Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

2-bromo-3,3,3-trifluoroprop-1-ene

EC Number: -
CAS Number: 1514-82-5

CLH-O-0000007363-75-01/F

Adopted

14 September 2023

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON 2-BROMO-3,3,3-TRIFLUOROPROP-1-ENE

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: 2-bromo-3,3,3-trifluoroprop-1-ene
EC number: -
CAS number: 1514-82-5
Dossier submitter: Spain

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
06.01.2023	United Kingdom	Labcorp Development SA (as OR registrant for the non-EU manufacturer)	Company-Manufacturer	1
Comment received				
2-Bromo-3,3,3-trifluoroprop-1-ene is a vital substance in fire extinguishers as a 'clean' fire extinguishing agent. The substance is of special importance to the aviation industry. The substance has a very low exposure profile, with long-term/repeated exposure not occurring. To give further background and context on the uses/exposures of the substance, please see the attachment titled "AMPAC_2BTP_Comments on Fire Fighting and Exposure_Part 2" ECHA note – An attachment was submitted with the comment above. Refer to public attachment AMPC_2BTP_Comments on CLH consultation_Parts 1 and 2 (Public attachement).zip ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment AMPAC_2BTP_Comments on CLH_Part 1 (Confidential).pdf				
Dossier Submitter's Response				
Thank you for your comments. The classification of a substance reflects the type and severity of the intrinsic hazards of that substance. Therefore, considerations related to uses and exposure are not relevant for classification.				
RAC's response				
Thank you for your comments. The answer of the DS is supported.				

Date	Country	Organisation	Type of Organisation	Comment number
13.01.2023	Germany	<confidential>	Company-Importer	2
Comment received				
Our company imports 2-bromo-3,3,3-trifluoroprop-1-ene (generically known as 2-BTP; CAS# 1514-82-5) for use as a fire extinguishing agent in handheld extinguishers for use onboard aircraft. These special life-safety extinguishers are replacing the halon 1211 extinguishers, which are being phased out due to the ozone depletion properties of halon 1211. It has been approximately six years since the commercialization of the extinguishers containing 2-BTP, and 2-BTP, based on its combination of properties, is the sole substance that has been accepted to replace halon 1211 for aviation handheld extinguishers. The aviation industry continues to work on additional aircraft model approvals in order to complete its full transition away from halon 1211 by the December 2025 Critical Use End Date under Commission Regulation (EU) No. 744/2010. ECHA note – An attachment was submitted with the comment above. Refer to public attachment umlaut Statement ECHA_incl attachments_20230112.pdf				
Dossier Submitter's Response				
Thank you for your comments. Please, see response to Comment number 1.				
RAC's response				
Thank you for your comments. The answer of the DS is supported.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
09.01.2023	Germany		MemberState	3
Comment received				
The DE CA agrees that a classification as Repr. 1B (H360FD) is warranted. Please review the data and consider to maybe adapting the NOAECs to 50 ppm. Fertility Adverse effects on fertility and reproductive performance are documented in two reliable inhalation OECD TG 421 studies using rats (Anonymous 2013c, Anonymous 2014). In the first study (Anonymous 2013c, identified as supporting study by the registrant), several effects related to sexual function and fertility were observed at the low dose (198 ppm) such as prolonged oestrous cycle, effects on sperm parameters (motility, velocity, number of abnormal sperm), longer duration of gestation, and reduced implantation counts. Additionally, at higher concentrations reduced male reproductive organ weights and longer mean pre-coital intervals were observed in parental animals. In the second OECD TG 421 study (Anonymous, 2014), identified as the key study, lower concentrations of 2-bromo-3,3,3-trifluoroprop-1-ene also resulted in longer mean pre-coital intervals (LOAEC: 175 ppm) and longer mean gestation lengths (LOAEC: 100 ppm) without significant effects on mean body weights in males or females of parental animals. Additionally, the significantly reduced absolute and relative pituitary weights in males and dams starting from 100 ppm support the fertility effects. These findings are in accordance with the first study mentioned above.				

Overall, clear evidence of reproductive toxicity on sexual function and fertility was demonstrated in the screening studies justifying a classification of 2-bromo-3,3,3-trifluoroprop-1-ene as Repr. 1B (H360F).

Developmental Toxicity
In the first inhalation reproduction/developmental toxicity screening study (Anonymous, 2013c), exposure to 2-bromo-3,3,3-trifluoroprop-1-ene led to a reduced post-implantation survival index (86.6% at 198 ppm, 63% at 505 ppm and 25% at 2900 ppm compared to 94.3% for control), live birth index (96.4% at 198 ppm, 71.2% at 505 ppm and 33.3% at 2900 ppm compared to 99.3% for control), and viability index (89.6% at 198 ppm, 57.9% at 505 ppm and 0% at 2900 ppm compared to 98.6% for control) with a clear dose response. These effects started at concentrations in the absence of maternal toxicity. The death of dams around parturition and shortly thereafter was considered as related to dystocia and therefore not considered as overt maternal toxicity.

In the second screening study (Anonymous, 2014), rats were exposed to 0, 50, 100 and 175 ppm 2-bromo-3,3,3-trifluoroprop-1-ene. A decrease of post-natal survival (84.1% at 100 ppm and 67.9% at 175 ppm compared to 92.8% for control) was observed in a dose-dependent manner as well as an increase of the incidence of interventricular septal defects (one pup from one litter and five pups from two litters in the mid and high dose group, respectively, vs. 0 pups from the control group).

Overall, clear evidence of severe developmental toxicity was observed after exposure to 2-bromo-3,3,3-trifluoroprop-1-ene in both studies, as evident from the increased number of deaths of developing organisms. Therefore, a classification as Repr. 1B (H360D) is supported.

Parental toxicity
Parental toxicity was documented in particular in the first OECD TG 421 study (Anonymous 2013c) with significantly reduced mean body weights of up to −9.9%, −15.0%, −20.3%, in low-dose (198 ppm), mid-dose (505 ppm) and high-dose (2900 ppm) male animals. Hence, the maximal tolerated dose is exceeded in the mid- and high-dose of males. Male mean body weight gain is reduced starting at the low dose (−22.6% after entire period). No significant effects on mean body weight were observed for dams in the low dose group, and a significant up to −8% reduction of dams in the mid dose group during gestation and up to −12.9% during lactation. Female mean body weight gain is reduced starting at the mid dose during gestation (−8.05%) and at the low dose during lactation (−40.5%).

The DE CA agrees that this should not be regarded as a dramatic reduction in absolute body weight and it is unlikely that observed fertility or developmental effects are a secondary consequence of this systemic toxicity. Additionally, fertility effects as well as developmental effects start at concentrations below the onset of marked paternal toxicity (see above).

Additional comment to section 10.10. (Reproductive toxicity)
Please describe more details to clarify the dose regime and duration of exposure in table 8 for both studies. Even though the study report submitter used the term, please delete the term "acute" in the description "special acute 5-min exposure group of 10000 ppm" since it could be misconstrued in terms of the endpoint reproductive toxicity because the high dose exposure was applied daily. Please differentiate clearly the two dosage regimes 0 – 175 ppm and 10000 ppm within the tables 26 - 30 and 36 - 39 since the current

presentation can lead to misunderstandings (dosage regimes are different but could be understood as equal when written in one table).

From the study details in IUCLID, it appears that the two different exposure regimes with doses 0 – 175 ppm and 10000 ppm are not directly comparable and statistics with the 10000 ppm may be not reliable (missing data for controls, smaller chambers). Please clarify within text and tables or delete the dose 10000 ppm, because it seems not the case that the related results give much more additional and necessary information.

Acute effects (Anonymous 2014) should be described in the section "acute toxicity"/deleted from section "reproductive toxicity".

Dossier Submitter's Response

Thank you for your comments and support for the classification of the substance as Repr. 1B (H360FD).

We agree with the descriptions made of the effects on sexual function and fertility, development and parental toxicity.

In relation to NOAECs for reproductive effects, we would like to explain that in the CLH proposal we have only included those that were established in the study reports or by the registrants in the IUCLID file. We have not concluded on the established values. Nevertheless, following your suggestion, we have reviewed the data.

Regarding the increase in the duration of gestation observed at 100 ppm in the second OECD TG 421 study, although the authors did not consider this finding as an adverse effect (see page 29 of the CLH report), we agree that this increase is dose-related and statistically significant and therefore, the NOAEC should be 50 ppm.

On the other hand, we consider that the NOAEC of 100 ppm is well established for developmental toxicity since the decrease in the postnatal survival did not achieve statistical significance at this dose level.

As regards the additional comment to section 10.10. (Reproductive toxicity), we appreciate and agree with your comments on the dose regime and duration of exposure. Thus, in Table 8 and Table 31, the second column (Test substance, dose levels and duration of exposure) should be modified as follows: "Concentrations: 0, 50, 100, 175 ppm (6 h/d); Special exposure group: 10000 ppm (5 min/d)".

Furthermore, we agree that the word "acute" should be deleted from the second column in Table 8 and Table 31. Accordingly, we also would like to modify the third column (Results) in Table 8 to replace "Acute exposure group (10000 ppm)" with *"Special exposure group (10000 ppm)"*.

In addition, due to the two different exposure regimes and to prevent misunderstandings in tables 26 - 30 and 36 - 39, we would add a *footnote (a)* linked to the last column (10000 ppm) indicating the following: *"Special 5-min/d exposure group".*

Finally, acute effects cannot be derived from Anonymous (2014) since as agreed there is not any acute exposure group but only daily exposure groups.

RAC's response

Thank you for your comments. The opinion of the DS about not to derive acute effects from Anonymous (2014) is supported. RAC notes that NOAEC is not relevant for classification proposal.

Date	Country	Organisation	Type of Organisation	Comment number
12.01.2023	United Kingdom	Health and Safety Executive	National Authority	4

Comment received

Reproductive Toxicity – Effects on Sexual Function and Fertility
In the OECD TG 421 inhalation reproduction/developmental toxicity screening test (Anonymous, 2013c), there were high numbers of sacrifices of F0 females at 505 and 2900 ppm (50% and 60%, respectively). For this reason, effects at 505 and 2900 ppm may not be relevant for the assessment of effects on sexual function and fertility. Some sacrifices took place due to animals having 'poor condition'. Is there any further information on what the author of the study considered to be poor condition and why these sacrifices occurred?
Additionally, although dose levels have been given for this study, it is possible that, owing to the whole-body exposure method, animals received a higher dose than stated via grooming.
Lastly, the DS has proposed classification with STOT SE 3; H336 (may cause drowsiness or dizziness) for narcotic effects. Might it be prudent to consider these effects when examining the reasons as to why reproductive effects such as changes in mating performance occurred in the study by Anonymous (2013s)?

Reproductive Toxicity – Adverse Effects on Development
We note that, in the OECD TG 421 inhalation reproduction/developmental toxicity screening test (Anonymous, 2014), there was a dose-dependent increase in incidence of interventricular septal defects. According to the effects listed in Table 31 of the CLH report, interventricular septal defects were not observed in the study by Anonymous (2013c). Were the same investigations, which revealed the occurrence of septal defects in the study by Anonymous (2014), also conducted in the study by Anonymous (2013)? If the same investigations were conducted, were interventricular septal defects observed in the study by Anonymous (2013c)?

Dossier Submitter's Response

Thank you for your comments.

In response to your comments on reproductive toxicity - <u>effects on sexual function and fertility</u>:

Regarding the first OECD TG 421 study (Anonymous, 2013c), it is important to highlight that F0 females at 2900 ppm were sacrificed in the late gestation period (GD 24-25). The poor clinical condition was related to pregnancy. Indeed, in most females, it was only observed prior to or around the delivery date. Additionally, an increase in the duration of gestation was observed at 2900 ppm (25.5 days with only one female littering *vs* 22-23 days in controls).

At 505 ppm, F0 females were sacrificed during lactation due to total litter loss. An increase in the gestation length was also observed at this dose level (23-25.5 days vs 22-23 days in controls).

Therefore, the mortality observed at 505 and 2900 ppm only in F0 females around the delivery date and shortly after linked to an increase in the gestation length is considered a sign of dystocia. Besides, the 'poor condition' was not reported for males and none of them was sacrificed at any dose tested.

In addition, it is important to take into account that the longer duration of gestation was also observed in the second OECD TG 421 study (Anonymous, 2014), where no systemic toxicity was detected.

On the other hand, the fact that in both studies pups showed a clear post-natal mortality must be added. In addition, the effects on fertility as well as the effects on development began at concentrations below the onset of marked parental toxicity.

Regarding your comment on the potential relationship between clinical signs and mating performance, in the first OECD TG 421 study (Anonymous, 2013c), findings such as underactivity, unresponsiveness, piloerection, partially closed eyelids or shallow and/or slow breathing were occasionally observed in the mid and high dose group in males and females, being reversible after the 6-hour exposure or before the end of the working day. However, the mating index was only reduced at the high dose level.

In response to your comments on reproductive toxicity - adverse effects on development:

The increase in the incidence of interventricular septal defect was only observed in the second OECD TG 421 study (Anonymous, 2014). It is noted that this investigation was not included in Anonymous (2013c). Nevertheless, the examination of visceral alterations in pups is not mandatory according to the OECD TG 421. Therefore, even though this finding was only reported in one of the two screening studies, its relevance cannot be ruled out since it is a severe developmental effect which occurred in the absence of systemic maternal toxicity.

RAC's response

Thank you for your comments. The answer of the DS is supported. Although grooming cannot be excluded with whole-body exposure method, the volatility of the substance suggest that the major route of exposure would be via inhalation. In addition, it has been shown that the use of restraining tubes can induced immobilization stress in rat during inhalation studies (Everds et al., 2013).

Date	Country	Organisation	Type of Organisation	Comment number
13.01.2023	Germany	<confidential>	Company-Importer	5

Comment received

The additional analysis submitted by our supplier (referenced in the attachments) reflects that there are valid reasons why the most appropriate reproductive classification for 2-BTP is Category 2 (H361: Suspected of damaging fertility or the unborn child). Therefore, we do not endorse a change to Category 1B (H360: May damage fertility or the unborn child).

Under CLP guidelines, it is also possible to add clarification to the generic hazard statements to better define the specific effect or route of exposure. The current analysis shows that a short exposure period to high concentration can be tolerated but more prolonged repeated exposures at lower dose concentrations can lead to adverse reactions.

Therefore, we believe the appropriate hazard statement would be "Suspected of damaging fertility or the unborn child through prolonged repeated inhalation exposures."

ECHA note – An attachment was submitted with the comment above. Refer to public attachment umlaut Statement ECHA_incl attachments_20230112.pdf

Dossier Submitter's Response

Thank you for your comments.

In the background section of the attachment to your comment (Part 1) you mainly argue the following: "*There is no clear evidence of reproductive or development effects in the absence of other non-specific consequences and available interspecies and mechanistic information also raises question about the human relevancy of the effects observed. Therefore, the most appropriate classification for 2-BTP would be Category 2 (H361: Suspected of damaging fertility or the inborn child)".* Thereafter, you make a critical review of the adverse effects on sexual function and fertility and the effects on development to conclude on your classification justification for 2-BTP.

In response to your exhaustive review, we would like to highlight the following:

First, regarding the clinical signs, in the first OECD TG 421 study (Anonymous, 2013c), findings such as underactivity, unresponsiveness, piloerection, partially closed eyelids or shallow and/or slow breathing were occasionally observed in the mid and high dose group in males and females, being reversible after the 6-hour exposure or before the end of the working day. Similar findings were reported in the OECD TG 413 study (Anonymous, 2013d) and, in the same way, they were transient and no deaths were documented. Consequently, we do not consider the narcotic effect as the cause of the deaths observed in the screening study since no deaths occurred in the subchronic study. Furthermore the narcotic effect in F0 males did not result in a poor clinical condition leading to death.

Second, regarding your considerations on body weight, food and water consumption and the "non-specific" parental general toxicity, it has to be noted that in the first OECD TG 421 study (Anonymous, 2013c), reductions in body weight gain were not accompanied by important decreases in mean body weights (<20% for males and <15% for females during the entire period and, specifically, 8.05% during the gestation period) and cannot be considered as a marked systemic toxicity. In this study, reductions in food consumption were also observed in males and females, being more evident in females during gestation and lactation. On the other hand, in the second OECD TG 421 inhalation screening study (Anonymous, 2014), no systemic effects were observed at lower doses.

For this reason, the decreases in body weight should not be regarded as a "dramatic reduction in absolute body weight" (as considered in the document) and the effects on sexual function and fertility or development were unlikely to be a secondary consequence of this toxicity. It is important to highlight that both fertility and developmental effects were noted at concentrations below the onset of marked parental toxicity.

In addition, despite the reductions in body weight were more pronounced in males, it should be mentioned that males did not show poor clinical condition in any of the studies reported beforehand. Indeed, a clear poor clinical condition was only reported in females during or shortly after pregnancy. This fact, together with the increase in the duration of gestation, is considered a clear sign of dystocia and therefore, the consideration for the classification as Category 1B is fulfilled, since the information available provides a "clear evidence of an adverse effect on sexual function and fertility in the absence of other toxic

effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of other toxic effects".

As described in the CLH report, in relation to the effects on sexual function and fertility, consistent effects were noted in the two OECD TG 421 studies, such as longer mean pre-coital interval and longer duration of gestation. Additionally, several adverse effects, such as longer estrous cycles, decreases in mating index, copulation plugs, sperm counts, fertility and gestation indices and number of implantations, and changes in male reproductive organ weights were clearly observed in the first study. We consider that all these effects show a clear evidence of adverse effects on sexual function and fertility that justify the classification as Repr. 1B (H360F).

On the other hand, 2-BTP shows a concern for development based on the reduction of post-natal survival with a clear dose-dependency. In addition, although the increase in the incidence of interventricular septal defect was only observed in the OECD TG 421 study (Anonymous, 2014), it is a severe developmental effect which occurred in the absence of systemic maternal toxicity and, consequently, it cannot be disregarded.

To sum up, we consider that there is enough information from the studies to classify the substance as Repr. 1B (H360FD).

RAC's response

Thank you for your comments. The answer of the DS is supported.
According to CLP guidance (ECHA, 2017): "*A detailed assessment of toxicity in pregnant animals cannot be extrapolated from studies with non-pregnant animals. However information from general toxicity studies might give an indication of the maternal toxicity that could be anticipated in a subsequent developmental toxicity study.*" This is particularly true for the acute toxicity studies (Anonymous, 2004 and 2013d), as there were performed via noose only exposure, unlike the reproduction/developmental toxicity screening test (Anonymous 2013c and 2014). Although the animals from the 13-weeks inhalation study (Anonymous, 2013d) were also full body exposed, the exposure duration was longer and do not correspond to the same protocol (5 days/weeks compared to 7 days/weeks for the reproduction/developmental toxicity studies). Please also note that females were untreated between GD20 and LD4 in Anonymous (2013c), and treated until GD20 only in Anonymous (2014). Therefore, the possibility that adverse effects on pups were due to indirect toxicity due to transient RTI and CNS effects and lack of maternal care seem less plausible.
Regarding the possibility that effects on reproductive parameters and development were mediated by stress and non-specific toxicity, RAC notes that both studies has been performed according to the OECD guidelines. Therefore, in absence of any mechanistic data to confirm or infirm any mode of action, the human relevance cannot be excluded and the effects are considered relevant for classification.

Date	Country	Organisation	Type of Organisation	Comment number
06.01.2023	United Kingdom	Labcorp Development SA (as OR registrant for the non-EU manufacturer)	Company-Manufacturer	6

Comment received

Labcorp does not support the CLH proposal for classification as Repr. 1B (H360FD) and supports the current self-classification as Repr. 2 (H361) to be the appropriate

classification.
Based on a review of the available information, there is no clear evidence of reproductive or development effects in the absence of other non-specific consequences and available interspecies and mechanistic information also raises question about the human relevancy of the effects observed.
There is not sufficient evidence for reproductive or development effects without other non-specific effects to support classification as 1B, based on parental general toxicity, non-specific toxicity, lack of consistency, mode of action and inter-species variability evaluations.
There is evidence of primary general non-specific toxicity that can secondarily affect reproduction and development that cannot be excluded. Since the evidence is not clear for Category 1B, the most appropriate classification is be Category 2 (H361: Suspected of damaging fertility or the unborn child).
A full justification in support of Cat. 2, including comments on specific areas of the CLH dossier, are given in the attachment titled "AMPAC_2BTP_Comments on CLH_Part 1". Please refer to this document for the full comments and arguments on the reproductive toxicity data and CLH dossier.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment AMPC_2BTP_Comments on CLH consultation_Parts 1 and 2 (Public attachement).zip
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment AMPAC_2BTP_Comments on CLH_Part 1 (Confidential).pdf

Dossier Submitter's Response

Thank you for your comments.

Please, see response to the previous Comment number 5.

RAC's response

Thank you for your comments. The answer of the DS is supported.

Date	Country	Organisation	Type of Organisation	Comment number
12.01.2023	France		MemberState	7

Comment received

FR has some comments:

Sexual function and fertility:
In the first OECD 421 reprotoxicity study (Anonymous 2013c), it was proposed: « NOAEC for fertility and reproductive effects was established below 198 ppm, based on reproductive effects observed in parental animals".

There are effects on sperm measurement at all doses (decreased sperm count in vaginal smear, increased abnormal sperm, decreased sperm velocity) and on sexual organ weights in male reproductive data (decrease of relative prostate weights) associated with macroscopic observation in prostate from the mid-dose (but not particular microscopic findings).
There are also significant increases of oestrus cycle length and of duration of gestation in females from the low dose (198 ppm) with a dose-related response. Effects were observed without maternal toxicity.

At the top dose, there is a decrease in fertility index (60%) and in gestation index (-

17%), with systemic toxicity (mortality, underreactivity, decreased body weight). It is noted that two females not mated present clinical signs, without further information in the report. It is not clear if this fertility index at the top dose can be due to the systemic toxicity.

The toxicity of the substance at the top dose (500 ppm) seems quite high (mortality, underreactivity, decreased body weight). Reproductive toxicity should be taken with caution at the top dose and analysed at the light of the general toxicity.

In the second OECD 421 reprotoxic study (anonymous 2014), there is a significant dose-related increase of the gestation length (days) for F0 females at the two highest doses (100 and 175 ppm) and a higher mean pre-coital interval at the top dose (175 ppm). The increase of the gestation length is consistent with the previous study. However, sperm effects are not found here. This may be explained by the lowest tested doses in this study compared to the previous one.

FR considers that this case is borderline between category Repro 1B and Repro 2 for fertility. Sperm effects were observed at all doses only in the first study and fertility effect occurs only at the top dose associated with general toxicity. This can tend to category 2. However, it is noted that although a drastic sperm alteration is needed to affect fertility in rodent, these effects on sperm are of particular relevance for (subfertile) humans. Effects on gestation length and on oestrus cycles are in favour of Repro 1B.

Development:
In the first study, there is a significant decrease of the total and live litter size from the low dose (198 ppm). The post-implantation survival decreased from the mid-dose (505 ppm). The decrease in body weight of the females during gestation is maybe due to fetal mortality rather than direct toxicity of the substance.

In the second study, there is also decreased offspring viability although no statistically significant. It is noted that the tested doses were lower than the previous study.

FR supports category Repro 1B for development.

Dossier Submitter's Response

Thank you for your comments and your support for the classification of the substance as Repr. 1B (H360D).

Regarding the classification for sexual function and fertility, in the OECD TG 421 study (Anonymous, 2013c) a decrease in the fertility index was observed at 2900 ppm because three females failed to mate. As stated in your comments, two of them showed apparent clinical signs (hunched posture and piloerection), but in the other one, no evidence of systemic effects was observed. Additionally, a fourth female successfully mated showed no evidence of pregnancy, in the absence of clinical signs. Considering that two dams showed clinical signs and the other two did not, we cannot clearly ensure that this decrease was clearly due to systemic toxicity. It is important to highlight that a non-statistically significant slight reduction in the fertility index is also observed at 198 ppm (90% *vs* 100 % in the control group) although no change occurs at 505 ppm.

In the same study, in addition to the effects on fertility index, reproductive effects such as longer mean pre-coital interval and longer duration of gestation were consistently observed at all doses tested and not only at the top dose.

We also would like to highlight that the clinical signs mentioned at the top dose (2900 ppm) were reversible after the daily 6-hour exposure or before the end of the working day. Additionally, the reduction in mean body weight gain was mainly observed in males, being less pronounced in females during gestation and lactation and was only accompanied by slight decreases in mean body weight values (<20% in males; <15% in females during the entire period).

In view of the observed effects, the 'poor clinical condition' reported in females seems to be clearly related to pregnancy at mid and top doses and was mainly observed prior to or around the delivery date. Additionally, an increase in the duration of gestation was observed at all doses tested, not only in the first OECD TG 421 study (Anonymous, 2013c) but also in the second one (Anonymous, 2014). Therefore, we conclude that the 'bad condition' is related to the suffering of the dams during the delivery period or shortly after and should not be considered as a systemic effect but a clear sign of dystocia. On the other hand, the 'poor condition' was not observed in males and none of them was sacrificed at any dose tested.

In addition, as described in the CLH report, consistent effects were noted in the two OECD TG 421 studies, such as longer mean pre-coital interval and longer duration of gestation. Additionally, several adverse effects, such as longer estrous cycles, decreases in mating index, copulation plugs, sperm counts, fertility and gestation indices and number of implantations, and changes in male reproductive organ weights were clearly observed in the first study.

Overall, clear evidence of toxicity on sexual function and fertility was demonstrated in both screening studies justifying the classification of 2-bromo-3,3,3-trifluoroprop-1-ene as Repr. 1B (H360F).

RAC's response

Thank you for your comments. The answer of the DS is supported.

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
09.01.2023	Germany		MemberState	8

Comment received

The DE CA agrees with the dossier submitter that a classification as STOT SE 3 (H335 and H336) is warranted for this substance because of respiratory tract irritation and narcotic effects observed in acute exposure studies as summarised in table 40 of the CLH proposal.

According to table 40: Summary table of animal studies on STOT SE, Anonymous, 2013d (OECD TG 413), a "NOAEC was established at 199 ppm based on the adverse effects observed related to chronic inflammation of the heart, transient clinical signs and histopathology changes related to irritation of the respiratory tract, lower body weight gain and food consumption and CNS effects (grip strength and motor activity)."

The test concentration could also be considered as LOAEC, because the chronic inflammation of the heart starts already at the lowest test concentration. Despite effects

being considered minimal, they occur in four out of ten animals and a clear dose-response is obvious. However, also a LOAEC of 199 ppm would be outside the guidance value range for STOT SE 2 classification for vapour inhalation (0.2 < C ≤ 1.0 mg/L/6 h/d; 0.0408 x 199 x 174.947 = 1424.34 mg/m³ = 1.424 mg/L). (https://cfpub.epa.gov/ncer_abstracts/index.cfm/fuseaction/display.files/fileid/14285)

In addition to the two acute exposure studies summarised in table 40, the OECD TG 421 study, Anonymous (2014), summarised in table 8, is suitable for STOT SE assessment with the single acute exposure group of 10000 ppm.

Dossier Submitter's Response

Thank you for your comments and support for the classification of the substance as STOT SE 3 (H335 and H336).

We appreciate your considerations regarding NOAEC and LOAEC.

In relation to the exposure group of 10000 ppm in the OECD TG 421 study (Anonymous, 2014), although data could be suitable for STOT SE assessment, they are not really "acute" exposure data. Indeed, as commented by you (see comment number 3), the duration of exposure is 5 min/d along the days of the study.

We think that information from this special group is well included at the end of Table 8 since it reflects observations included in the OECD TG 421 study. Therefore, we prefer not to repeat once again the findings in Table 40.

RAC's response

Thank you for your comments. Please note that NOAEC is not relevant for classification proposal.

Date	Country	Organisation	Type of Organisation	Comment number
12.01.2023	United Kingdom	Health and Safety Executive	National Authority	9

Comment received

STOT SE
We note that, in the OECD TG 403 acute inhalation toxicity study (Anonymous, 2004), there was 100% mortality at the top dose of 26580 ppm. Additionally, the top dose in this study exceeds the limit dose of 20 mg/L for vapours stated in Table 2, Appendix II of OECD GD 39. As STOT SE covers non-lethal specific target organ effects, we would question whether the effects seen on breathing and motor activity and the presence of nasal discharge and excessive salivation at this dose are relevant for STOT SE classification.
Additionally, the dose level of 5% v/v used in the supporting non-guideline acute inhalation toxicity study (Anonymous, 1999) was extremely high (equivalent to around 50,000 ppm, again exceeding the limit dose of 20 mg/L stated in Table 2, Appendix II of OECD GD 39). This dose exceeded the lethal dose used in Anonymous (2004), and it is likely that no deaths were reported due to the short observation period in this study (only 30 minutes). Were animals monitored for adverse effects after the end of the exposure period?
Lastly, we note that in the 90-day subchronic study (Anonymous, 2013d), transient clinical signs indicative of exposure to an irritant, such as 'shallow breathing, piloerection, grinding teeth and hunched posture' (page 48 of the CLH report) were observed during the 13-week exposure, along with potential central nervous system effects including

underactivity. Effects seen at the end of a 90-day subchronic study are not relevant for acute STOT SE classification. Does the DS have any further information on the extent of these effects at the beginning of the exposure period (i.e., after one or two exposures)?

Dossier Submitter's Response

Thank you for your comments.

First, in relation to the OECD TG 403 study (Anonymous, 2004), we agree with you that the effects observed at the top dose of 26580 ppm are not relevant for the classification of 2-BTP as STOT SE since it is a lethal dose that causes the death of all treated animals. Nevertheless, as it is described in section 10.11.1 of the CLH report, at 5173 ppm all animals survived to the end of the 14-day post-exposure observation period. Therefore, we consider that the effects observed at the low dose (i.e. clear or red nasal discharge noted immediately following the exposure and discolouration of the lungs due to vascular congestion) are relevant for classification.

Additionally, the information provided by the Industry indicates that in both dose groups during exposure, labored breathing or gasping were reported during the last hour of each exposure. Besides, following the exposures, clear or red nasal discharge, excessive salivation, labored breathing and moist rales were observed.

In relation to that study, we acknowledge that the above information is not clearly identified in Table 40 of the CLH report even though it is specified in the summary. Therefore, Table 40 should be updated to include the clinical signs observed in the low-dose group.

Second, regarding the non-guideline acute inhalation toxicity study (Anonymous, 1999) we would like to highlight that the information provided is scarce. We also agree with you that the dose was too high, but probably due to the very short exposure period of only 30 minutes, all animals survived. However, both relaxed breathing shortly after exposure and anesthesized appearance of animals for a few minutes were noted, and these observations are considered as relevant effects for the classification of 2-BTP as STOT SE 3.

In reply to your question on the monitoring of the adverse effects, we confirm that according to the available information from the Industry, animals were observed for a subsequent 2-hours post-exposure. Clinical signs such as relaxed breathing and apparent sedation were observed shortly after the exposure, returning to normal within 10-minutes post-exposure. In addition, the IUCLID file indicates that, approximately 2 hours after the end of the exposure period, the rats were sacrificed and a gross necropsy including the measurement of organ weights and gross observation were conducted (lungs, liver, heart, spleen, and kidneys).

Therefore, due to the fact that the clinical signs are similar to those observed in other studies, this information is considered as a part of the weight of evidence to support the classification as STOT SE 3.

Concerning the transient clinical signs associated with dosing observed in the OECD TG 413 study (Anonymous, 2013d), it is noted that they were observed at the beginning of the exposure period. Taking into account the individual data provided, mainly in the mid- and high-dose groups, these effects were observed from the first day of exposure and approximately two hours and four hours during exposure, not being observed one or two hours after completion of dosing or at the end of the working day.

Overall, we consider that all these data support the classification of the substance as STOT SE 3.

RAC's response

Thank you for your comment. The answer of the DS is supported.

Date	Country	Organisation	Type of Organisation	Comment number
12.01.2023	France		MemberState	10

Comment received

STOT SE3 H335 (RTI) or 336 (NE)

According to the CLH report, "the specific target organ toxicity (single exposure) of 2-BTP has been investigated in two acute inhalation toxicity studies (one key study study according to OECD TG 403 and a non-guideline supporting study) and in a subchronic inhalation toxicity study in SD rats".

Since effects from a 90-day study are used for this endpoint, it is not clear why results from the 2 OECD 421 studies are not also taken into account. In particular, a special acute exposure group was included in the second one.

Respiratory tract irritation (H335):
In the second OECD 421 study (2014), there was an acute exposure group (10000 ppm during 5 min). In this study, there was no effect on lungs weight. There were decreased respiration only the first day of exposure and red and/or clear material around the mouth and/or nose noted for both sexes at 15 minutes and/or 1 hour following exposure. No similar clinical effects were reported at other concentrations in the main study and neither in the first OECD 421 study at higher concentrations.

In the OECD 403 study (2004), there were laboured breathing and red nasal discharge reported at 26580 ppm. At this highest dose, all animals died by day 2-post-exposure. At the lowest dose, there was discoloration of the lungs due to vascular congestion.

In the 90-day inhalation (OECD 413) study, rats were exposed to 199, 505 and 2876 ppm. Clinical signs included shallow and slow breathing from 505 ppm. The lungs weights were significant increased from the mid dose for females only. Histopathological changes were observed in the nasal turbinates (atrophy/ disorganisation/ vacuolation of the olfactory epithelium and nasolacrimal duct inflammation) at the two highest doses. These effects occurred at doses that also induces lesions on different organs (heart, liver, pancreas, spleen, thymus).

Do you have information on irritative potential of the substance after dermal or eye contact?

Based on the multiple lesions reported in the 90-day study, have you considered the need for STOT RE classification rather than STOT SE?

Narcotic effects (H336):
In the acute inhalation studies (OECD 403), the only effect observed is a decrease of the motor activity, at the highest dose (26580 ppm), but all animals died by day 2 post-exposure.

In the OECD 413 study, there is underreactivity reported at all doses. Sensory reactivity was unaffected at all doses. Motor activity was significant statistically decreased from the mid dose (505 ppm).

Since the proposed classification is STOT SE, could you confirm that these effects started from the beginning of the exposure (and not due to repeated exposure)?

Moreover, these effects occurred altogether with lesions in several organs. From the low dose (199 ppm), there are effects on weights changes (thyroid) and histopathological changes (pancreas, heart, spleen) accompanied by biochemistry and haematology changes.

In the first OECD 421 study, the clinical signs such as underactivity and unresponsiveness are observed at all doses (from 198 ppm). These effects are occasionally observed and reversible after 6 hour exposure or before the end of the working day. These effects were not observed in the second OECD 421 study. However, in the special acute exposure group, hypoactivity was reported at 10 000 ppm only on the first day of exposure and resolved by 1 hour following exposure.

It is not clear if the effects reported on reactivity in all these studies are related to a toxicity to SNC or a general toxicity. According to CLP guidance, classification in category 3 is primarily based on human data, even if animal data can be included in the evaluation. Considering all these elements, FR questions if the effects reported in the experimental studies are sufficient to justify a classification.

Dossier Submitter's Response

Thank you for your comments.

First, we would like to note that not only the information from the OECD TG 413 study, but also the one from the OECD TG 421 studies (mainly from Anonymous, 2013c) have been taken into account for the classification of the substance as STOT SE 3. We did not consider it necessary to repeat the relevant effects from OECD TG 421 studies in Table 40 for STOT SE since they were included in Table 8. Even so, these effects are certainly part of the weight of evidence and have been discussed in section 10.11.1.

In respect of the 10000 ppm exposure group in the OECD TG 421 study (Anonymous, 2014), although data could be suitable for STOT SE assessment, they are not really "acute" exposure data (see our response to comment number 8).

Second, regarding your comments on the respiratory tract irritation (H335):

In relation to the acute inhalation toxicity study (Anonymous, 2004), the effects observed at the top dose of 26580 ppm are not relevant for the classification of 2-BTP as STOT SE since it is a lethal dose that causes the death of all treated animals. Nevertheless, the effects observed at 5173 ppm (clear or red nasal discharge noted immediately following the exposure and discolouration of the lungs due to vascular congestion) are relevant for classification (see our previous response to comment number 9).

On the other hand, we agree with your description of the effects reported in the OECD TG 413 study (Anonymous, 2013d). In this study, clinical signs generally resolved quickly on cessation of exposure to the test article. Following the 4-week recovery period, there was a complete recovery of test material-related histopathological changes seen in the liver, pancreas, heart, thymus, larynx and teeth and partial recovery for the findings seen in

the spleen (only two males at the high dose showed minimal capsular inflammation and/or slight thickening and only one female showed minimal thickening) and nasal turbinates (minimal to slight atrophy/disorganisation/vacuolation of the olfactory epithelium in nine males and seven females at the high dose).

Furthermore, studies related to the irritative potential of the substance after dermal or eye contact are included in the IUCLID file: an OECD TG 404 study (2012) and an OECD TG 405 study (2012). Both studies showed no evidence of corrosion or irritation in treated animals.

Therefore, taking into account the considerations above, we concluded that most of the effects observed were transient and those with partial recovery were of minimal or slight degree and do not justify the classification as STOT RE.

Third, regarding your comments on the narcotic effects (H336):

In the OECD TG 403 study (Anonymous, 2004) all animals died by day 2 post-exposure at the highest dose.

In the OECD TG 413 study, both underactivity, unresponsiveness and partially closed eyelids were observed at 505 and 2876 ppm (also in some animals at 198 ppm) from day 1 of exposure and, approximately 2 hours or 4 hours during exposure, but were not recorded 1 to 2 hours after completion of dosing or as late as possible in the working day. These effects were observed in both sexes and no deaths were reported. Thus, in the CLH report (page 48) we state that "*in the subchronic toxicity study (Anonymous, 2013d), possible effects on the central nervous system (underactivity and partially closed eyelids) were evident from the beginning of the exposure"*.

In addition, in the OECD TG 421 study (Anonymous, 2013c), transient clinical signs such as underactivity and unresponsiveness were observed, after the first days of daily 6-hour exposure, at all doses tested (2900, 505 and 198 ppm) and hypoactivity was reported at 10000 ppm, only on the first day of exposure and resolved by 1 hour following exposure.

Regarding your consideration of whether this reactivity is due to systemic toxicity rather than an effect on SNC, in the OECD TG 403 study (2004), effects on motor activity were seen in absence of general toxicity. Furthermore, in the 90-day repeated dose toxicity study (Anonymous, 2013d), as already mentioned, underactivity, unresponsiveness and partially closed eyelids were reported from the first days of exposure. In addition, a decrease in motor activity was observed in both high beam and low beam throughout most of the 1-hour recording period during week 12 of treatment, mainly at the dose of 2876 ppm and in some periods at 505 ppm. However, during the 4-week recovery period these effects return to normal values. Finally, in relation to general toxicity, the decrease in the weight of certain organs is not relevant because it returned to normal values during the recovery period, and the macroscopic effects observed (adhesions or thickening in the spleen) returned to similar values to those observed in the control group in the recovery period. Something similar happened with histopathology and haematology findings so, from our point of view, it cannot be considered that the effects on the CNS were due to systemic toxicity.

In general, as established in point 3.8.1.3 of the CLP regulation, the adverse effects considered for classifying the substance as STOT SE can be: "*adverse health effects produced by a single exposure, include consistent and identifiable toxic effects in humans, or, in experimental animals, toxicologically significant changes which have affected the*

function or morphology of a tissue/organ, or have produced serious changes to the biochemistry or haematology of the organism, and these changes are relevant for human health".

In particular, although classification in Category 3 for respiratory tract irritation is primarily based on human data, point 3.8.2.2.1(d) of the CLP Regulation states the following: "*there are currently no validated animal tests that deal specifically with RTI, however, useful information may be obtained from the single and repeated inhalation toxicity tests. For example, animal studies may provide useful information in terms of clinical signs of toxicity (dyspnoea, rhinitis, etc) and histopathology (e.g. hyperemia, edema, minimal inflammation, and thickened mucous layer) which are reversible and may be reflective of the characteristic clinical symptoms described above. Such animal studies can be used as part of weight of evidence evaluation".*

In a similar way, for classifying substances as Category 3 for narcotic effects: "*narcotic effects observed in animal studies may include lethargy, lack of coordination, loss of righting reflex, and ataxia. If these effects are not transient in nature, then they shall be considered to support classification for Category 1 or 2 specific target organ toxicity single exposure".*

To conclude, from our point of view and taking into account these considerations, animal data can therefore be used to classify the substance as STOT SE. In this case, there is enough information to consider these findings as acute and transient effects and, consequently, to classify the substance as STOT SE 3 (H335 and H336).

RAC's response

Thank you for your comment. The answer of the DS is supported.

Date	Country	Organisation	Type of Organisation	Comment number
06.01.2023	United Kingdom	Labcorp Development SA (as OR registrant for the non-EU manufacturer)	Company-Manufacturer	11

Comment received

We support the proposed harmonised classification for STOT SE3 (H335 and H336) and this is in line with the current self-classification.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment AMPC_2BTP_Comments on CLH consultation_Parts 1 and 2 (Public attachement).zip
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment AMPAC_2BTP_Comments on CLH_Part 1 (Confidential).pdf

Dossier Submitter's Response

Thank you for your comments and support for the classification of 2-BTP as STOT SE 3 (H335 and H336).

RAC's response

Thank you for your comment. The answer of the DS is supported.

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON 2-BROMO-3,3,3-TRIFLUOROPROP-1-ENE

PUBLIC ATTACHMENTS
1. umlaut Statement ECHA_incl attachments_20230112.pdf [Please refer to comment No. 2, 5]
2. AMPC_2BTP_Comments on CLH consultation_Parts 1 and 2 (Public attachement).zip [Please refer to comment No. 1, 6, 11]

CONFIDENTIAL ATTACHMENTS
1. AMPAC_2BTP_Comments on CLH_Part 1 (Confidential).pdf [Please refer to comment No. 1, 6, 11]