS).
RAC's response
Noted. See answer to comment 4 above.

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
05.02.2020	Germany		MemberState	6
Comment received				
We agree that a genotoxic potential of benfluralin is not likely. The three in vivo micronucleus assays in the mouse and in the rat may have their weaknesses but did not point to a clastogenic potential. It should be also taken into consideration that two new in vitro micronucleus assays in human lymphocytes were negative.				
Dossier Submitter's Response				
Thank you for the comment. Benfluralin was not genotoxic/mutagenic in vitro or in vivo in the available studies. It should be noted that the 2-year mouse study was conducted with a batch of benfluralin containing a higher level of EBNA (0.31 mg/kg) than the highest technical specification tested (0.085 mg/kg) in the standard genotoxicity battery of in vitro and in vivo assays.				
RAC's response				
Agreed. There is no strong evidence to propose classification for mutagenicity based on the tested batches of benfluralin.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
06.02.2020	Germany	Gowean Crop Protection Ltd.	Company-Manufacturer	7
Comment received				
Reproductive Toxicity: NO CLASSIFICATION is appropriate CLH Report proposal to classify benfluralin for reproductive and developmental toxicity is discussed in the attached document with particular respect to maternal toxicity. • Decreased litter size in a 2-generation study occurred at a dose level associated with marked maternal toxicity; weight gains of F0 dams were 35% less than controls up to the point of birth, with body weight loss during the initial lactation periods. Animals food intake was also impaired throughout the study and a significant degree of anaemia in the maternal must be expected based on comparison to repeated dose studies with Benfluralin. This marked deficit undoubtedly affected the ability of the dams to maintain pregnancy to the same level of controls. • This same marked toxicological impairment present throughout gestation and lactation, accounts for increased pup loss early in lactation and a decreased weaning index. Pup				

loss seen in late lactation was more likely attributable to benfluralin intake from diet, in the absence of any maternal process. This is clearly demonstrated by mortality in post-weaning pups at 21-28 days of age, where intake from diet will be particularly elevated as a consequence of the high food intake to body weight ratio of these smaller animals, but also due to their age. In such young animals, pup organ systems which are pivotal in metabolism and elimination are still immature, leading to elevated systemic exposure through reduced clearance. The mortality in these pups further indicates that the dose sustained by parental animals, must have approached lethal levels. There is no need to postulate any transfer in milk for the toxicity seen in the weanlings.

• In the developmental toxicity study in rats, an increased incidence of vertebral centrum variants in foetuses clearly correlates with decreases in corrected maternal weight gain, and is a secondary consequence of effects on the dam.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Benfluralin_CLH_Statement Reprotoxicity_Final_Redacted.pdf
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Benfluralin_CLH_Statement Reprotoxicity_Final.pdf

Dossier Submitter's Response

Noted, thank you for the comment. One of the manifestations of developmental toxicity includes death of the developing organism. In the two-generation study, the reduced weight and survival of the pups occurred together with reduced maternal health. According to the CLP criteria, developmental effects that occur in the presence of maternal toxicity are considered to be evidence of developmental toxicity, unless it can be unequivocally demonstrated on a case-by-case basis that the developmental effects are secondary to maternal toxicity.

Based on the available data, there is no information regarding the rearing of the pups. It is therefore not certain if maternal toxicity solely contributed to the effects in the pups. Furthermore, as pointed out in the CLH-dossier, the following finding should not be disregarded "the test article was found to accumulate in the abdominal cavity in F1 animals and in the abdominal fat in F1-pups (revealed by extended necropsy in F1-pups only). Since benfluralin was detected in the abdominal fat in the F2 generation it is highly likely that the pups were exposed in the uterus and/or via the milk".

Our precautionary proposal of classification for developmental toxicity in the rat (Repr. 2, H361d) is therefore maintained.

The alternative position and the proposal submitted by the applicant to be considered by RAC.

RAC's response

Noted. RAC considers the effects on pups and jueveniles a developmental effect. RAC notes the arguments presented by industry but highlights that the available data from the rat 2-generation study do not explain or allow for concluding on the cause of the post-natal effects on pups. The effects were not considered to be solely secondary effects of the observed maternal toxicity and are therefore relevant for classification. RAC proposes classification as Repr. 2 for development.

Date	Country	Organisation	Type of Organisation	Comment number
05.02.2020	Germany		MemberState	8

Comment received

The first reproductive study (1973) with continuous administration over five generations is not acceptable from a today's point of view and, therefore, not suitable for classification purposes. Similarly, the many deficits of the more recent two-generation study make a reliable assessment of reproductive toxicity with regard to classification and labelling difficult. In particular, the missing information on implantation sites (a parameter that might help to interpret the reduced litter size and the lower number of liveborn pups) and on pup development is of concern. In addition, no conclusion with regard to ED properties (EAS modality) can be drawn. However, based on the available data on fertility and reproductive performance, there is no sufficient evidence that would warrant classification for reproductive toxicity. There was a clear effect on litter size but maternal toxicity at the top dose level must not be ignored.

Offspring toxicity should be considered in a different way even though there is no evidence of a particular vulnerability of very young animals. At the top dose level of 5000 ppm, but not at 1000 ppm, the difference in mean pup weight as compared to the control group becomes much bigger during the lactation period. This holds true for both generations. This finding could indeed suggest an effect of benfluralin by exposure of the very young animals via the milk. At least among high dose F2 pups, survival was reduced during lactation. More frequently, pops were pale and cold to touch in this group but also in high dose F1 pups. Sometimes, milk was absent from stomach suggesting inadequate nursing. Excretion of benfluralin via the milk has been demonstrated in a cow and this confirms a respective expectation, based on physico-chemical properties (lipophilicity) and ADME results (certain affinity to fatty tissues) even though rat milk was not examined for benfluralin or its residues. On balance, the proposal to classify benfluralin for effects via lactation (H362) is supported. Indeed, it is hardly possible to distinguish whether the effects were due to direct exposure of the pups to benfluralin in the milk, or the result of either reduced milk production or impaired nursing behaviour that both might be explained by maternal toxicity. However, at least the latter mechanism might also give a justification for this classification. A cross-fostering study that might be helpful for a more informed decision is not available.

In contrast, the proposal to classify benfluralin for developmental toxicity in the rat (Repr. 2, H361d) is not supported. The lower litter size in the two-generation study at 5000 ppm is most likely attributable to maternal toxicity and was not considered severe enough to warrant classification for reproductive toxicity which would be the more appropriate. Offspring effects in the two-generation study are sufficiently covered by the proposal H362 for presumed lactational effects. The only finding in the developmental toxicity in the rat was an increase in unossified vertebral centra, i.e., a variation suggesting some developmental delay. Even though variations may be used as basis for classification, such a delay is usually not considered sufficient to substantiate a respective proposal.

Dossier Submitter's Response

Noted, thank you for the comment. Agreed that the available information still support classification for adverse effects on or via lactation (H362).

Regarding the proposed classification for developmental toxicity in the rat (Repr. 2, H361d), see our reply, comment number 7.

RAC's response
RAC agrees with the DS and supports classification for developmental effects. RAC considers the reduction in post-natal body weights a severe effect, along with increased lethality and considers both to support a classification for development. This is in line with the definition of developmental toxicity as outlined in the CLP Regulation, Annex I, 3.7.1.4., Adverse effects on development of the offspring. RAC finds no robust data to support classification for effects on or via lactation.

Date	Country	Organisation	Type of Organisation	Comment number
04.02.2020	Germany	Gowan Corp Protection Ltd.	Company-Manufacturer	9

Comment received

Adverse effects on or via lactation: NO CLASSIFICATION is appropriate

In the cow and goat metabolism studies, parent benfluralin was not detected in milk. In the cow study, very low concentrations of total radioactivity (0.006 mg equivalent benfluralin/kg) consisting of multiple components were detected in the milk. In the goat study, there was no statistically significant radioactive residue in the milk at any time. In the Annex to the CLH report 9Page 67), the Dossier Submitter states "In the metabolism study in cow no parent compound was recovered in any of the matrices suggesting that benfluralin was rapidly and extensively metabolised. Due to the low radioactive residue levels in the tissues and the numerous compounds constituting the total radioactive residues, no further metabolites characterization was attempted".

In addition, the Conclusion from Pesticides Peer Review Meeting 184 (September 2018) was as follows "The meeting was of the opinion that the submitted livestock metabolism studies were not compliant with the current test guidelines and for the time being reliable residue definitions in animal matrices cannot be derived. These data are however not triggered according to the representative uses and also when the authorized uses are considered (Art.12 MRL review)".
That is the representative crops (lettuce and chicory) are not fed to livestock and therefore the transfer of residues to milk intended for human consumption is highly unlikely.

In multigeneration studies, test compound intakes of offspring are not measured during the weaning period since diet consumption by the dam and the offspring cannot be separated. Rat pups at day 14 were approximately 20g in weight, and if one makes the assumption that food consumption will be broadly similar to mice of 20g weight (therefore; food consumption ca. 4.4 g/day) then in the benfluralin study (top dose 5000 ppm in diet) young rats might intake as much as 1100 mg/kg bw/day via diet. In contrast, at birth rat pups were ca. 5g in weight; assuming the same relative food intake to bodyweight (25%) then intake from milk containing 0.006 mg benfluralin (or metabolites) /kg milk then intakes are of the order of 0.002 mg/kg bw/day. Industry submits that toxicity via transfer in milk is therefore not a credible proposal. RAC will note that approximation of food consumption values has no influence on the magnitude of difference.

In pups at 14-28 days of age, intakes of benfluralin from diet might potentially approach toxic levels; and from 21-28 days of age the nutrition of the offspring will be entirely via diet since pups have been separated from the dam. Toxicity in offspring of 14-28 days of

age can be attributed to high benfluralin intakes as a result of the very high food consumption-to-bodyweight ratios of young animals.
Dossier Submitter's Response
Noted, thank you for the comment. Based on available data, benfluralin is widely distributed, showing some affinity to fat, extensively metabolised and rapidly eliminated, mainly via faeces. There are a high number of metabolites retrieved in urine (EFSA has established a data gap for the applicant to propose a residue definition for body fluids and tissues (blood and urine) relevant to human biomonitoring of the substance). In the metabolism study in cow, low concentrations of total radioactivity (0.006 mg equivalent benfluralin/kg) was detected in the milk (parent compound was not detected). The cow was only dosed for three days. Due to the short exposure period it is in the CLH-dossier stated that "the parent compound constituted 34% (0.090 mg/kg) of the TRR in skin/fat and 4% (0.09 mg/kg) of the TRR in eggs following administration of benfluralin for 10 days at dietary concentration of 15 mg/kg in a poultry metabolism study. This may indicate that accumulation of benfluran or most likely metabolites in fat and milk may occur if a cow is dosed for a longer period". In the two-generation reproductive toxicity the rat milk was not examined for benfluralin or its residues. It cannot, however, be excluded that the substance was transferred via the milk since body weight decreases and pup mortality was already increased in the first days of lactation (up to d4, where no autonomic feeding of the pups was expected). DS still supports classification for adverse effects on or via lactation.
RAC's response
RAC does not support classification for effects on or via lactation.

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
05.02.2020	Germany		MemberState	10
Comment received				
It is agreed that the study results do not support classification of benfluralin for acute toxicity. The two dermal studies in rabbits, however, support a need for classification of the test substance as a skin irritant. With regard to inhalative toxicity, it must be acknowledged that the only available study might be not suitable for classification purposes since the MMAD was much too high (i.e., 24.-26 µm as compared to the recommended size of 1 – 4 µm). For a decision whether a reliable conclusion may be drawn or a data gap should be indicated, it might be helpful to clarify what the MMAD under realistic conditions of human exposure will be.				
Dossier Submitter's Response				
Noted, thank you for the comment. In the available acute inhalation study, the notifier brought under attention the technical difficulty to generate an inhalable dust fraction from the wet cake. The LC50 (4 hr, aerosol) for male and female rats was >2.16 mg/L air, which was the highest technically attainable concentration. The limit dose (5 mg/L) was not attained, but due to the difficulty in generating a respirable fraction and that the effects were not severe enough to result in mortality in one half or more of the animals, classification for acute inhalation toxicity was not considered as required for benfluralin.				
RAC's response				
RAC agrees with the DS.				

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
05.02.2020	Germany		MemberState	11
Comment received				
The proposed classification of skin irritation (Skin Irrit. 2, H315) is supported. It is based on the acute studies that revealed persistent findings even though the oedema and erythema scores alone might be not sufficient. In addition, a need for classification was confirmed by the findings in the acute and subacute dermal toxicity studies in rabbits.				
Dossier Submitter's Response				
Thank you for the comment. DS agrees that benfluralin meets the criteria for "Skin Irrit. 2" (H315).				
RAC's response				
Agreed. RAC notes evidence from several study types in support of Skin Irrit. 2; H315.				

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
05.02.2020	Germany		MemberState	12
Comment received				
The findings in the eye irritation study clearly point to a need for classification. However, taking into account the severity degrees and the reversibility of damage, category 2 is in fact more appropriate than category 1. Accordingly, the proposal of "Eye Irrit. 2" (H319) is supported.				
Dossier Submitter's Response				
Thank you for the comment. DS agrees that benfluralin meets the criteria for "Eye Irrit. 2" (H319)				
RAC's response				
Agreed. Classification for Eye irritaton in Category 2 is supported.				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
05.02.2020	Germany		MemberState	13
Comment received				
In two independent studies, performed by different methods, benfluralin proved clearly positive for skin sensitisation. Therefore, the classification proposal "Skin Sens. 1" (H317) is supported. We also agree that sub-classification is not possible since, on one hand, there was a strong positive effect in terms of the number of responding animals but, on the other hand, the concentrations used for induction, in particular in the maximisation test, were quite high.				
Dossier Submitter's Response				
Thank you for the comment. DS agrees that benfluralin meets the criteria for "Skin Sens. 1" (H317).				
RAC's response				
RAC agrees with the DS' proposal to classify as Skin Sens. 1, H317.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
05.02.2020	Germany		MemberState	14
Comment received				
The proposal for STOT SE 2 is backed by three deaths in the acute inhalative study in rats with congestion of the lungs or the liver being the most remarkable pathological finding. In addition, the reversible clinical signs in survivors in the same study are used to further substantiate this proposal. The approach taken here by the DS appears rather unusual although, from a more formal point of view, the guidance values indeed suggest that Category 2 might be appropriate. Two questions should be taken into consideration. On one hand, STOT SE is intended to cover non-lethal target organ toxicity. In this case, it cannot be excluded that the congestion had directly contributed to death. On the other hand, it seems that the DS would like to classify for effects occurring in an acute study that were not severe enough to result in mortality in one half or more of the animals. Otherwise, they would have resulted in a classification for acute toxicity. If this approach would be taken, we would see in future many similar cases since transient effects are common at least in oral and inhalative studies in which high doses or concentrations are usually applied. We have our doubts if this was the intention when the STOT SE classification was introduced. Last but not least, it can be doubted if the acute inhalation study was actually suitable for classification purposes, just because of the high MMAD (see above). If so, this doubt should apply for a possible STOT SE classification. For all these more general doubts, we do not support the proposal.				
Dossier Submitter's Response				
Noted, thank you for the comment. DS agrees that the approach is unusual. The proposal for classification for STOT SE was raised on the concern that although the MMAD in the acute inhalation was high, a fraction of smaller size particles (6-7 µm) was also found. In the study report "The animals were killed on day 15 and subjected to necropsy, which included examination of external body orifices, general bodily condition and organs/tissues in the thoracic and abdominal cavities". Whether inhalation of benfluralin caused an inflammatory response, and to what extend this was caused by larger particles deposited in the upper parts of the lungs, or particles of smaller size reaching the deeper parts of the respiratory system in the animals, is uncertain, based on the reported findings. Therefore the classification was based on the hepatic and pulmonary congestion observed in two males and one female which died during exposure to 2.16 mg benfluralin/L air.				
RAC's response				
RAC agrees with the MSCA that there are several points that raise doubts as to whether a STOT SE classification is appropriate in this case. RAC does not support classification with STOT SE.				

Date	Country	Organisation	Type of Organisation	Comment number
04.02.2020	Germany	Gowan Corp Protection Ltd.	Company-Manufacturer	15
Comment received				
STOT SE: NO CLASSIFICATION is appropriate No classification is appropriate on the basis of the highlighted findings, which are a post-				

mortem artefact. The findings are only present because the animals were found dead, so not autopsied immediately after death. When an animal dies blood naturally settles into vascular soft tissue before eventually clotting. The lungs and liver are particularly prone to this blood pooling. Because the blood clots in situ, it fails to be displaced (e.g. by exsanguination followed by inflation of the lungs with fixative) as typically happens in animals necropsied following sacrifice. Indeed, because blood has clotted in situ the lungs cannot be inflated. The consequent appearance of these tissues is frequently reported as "congestion" or "consolidation", and is recognised as an artefact of inhalation studies. No pathology (tissue disease) is implied, and this artefact does not represent "specific target organ toxicity" in any way. Symptoms were reported in a proportion of animals in the acute inhalation study, as also in the acute oral study. These findings were at dose levels associated with mortality and again, do not represent "specific target organ toxicity".
Dossier Submitter's Response
Noted, thank you for the comment. See our reply to comment number 14.
RAC's response
Noted. RAC considers this highly plausible in the absence of any supporting pathological effects in the three decidents or at scheduled necropsy for the surviving animals.

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
05.02.2020	Germany		MemberState	16
Comment received				
We agree that classification for STOT RE is not needed. Adverse effects that might justify such a need were confined to dose levels above the guidance values or were, in particular with regard to kidney effects, species-specific.				
Dossier Submitter's Response				
Thank you for the comment. DS is still of the opinion that classification for STOT RE is not needed.				
RAC's response				
RAC agrees with the DS.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
04.02.2020	France		MemberState	17
Comment received				
FR agrees with the proposal of classification for environmental hazards and with the proposed M factors (acute and chronic).				
Dossier Submitter's Response				
Thank you for the comment. DS still supports the proposal of classification for environmental hazards and with the proposed M factors (acute and chronic).				
RAC's response				
Thank you for the comment.				

OTHER HAZARDS AND ENDPOINTS – Physical Hazards

Date	Country	Organisation	Type of Organisation	Comment number
04.02.2020	Germany	Gowan Corp Protection Ltd.	Company-Manufacturer	18

Comment received
Explosive properties: NO CLASSIFICATION is appropriate EC Method A14 (Garofani, S., 2001); Conclusion: Not explosive. The available data should take precedence over the dossier submitter's observations that benfluralin contains groups associated with explosive properties.
Dossier Submitter's Response
Noted, thank you for the comment. Negative results of the EU method A.14 is not sufficient to conclusively exclude explosive properties, and the full screening procedure (Annex I 2.1.4.2) should be used instead.
RAC's response
Thank you for the comment. EU standard method A.14 is not in line with CLP criteria. The chemical structure of benfluralin contains functional groups associated with explosive properties, oxygen balance is -143.2, which is above the limit of -200. The classification (acceptance) procedure for the class of explosives (CLP, Section 2.1.2) has to be applied.

PUBLIC ATTACHMENTS
1. Benfluralin_CLH_Statement Reprotoxicity_Final_Redacted.pdf [Please refer to comment No. 7]

CONFIDENTIAL ATTACHMENTS
1. Benfluralin_CLH_Statement Reprotoxicity_Final.pdf [Please refer to comment No. 7]2. Benfluralin_comments to carcinogenicity CLH.zip [Please refer to comment No. 1, 5]