MINISTERIO
DE SANIDAD

SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

2-bromo-3,3,3-trifluoroprop-1-ene (2-BTP)

EC No 627-872-0

CAS No 1514-82-5

Evaluating Member State: Spain

Dated: 22 July 2020

Evaluating Member State Competent Authority

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Year of evaluation in CoRAP: 2019

Member State concluded the evaluation without any further need to ask more information from the registrants under Article 46(1) decision.

Further information on registered substances here:

http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

DISCLAIMER

This document has been prepared by the evaluating Member State as a part of the substance evaluation process under the REACH Regulation (EC) No 1907/2006. The information and views set out in this document are those of the author and do not necessarily reflect the position or opinion of the European Chemicals Agency or other Member States. The Agency does not guarantee the accuracy of the information included in the document. Neither the Agency nor the evaluating Member State nor any person acting on either of their behalves may be held liable for the use which may be made of the information contained therein. Statements made or information contained in the document are without prejudice to any further regulatory work that the Agency or Member States may initiate at a later stage.

Foreword

Substance evaluation is an evaluation process under REACH Regulation (EC) No. 1907/2006. Under this process the Member States perform the evaluation and ECHA secretariat coordinates the work. The Community rolling action plan (CoRAP) of substances subject to evaluation, is updated and published annually on the ECHA web site[1].

Substance evaluation is a concern driven process, which aims to clarify whether a substance constitutes a risk to human health or the environment. Member States evaluate assigned substances in the CoRAP with the objective to clarify the potential concern and, if necessary, to request further information from the registrant(s) concerning the substance. If the evaluating Member State concludes that no further information needs to be requested, the substance evaluation is completed. If additional information is required, this is sought by the evaluating Member State. The evaluating Member State then draws conclusions on how to use the existing and obtained information for the safe use of the substance.

This Conclusion document, as required by Article 48 of the REACH Regulation, provides the final outcome of the Substance Evaluation carried out by the evaluating Member State. The document consists of two parts i.e. A) the conclusion and B) the evaluation report. In the conclusion part A, the evaluating Member State considers how the information on the substance can be used for the purposes of regulatory risk management such as identification of substances of very high concern (SVHC), restriction and/or classification and labelling. In the evaluation report part B the document provides explanation how the evaluating Member State assessed and drew the conclusions from the information available.

With this Conclusion document the substance evaluation process is finished and the Commission, the Registrant(s) of the substance and the Competent Authorities of the other Member States are informed of the considerations of the evaluating Member State. In case the evaluating Member State proposes further regulatory risk management measures, this document shall not be considered initiating those other measures or processes. Further analyses may need to be performed which may change the proposed regulatory measures in this document. Since this document only reflects the views of the evaluating Member State, it does not preclude other Member States or the European Commission from initiating regulatory risk management measures which they deem appropriate.

[1] http://echa.europa.eu/regulations/reach/evaluation/substance-evaluation/community-rolling-action-plan

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Part A. Conclusion

1. CONCERN(S) SUBJECT TO EVALUATION

2-Bromo-3,3,3,-trifluoroprop-1-ene (2-BTP) was originally selected for substance evaluation in order to clarify concerns about:

- CMR/suspected R
- Potential ED (HH)

During the evaluation no other concern was identified.

The evaluation of 2-BTP was targeted at human health endpoints.

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

In December 2019 ECHA adopted a decision on compliance check for this substance asking for additional information regarding environmental endpoints.

3. CONCLUSION OF SUBSTANCE EVALUATION

The evaluation of the available information on the substance has led the evaluating Member State to the following conclusions, as summarised in the table below.

Table 1

CONCLUSION OF SUBSTANCE EVALUATION	
Conclusions	**Tick box**
Need for follow-up regulatory action at EU level	**X**
Harmonised Classification and Labelling	**X**
Identification as SVHC (authorisation)	
Restrictions	
Other EU-wide measures	
No need for regulatory follow-up action at EU level	

2-BTP was originally selected for substance evaluation since the hazard and exposure information on the substance showed a potential risk to human health related to CMR (Suspected R) and potential ED (HH) properties.

Regarding hazard, the available information shows that the substance causes adverse effects on reproduction, potentially leading to impairment of sexual function and fertility and on development.

The hazard is derived from two GLP-compliant OECD TG 421 inhalation reproductive/developmental toxicity screening studies in rats included in the registration dossier. Please, refer to section 7.9.7. for more detailed information.

The available information suggests that the adverse effects on reproduction may result from endocrine activity and therefore 2-BTP may have a potential endocrine disruption

mode of action. The findings concerning indications of higher pre-coital interval and gestation length, decreases in pituitary weight and lower postnatal survival, observed consistently in both OECD TG 421 screening studies, cause a concern for ED mode(s) of action.

Nevertheless, due to the differences in the adverse effects observed in both studies and to investigate a potential endocrine disruption mode of action, the preliminary intention was to ask for additional information. With this aim, a written consultation to the ED EG was launched in October 2019.

On the other hand, the substance was described to be used at industrial sites for refilling and maintenance of fire extinguishers and exceptionally by consumers in case of their emergency discharge. The exposure assessment included in the CSR was too generic and although exposure was low (RCR < 1), the substance fulfilled the exposure criteria for CoRAP inclusion.

In December 2019, during the 12-month substance evaluation period, the registrant has submitted an update of the registration dossier to ECHA. As a consequence of this dossier registration update, the initial conditions for inclusion of the substance in the CoRAP have changed.

In the updated CSR, there is only one use identified for this imported substance: Filling of hand-held fire extinguishers. The worker exposure scenario and its contributing scenarios were restructured including more detailed information describing OCs/RMMs. Filling operations are now described to take place within closed systems. The conditions of use now described permit the refinement of the exposure assessment to a level significantly lower. The registrant has reported that there are only 'trace' exposures in filling operations. The new approach for exposure estimation results in a significant reduction of the highest RCR values (RCRs < 0.023).

In addition, the consumer exposure scenario description has also been improved. Fire extinguishers containing 2-BTP are considered high performance. According to the information reported by the registrant, the primary current use in Europe is for aviation fire protection, specifically on board aircraft from hand-held (portable) fire extinguishers where discharge occurrences are very low. Considering the information provided, no routine exposure is anticipated. Therefore, long-term exposure is not expected.

See Section 7.12. for more details on workers and consumers exposure scenarios.

Any request in SEv must be justified by existing hazard information and likelihood of exposure/emission (potential risk). The evaluating MSCA (the eMSCA) assessed the new information and concluded that the substance does not longer meet the exposure criteria for substance evaluation. Dossier update contains now new/revised information about exposure which removes the potential risk and thus the original concerns are not justified anymore.

Based on the available information, the eMSCA can conclude that there is sufficient evidence to consider that the substance causes adverse effects on reproduction, sexual function and fertility and development, meeting the criteria for classification as toxic for reproduction according to CLP Regulation.

If in future new uses are identified under REACH, or there are new registrants of this substance, authorities shall consider including the substance again in the CoRAP for obtaining the information which is considered important/necessary to clarify the remaining ED concern related to potential human exposure. In such a situation the registrant(s) are recommended to take note of these conclusions.

4. FOLLOW-UP AT EU LEVEL

4.1. Need for follow-up regulatory action at EU level

4.1.1. Harmonised Classification and Labelling

As indicated previously, adverse effects on both sexual function and fertility and development were noted in two OECD TG 421 studies. Effects show dose-dependency and are considered to be substance specific and adverse.

The CLP regulation criteria for classification as reproductive toxicants are as follows:

The classification in Category 1A (Known human reproductive toxicant) *"is largely based on evidence from humans"*.

The classification of a substance in Category 1B (Presumed human reproductive toxicant) *"is largely based on data from animal studies. Such data shall provide clear evidence of an adverse effect on sexual function and fertility or on development 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. However, when there is mechanistic information that raises doubt about the relevance of the effect for humans, classification in Category 2 may be more appropriate".*

Further, substances are classified in Category 2 (Suspected human reproductive toxicant), *"when there is some evidence from humans or experimental animals, possibly supplemented with other information, of an adverse effect on sexual function and fertility, or on development, and where the evidence is not sufficiently convincing to place the substance in Category 1. If deficiencies in the study make the quality of evidence less convincing, Category 2 could be the more appropriate classification. Such effects shall have been observed 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 the other toxic effects".*

In this way, the effects observed in the OECD TG 421 studies for 2-BTP (for details see Section 7.9.7. Toxicity to reproduction (effects on fertility and developmental toxicity)) are considered sufficient to meet the criteria for classification as Repr. 2 (H361df) according to CLP Regulation and might fulfill Repr. 1B (H360FD).

2-BTP is neither self-classified nor has a harmonised classification for its reproductive effects. Therefore, in accordance with CLP Art. 36, CLH was identified as the regulatory follow-up action at EU level for this substance.

In addition, it is noted that the substance is self-classified as STOT SE 3 (H335: May cause respiratory irritation) and STOT SE (H336: May cause drowsiness or dizziness).

Thus, a CLH dossier should be prepared proposing a new entry in Annex VI to CLP Regulation to address all relevant (self)classifications.

4.1.2. Identification as a substance of very high concern, SVHC (first step towards authorisation)

Not applicable.

4.1.3. Restriction

Not applicable.

4.1.4. Other EU-wide regulatory risk management measures

Not applicable.

5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

5.1. No need for regulatory follow-up at EU level

Not applicable.

5.2. Other actions

Not applicable.

6. TENTATIVE PLAN FOR FOLLOW-UP ACTIONS (IF NECESSARY)

Table 2

FOLLOW-UP		
Follow-up action	**Date for intention**	**Actor**
Harmonised classification and labelling. CLH proposal for inclusion in Annex VI to CLP	*2020*	*ES MSCA*

Part B. Substance evaluation

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

2-bromo-3,3,3-trifluoroprop-1-ene (2-BTP) was originally selected for substance evaluation in order to clarify concerns about:

- CMR/suspected R
- Potential ED (HH)

During the evaluation no other concern was identified.

The evaluation of 2-BTP was targeted at human health endpoints.

Table 3

EVALUATED ENDPOINTS	
Endpoint evaluated	**Outcome/conclusion**
Toxicity for reproduction	*Harmonised C&L process to be initiated.*

Endocrine disruption	*A potential ED MoA is suspected. A potential risk to human health based on combination of hazard and exposure information cannot be proven due to the lack of exposure.*

7.2. Procedure

Pursuant to Article 44(2) of the REACH Regulation, 2-BTP was included on the Community rolling action plan (CoRAP) for evaluation in 2019. The Competent Authority of Spain was appointed to carry out the evaluation.

The evaluation was first based on the data contained in the IUCLID dataset that was compiled on 19th March 2019, including the chemical safety report. Furthermore, a literature search was also carried out by the Spanish evaluating MSCA at the beginning of the evaluation procedure in March 2019.

The evaluation of 2-BTP was targeted at human health endpoints and focused on the grounds for concern that were included in the justification document for the inclusion of the substance in the CoRAP. However, all human health hazard endpoints were evaluated.

In December 2019 the registration dossier was updated. In the updated CSR, the worker exposure scenario and its contributing scenarios were restructured including more detailed information describing OCs/RMMs. In addition, the consumer exposure scenario description was also improved.

The evaluating MSCA assessed the new information and concluded that the substance does not longer meet the exposure criteria for substance evaluation. Consequently, the eMSCA has decided to conclude the SEV without asking for additional information.

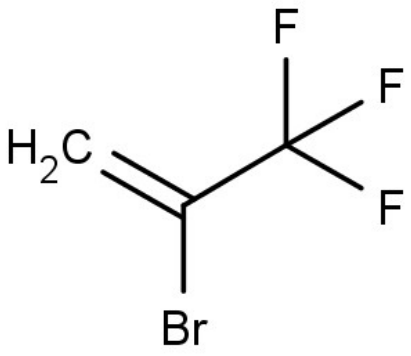
7.3. Identity of the substance

Table 4

SUBSTANCE IDENTITY	
Public name:	2-bromo-3,3,3-trifluoroprop-1-ene
EC number:	627-872-0
CAS number:	1514-82-5
Index number in Annex VI of the CLP Regulation:	n.a.
Molecular formula:	$C_3H_2BrF_3$
Molecular weight range:	174.947
Synonyms:	2-BTP AAWG Agent #873 Agent 873 BTP Halotron BrX NMERI Agent #873 Propene, 2-bromo-3,3,3-trifluro- 2-Bromo-3,3,3-trifluoropropene 3,3,3-Trifluoro-2-bromopropene Halon 1323 NSC 117350 2-bromo-3,3,3-trifluoroprop-1-ene

Type of substance ☒ Mono-constituent ☐ Multi-constituent ☐ UVCB

Structural formula:



7.4. Physico-chemical properties

Table 5

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES	
Property	**Value**
Physical state at 20 °C and 101.3 kPa	Liquid
Vapour pressure	82000 Pa at 25 °C
Water solubility	1 g/L at 20 °C
Partition coefficient n-octanol/water (Log Kow)	2.7 at 25 °C
Flammability	Not flammable.
Explosive properties	Predicted non-explosive, on the basis of a theoretical assessment.
Oxidising properties	Not oxidising on the basis of an assessment of the chemical structure.
Relative density	1.65 at 20 °C
Melting / freezing point	< -50 °C
Boiling point	34.4 °C at 1013 mbar
Flash point	No flashpoint observed below the boiling point.

7.5. Manufacture and uses

7.5.1. Quantities

Table 6

AGGREGATED TONNAGE (PER YEAR)				
☐ 1 – 10 t	☒ 10 – 100 t	☐ 100 – 1000 t	☐ 1000- 10,000 t	☐ 10,000-50,000 t
☐ 50,000 – 100,000 t	☐ 100,000 – 500,000 t	☐ 500,000 – 1000,000 t	☐ > 1000,000 t	☐ Confidential

2-BTP is manufactured outside the EU. According to the information from registration, the production volume imported to the EU is between 100-1000 tonnes per year.

7.5.2. Overview of uses

The substance is imported into the EU. It is described to be transferred to fire extinguisher cylinders via a closed system at dedicated facilities. The only possibility for consumers exposure is in case of their emergency discharge within an aircraft.

Table 7

USES	Use(s)
Uses as intermediate	
Formulation	Filling of hand-held fire extinguisher
Uses at industrial sites	
Uses by professional workers	
Consumer Uses	End use of fire extinguishers within the aviation industry: Emergency discharge of fire extinguishers within the aviation industry
Article service life	

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

No harmonised classification is available.

7.6.2. Self-classification

- In the registration(s):

STOT SE 3 (H335: May cause respiratory irritation)
STOT SE 3 (H336: May cause drowsiness or dizziness)

- The following hazard classes are in addition notified among the aggregated self-classifications in the C&L Inventory:

Not classified
Flam. Liq. 1 (H224: Extremely flammable liquid and vapour)
Self-react. F (H242: Heating may cause a fire)
Acute Tox. 4 (H302: Harmful if swallowed)
Acute Tox. 4 (H312: Harmful in contact with skin)
Acute Tox. 4 (H332: Harmful if inhaled)
Muta. 2 (H341: Suspected of causing genetic defects)
H319: Causes serious eye irritation
H315: Causes skin irritation

7.7. Environmental fate properties

2-BTP evaluation was targeted at human health and therefore, no environmental risk assessment has been carried out.

7.8. Environmental hazard assessment

2-BTP evaluation was targeted at human health and therefore, no environmental risk assessment has been carried out.

7.9. Human Health hazard assessment

7.9.1. Toxicokinetics

There is no specific toxicokinetic study performed with 2-BTP.

A toxicokinetic assessment was provided based on the physicochemical properties of the substance, the available data from an *in vitro* method to determine partition coefficients (Battelle, 2013), and the *in vivo* toxicological studies included in the registration dossier.

Accordingly, 2-BTP is readily absorbed via the lungs. Also it is considered likely that 2-BTP will cross the skin barrier, although dermal exposure will be limited by the compound volatility and boiling point close to body temperature. There is no available information regarding absorption via the oral route. Systemic distribution to liver, spleen, heart and reproductive organs in rats or dogs is supported by the toxicity studies and the partition coefficient values. Although no data are available on metabolism in the existing toxicity studies, histopathological changes in the liver observed in the subchronic toxicity study suggest some metabolic activity. Similarly there is no data on excretion; however, rapid excretion and a lack of bioaccumulation were supported by a post-exposure quick blood concentration decrease and a rapid recovery of the clinical signs observed in a study in dogs (Unnamed report, 2013a) as well as by its partition coefficient (Battelle, 2013).

7.9.2. Acute toxicity and Corrosion/Irritation

7.9.2.1. Acute toxicity

The acute toxicity of 2-BTP has been investigated via the inhalation route. No information regarding oral or dermal administration of the substance is available, since the registrant waived these information requirements based on the high volatility of the substance. 2-BTP is a liquid at room temperature, boiling at approximately physiological temperature (34 °C at 1013 mbar). Therefore, it is anticipated that under any foreseeable use conditions inhaled exposure will involve the substance in a vapour state.

In a well-conducted toxicity study included in the registration dossier as the key study (Unnamed report, 2004), a LC_{50} of 11726 ppm (= 83900 mg/m^3) was determined for 2-BTP following a 4-hour inhalation exposure in rats. On this basis the substance does not meet the classification criteria for acute toxicity according to the CLP Regulation.

However, inhalation exposure to 2-BTP appears to induce temporary depression of the central nervous system, noted by the decrease activity observed in the key study at the highest concentration tested, and the temporary anesthesia seen in the supporting study (Unnamed report, 1999). According to this, the registrant considered that a classification for specific target organ toxicity (single exposure), category 3 (H336: may cause drowsiness or dizziness) should be applied.

Based on the available information, the eMSCA can support these conclusions.

7.9.2.2. Irritation

2-BTP was evaluated for skin and eye irritation potential in both GLP studies according to OECD TG 404 (Unnamed report, 2012a) and OECD TG 405 (Unnamed report, 2012b) respectively. These *in vivo* key studies show that 2-BTP is neither a skin nor an eye irritant.

Despite the absence of a specific study to assess irritation of the respiratory tract, respiratory irritation was reported in the acute and subchronic toxicity studies by the inhalation route.

In the acute toxicity study (Unnamed report, 2004), clear or red nasal discharge were noted at the two concentrations tested immediately following the exposure to 2-BTP. Rats from both exposure levels had red discolorations of the lungs and fluid was present in the lungs of one male from the highest exposure level. Bronchiolar lesions with desquamated epithelium, bronchiolar/peribronchiolar acute/subacute inflammation were also observed at the highest dose level.

In the subchronic toxicity study (Unnamed report, 2013b), transient clinical signs (shallow breathing, piloerection, grinding teeth and hunched posture) related to inhalation of an irritant material were evident during and after exposure at the three exposure levels tested. Histopathological treatment-related changes were also observed in the nasal turbinates (findings related to minor local irritants) and larynx (ventral squamous metaplasia) at the two highest doses. Following the four-week recovery period, histopathological changes seen in the larynx were fully reversible but only partial recovery was seen in the nasal turbinates (atrophy/disorganisation/vacuolation of the olfactory epithelium and nasolacrimal duct inflammation).

Based on the irritation observed in the respiratory tract in the acute and subchronic studies, the substance is self-classified by the registrant as STOT SE 3 (H335: May cause respiratory irritation).

Based on the available information, the eMSCA can support these conclusions.

7.9.3. Sensitisation

There is no information available on the potential for 2-BTP to produce skin or respiratory sensitisation. A study waiver was submitted on the basis that 2-BTP is highly volatile and boils close to physiological temperature. According to this, the study was considered not technically feasible.

No information on potential human sensitisation is available.

Based on the physico-chemical properties of the substance, the eMSCA can support these conclusions.

7.9.4. Repeated dose toxicity

The effects of a repeated exposure to 2-BTP were examined in a subchronic inhalation toxicity study included in the registration dossier (Unnamed report, 2013b), performed according to OECD TG 413 and flagged as a key study.

2-BTP was administered to groups of ten Crl:CD (SD) rats per sex and dose level, using a whole-body exposure system, at aerosol concentrations of 0, 199, 505 and 2876 ppm, for

a period of 13 weeks (6 hours/day, 5 days/week). Ten male and ten female rats were additionally assigned to control and high dose groups and treated for 13 weeks followed by a four-week period to assess recovery from any treatment related effect.

Doses were selected based on the results obtained in a two-week dose range finding study, where three groups of rats were exposed to the substance at aerosol concentrations of 533, 1167 and 2980 ppm. These exposures resulted in transient clinical signs in all treated animals and histopathological changes in the nasal turbinates at the two highest doses tested, which was considered related to inhalation of an irritant material. Systemic effects such as reduced body weight gain or food consumption were also observed for all treated males, but not considered adverse.

In the main study, mortality was observed twice weekly and clinical signs of toxicity were observed weekly. Body weight measurements were performed throughout the study period. Ophthalmoscopic examination, haematology, clinical chemistry, urinalysis, neurobehavioral examination, organ weights, gross pathology or histopathology were performed as well.

During the study, treatment-related but transient clinical signs, related to inhalation of an irritant material, such as shallow breathing, piloerection, grinding teeth and hunched posture or possible CNS effects such as unresponsiveness to external stimuli, underactivity and partially closed eyelids, were observed during and after exposure at all dose levels tested.

A treatment-related decrease in body weight gain was observed in males and females dosed with 505 and 2876 ppm. Food consumption was reduced in a similar way for animals exposed to 2876 ppm. Evidence of recovery was observed in animals previously exposed to 2876 ppm, after the four-week recovery period.

Several haematological changes such as reductions in total white blood cell, lymphocyte and eosinophil counts were observed in rats exposed to the substance. Nevertheless, only the changes in total white blood cells were remained observed during the four-week recovery period.

Clinical chemistry showed statistically significant increases in mean alkaline phosphatase (ALP) and aspartate amino transferase (AST) values for animals exposed to the substance. However, during the four-week recovery period, these values were similar to those observed in control animals. Statistically significant increases in mean values of urea were observed for all treated females and for males exposed to 505 and 2876 ppm. During week 4 of recovery, these values return to control values for the highest dose tested. Additionally, statistically significant increases in mean phosphate values were observed in females exposed to all doses tested and in males exposed to 2876 ppm.

Statistically significant decreases in thymus weight were recorded for males and females exposed to 2876 ppm but with a full recovery after the four-week recovery period. Salivary glands weights were statistically significantly lower than control values for all treated females, with full recovery during the four-week post-exposure period. Lung and bronchi weights were slightly higher at 505 and 2876 ppm in male rats, with similar values at the highest dose after the four-week recovery period.

Gross pathology examination showed teeth pallor in all animals exposed to 2876 ppm, in the majority of animals exposed to 505 ppm and in a few animals exposed to 199 ppm. During the four-week recovery period this effect was seen in all animals previously exposed to 2876 ppm.

Spleen capsular thickening was reported in the majority of males and some females exposed to 2876 ppm and in a few animals at 505 ppm. Adhesions were also noted in some females at these two doses. During the four-week recovery period, the capsular thickening in the spleen was only observed in one male exposed to 2876 ppm and adhesions were noted in some males an one female at the same dose.

Histopathological examination indicated slight and moderate degrees of chronic inflammation in the heart for males at 199 ppm and for both sexes at 505 and 2876 ppm, considered by the study director only adverse for the two highest doses. Complete recovery

of this chronic inflammation was seen during the four-week recovery period. Authors highlight that these changes may be related to the elevated ALP and AST levels measured during week 13 of exposure, however the toxicological relevance of this finding is unclear.

In addition, histopathological changes related to treatment were also observed in liver (centrilobular hepatocyte hypertrophy), spleen (capsular inflammation and/or thickening and adhesions), thymus (involution/atrophy), nasal turbinates (atrophy/disorganisation/vacuolation of the olfactory epithelium and nasolacrimal duct inflammation), larynx (ventral squamous metaplasia) and teeth (pulp cavity necrosis) at 505 and 2876 ppm. Acinar cell degranulation of the pancreas was observed in all doses tested. The study director considered also in this case that changes at 199 ppm were not adverse. A complete recovery from changes observed in liver, pancreas, thymus, larynx and teeth occurred following the four-week period. This recovery was partial for the effects observed in the spleen and nasal turbinates.
Neurobehavioral examinations showed a statistically significant reduction in grip strength values for animals exposed to 2876 ppm and for males exposed to 505 ppm. During week 4 of the recovery period, a partial recovery was observed for animals previously exposed to 2876 ppm.

Motor activity scores (high and low beam) were reduced in animals exposed to 2876 ppm on week 13 of treatment. This effect, but to a lesser extent, was also observed at 505 ppm. A partial recovery was noted during week 4 of the recovery period.

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 registrant has established a NOAEC of 199 ppm for rats.

Based on the available information, the eMSCA can support this conclusion.

7.9.5. Mutagenicity

The mutagenicity of 2-BTP has been investigated in three *in vitro* test systems reported in the IUCLID file.

Results obtained in an *in vitro* bacterial reverse mutation assay showed that 2-BTP was not mutagenic in several *Salmonella typhimurium* strains and in *E.coli* strain WP2 uvrA, in the absence or presence of metabolic activation system (S9 mix).

Clastogenicity was not observed in an *in vitro* chromosome aberration test performed in human peripheral blood lymphocytes, with and without S9 mix.

Negative responses were also observed in a mouse lymphoma L5178Y assay both with and without exogenous metabolic activation.

Overall, based on the negative responses for genotoxicity (gene mutation in bacteria and mammalian cells) and clastogenicity (chromosome aberration) observed, it can be concluded that 2-BTP does not showed mutagenic potential *in vitro*. Based on the available information, the eMSCA can support this conclusion.

7.9.6. Carcinogenicity

No information available.

7.9.7. Toxicity to reproduction (effects on fertility and developmental toxicity)

The effect of 2-BTP on reproduction was assessed in two inhalation reproductive/developmental toxicity screening studies in SD rats.

7.9.7.1. Effects on fertility

A GLP reproduction/developmental toxicity screening test in Crl:CD (SD) rats, flagged in the IUCLID as supporting study was conducted with 2-BTP according to OECD TG 421 (Unnamed report, 2013c). A summary of the study results is included in Table 10.

The substance was administered, by whole-body inhalation exposure, to groups of 10 animals per sex and dose level, at aerosol concentrations of 0, 198, 505 and 2900 ppm (achieved chamber concentrations). Animals were exposed from 15 days before pairing to day 10 of lactation, 6 hours/day, 7 days/week. Animals of the F1 generation were indirectly exposed during gestation and lactation.

The selection of these concentrations was based on the results of two-week dose-range finding studies. It has to be noted that the target exposure levels considered for this screening study were the same as those used in the sub-chronic inhalation toxicity study. The high exposure concentration was selected to allow assessment of reproductive effects at an exposure concentration anticipated to produce evidence of systemic toxicity. Lower concentrations were chosen to assess any possible effect observed.

Offspring observations are included in section 7.9.7.2 for developmental toxicity.

At 2900 ppm, two females were sacrificed on day 24 after mating. One of these dams had partially closed eyes, hunched posture and piloerection and the other one had piloerection and perigenital staining. Both females were pregnant. In addition, the single dam with a live litter born at this exposure level was killed for reasons of animal welfare following total litter loss. At 505 ppm, five females and litters were sacrificed during lactation due to the poor condition of the offspring.

During the 6 hour exposure, clinical findings such as underactivity, unresponsiveness, piloerection, partially closed eyelids and shallow and/or slow breathing were observed in males and females at 505 and 2900 ppm. In addition, hunched posture was occasionally observed in females at 2900 ppm. These clinical signs were reversible after the 6 hour exposure.

At 198 ppm, underactivity, unresponsiveness, piloerection and partially closed eyelids were noted as well, being reversible at the end of the exposure period, even though authors have considered that these effects occurred at a much reduced incidence than that observed at the highest doses.

Lower mean body weight gain was observed in males at all doses tested throughout the study. In females, lower mean body weight gain was observed at 2900 ppm prior to paring, at 505 and 2900 ppm during gestation and at 198 and 505 ppm during lactation (at this stage, no bodyweights were recorded at 2900 ppm since no litters survived at this dose). In addition, lower food intake was observed in both sexes at all treated doses prior to pairing and in females during the gestation phase. During lactation this decrease was noted at 198 and 505 ppm (no litters survived at the highest dose). An increase in water intake was noted for females prior to mating and during gestation for all groups but decreasing during lactation at 198 and 505 ppm.

Statistically significant longer oestrus cycles (6 days or longer) with more females having irregular cycles or being acyclic were observed at 505 and 2900 ppm, compared to the control group. At 198 ppm regular cycles were observed but with a tendency to be longer than controls (5 days). Sperm measures showed statistically significant reductions in percent progressively motile sperm, sperm velocity, sperm count in the cauda epididymis and increases in BCF (Beat Cross Frequency) and in abnormal sperm (breakages and abnormal head shape) at the highest dose. Statistically significant reductions in sperm velocity and increases in abnormal sperm were observed at the mid dose. Additionally, a statistically significant increase in abnormal sperm and a statistically significant reduction in sperm velocity were reported at the low dose tested.

At 2900 ppm, effects on fertility such as longer pre-coital interval, fewer copulation plugs, lower sperm count in the vaginal smear, extended duration of gestation (25 days) with only one female littering on day 25 of gestation and lower implantation counts were noted. For this reason the gestation index was reduced to 17%, reflecting the single litter born. At 505 ppm, the same effects, but slightly less pronounced, were reported; in this case the duration of gestation was between 23 and 25 days. At 198 ppm, a shift to longer duration of gestation (23 days), a slightly lower sperm count in the vaginal smear and lower implantation counts were also observed.

Decreases in prostate (48%, 26%, 23%), seminal vesicles (29%, 30%, 17%), and pituitary (23%, 15%, 15%) weights, compared to control, were observed at 2900, 505 and 198 ppm, respectively. In addition, at the highest dose tested, reduced epididymis (13%) weight was also noted. All these decreases were statistically significant with the exception of seminal vesicles weight at 198 ppm.

Gross pathology revealed intergroup differences in the prostate, spleen, incisor teeth and skin. Small prostates were seen in all males exposed to 2900 ppm, in the majority of males exposed to 505 ppm and only in one male at 198 ppm. Effects on spleen were related to capsular thickening observed in the majority of males of the three doses tested and in occasional females at the two highest doses. Capsular adhesions were also observed in occasional treated males in all groups, in a few females at 2900 ppm and in one female at 505 ppm. Pale incisor teeth were noted in males and females at the two highest doses tested. An increase in the incidence of hair loss was observed in some males exposed to 2900 ppm.

Microscopic examination confirmed spleen capsular/subcapsular inflammation, capsular thickening and/or adhesions/inflammation/fibrosis in the majority of males treated at all doses tested and in a few females treated at 505 and 2900 ppm. It has to be highlighted that no microscopic examination of the spleen was performed in the control group. Reduced size of corpora lutea were observed in some females treated at 2900 ppm. No changes were observed in testes, prostate and epididymis.

A NOAEC for reproductive performance was considered to lie below 198 ppm based on male and female reproductive effects (effects on sperm and oestrous cycles and a longer duration of gestation) observed in parental animals.

Table 8. Summary of the adverse effects on reproductive toxicity (Unnamed report, 2013)

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels, duration of exposure	Results	Reference
Reproduction/ developmental toxicity screening test via inhalation (OECD 421) GLP: Yes Rat/Crl:CD (SD) 10 animals/sex/dose	BTP (no purity identified) Inhalation: vapour (Whole body) Concentrations: 0, 198, 505, 2900 ppm Exposure: from 15 days before pairing to Day 10 of lactation.	**F0 - Parental generation** <u>Mortality and general clinical observations</u> *198 ppm* Underactivity, unresponsiveness piloerection, and partially closed eyelids. Reversible at the end of the exposure period. *505 ppm* Five females sacrificed due to poor condition. Underactivity, piloerection unresponsiveness, partially closed eyelids, shallow and/or slow breathing Reversible after 6-hour exposure *2900 ppm* Two females sacrificed due to poor condition Underactivity, piloerection unresponsiveness, partially closed eyelids, shallow and/or slow breathing. Occasionally, hunched posture. Reversible after 6-hour exposure <u>Body weight, food and water consumption</u> *198 ppm* Males: ↓ Body weight gain throughout study Females: ↓ Body weight gain during lactation. ↓ Food intake. Females: ↑ Water intake prior to pairing and during gestation and ↓ during lactation *505 ppm* Males: ↓ Body weight gain throughout study Females: ↓ Body weight gain during gestation and lactation. ↓ Food intake. Females: ↑ Water intake prior to pairing and during gestation and ↓ during lactation. *2900 ppm* Males: ↓ Body weight gain throughout study	Unnamed report, 2013

		Females: ↓ Body weight gain prior to pairing and during gestation. ↓ Food intake. Females: ↑ Water intake prior to pairing and during gestation. <u>Oestrus cycle</u> *505 and 2900 ppm* Longer oestrus cycles (6 days or longer). <u>Sperm measures</u> *198 ppm* ↓ Sperm velocity, ↑ abnormal sperm. *505 ppm* ↓ Sperm velocity, ↑ abnormal sperm (breakages and abnormal head shape) *2900 ppm* ↓ Sperm motility, velocity and number in the cauda epididymis. ↑ BCF and abnormal sperm (breakages and abnormal head shape) <u>Reproductive performance</u> *198 ppm* ↓ Sperm count in the vaginal smear ↑ Duration of gestation (23 days) ↓ (Slight) mean number of implantations *505 ppm* ↑ (Slight) pre-coital interval ↓ Copulation plugs ↓ Sperm count in the vaginal smear ↑ Duration of gestation (23-25 days) ↓ (Slight) implantation counts. *2900 ppm* ↑ Pre-coital interval. ↓ Copulation plugs ↓ Sperm count in the vaginal smear ↑ Duration of gestation (only 1♀ littering) ↓ Gestation index (17%) ↓ Implantation counts. <u>Organ weights</u> *198 ppm* ↓ Prostate (23%), seminal vesicles (17%) and pituitary (15%). *505 ppm* ↓ Prostate (26%), seminal vesicles (30%) and pituitary (15%). *2900 ppm* ↓ Prostate (48%), seminal vesicles (29%), epididymis (13%) and pituitary (23%). <u>Gross pathology</u>	

		198 ppm Males: spleen capsular thickening and adhesions *505 ppm* Males: small prostates, spleen capsular thickening and adhesions, pale incisor teeth Females (occasionally): spleen capsular thickening and adhesions, pale incisor teeth. *2900 ppm* Males: small prostates, spleen capsular thickening and adhesions, pale incisor teeth. Females (occasionally): spleen capsular thickening and adhesions, pale incisor teeth. <u>Histopathology</u> *198 ppm* Spleen capsular/subcapsular inflammation, capsular thickening and/or adhesions/inflammation/fibrosis in majority of males. *505 ppm* Spleen capsular/subcapsular inflammation, capsular thickening and/or adhesions/inflammation/fibrosis in majority of males and occasional females. *2900 ppm* Spleen capsular/subcapsular inflammation, capsular thickening and/or adhesions/inflammation/fibrosis in majority of males and some females. ↓ Size of corpora lutea in some females. **F1 – Offspring** <u>Viability</u> *198 ppm* ↓ Mean number of implantations (slight). ↓ Post-implantation survival resulting in a lower total and live litter size. ↓ Group mean survival from birth to day 10 post-partum. *505 ppm* ↓ Mean number of implantations (slight). ↓ Post-implantation survival, live birth index and viability index, resulting in a lower total and live litter size. Number of offspring sacrificed due to poor condition. *2900 ppm* ↓ Mean number of implantations.	

		Only 1 female produced a litter showing ↓ post-implantation survival (25%) and ↓ birth index (33%) with only one pup alive and sacrificed due to poor condition. <u>Body weight</u> *198 ppm* ↑ Pup weight (slight) on PND 1. ↓ Bodyweight gain from days 1-10. *505 ppm* ↓ Bodyweight gain from days 1-10. <u>Gross pathology</u> *505 ppm* No milk in the stomach of the offspring died or sacrificed prior to day 10. **NOAEC for fertility and reproductive effects was established below 198 ppm, based on reproductive effects observed in parental animals.** **NOAEC for developmental effects in the offspring was established below 198 ppm due to lower implantation rate, higher post-implantation survival and viability indices leading to lower litter size.**	

The registrant considered that it was not possible to assess the toxicity of the substance solely to reproduction as toxic effects on the reproductive performance and development were accompanied by general parental toxic effects related partly to narcotic and irritant properties. Since this study was considered as inconclusive, another reproductive/developmental toxicity screening study at lower doses was performed. It has to be highlighted that systemic effects observed in this study are in line with those observed in the subchronic inhalation study.

The reproductive toxicity of 2-BTP was evaluated in an additional GLP inhalation reproduction/developmental toxicity screening test performed according to OECD TG 421 and reported as the key study in the IUCLID dossier (Unnamed report, 2014). A summary of the study results is included in Table 11.

2-BTP was administered daily, via the inhalation route (whole body exposure), to groups of 12 Sprague-Dawley rats per sex and dose level at concentrations of 0, 50, 100 and 175 ppm, 6 hour/day. A special acute 5-minute exposure group of 10000 ppm was included to mimic and assess the effects of a single maximum exposure in humans since the test substance is intended to be used as a fire extinguishing agent. In this group, males and females were observed 15 minutes and one hour following the acute exposure.

Offspring observations are included in section 7.9.7.2. for developmental toxicity.

During the study, no mortality occurred at any dose group after 2-BTP exposure. At 10000 ppm, clinical findings such as hypoactivity, decreased respiration, completely shut eyelids and lacrimation were observed only on the first day of exposure and were resolved by one hour following exposure. Additionally, salivation and red and/or clear material around the mouth and/or nose were noted for both sexes at 15 minutes and/or one hour following exposure. No clinical findings were observed in the other treatment groups.

Lower mean body weight gains were observed throughout the exposure period in males dosed with 10000 ppm, resulted in a lower mean body weight on day 28. Lower mean food consumption was also noted for this group during the pre-mating period. Both effects were considered test substance-related and adverse. Nevertheless the registrant has considered that, since this exposure level was intended to mimic and assess the effects of a single maximum exposure in humans, reduction in mean body weight gain only after 28 days of exposure would not be relevant to a single exposure scenario at the same exposure level. No effects were reported for females.

Lower mean body weight gain was also noted in males of the 100 and 175 ppm groups during the latter half of the exposure period (days 21-28) leading to a slightly lower mean body weight gains during the entire exposure period of 28 days. Although these effects were generally statistically significant they were not of sufficient magnitude to affect mean body weights, and therefore were considered non-adverse. For females, lower mean body weight gains were observed during gestation but only on days 0-4 and 11-14 and returning to normal values at the end of this period. Test substance-related, higher mean maternal water consumption was noted in females at 175 ppm throughout gestation, and was considered by the authors of the study as adverse.

Higher mean pre-coital interval and longer mean gestation length were observed in females at 175 ppm, compared to the control group. These effects were considered test-substance related and adverse. At 100 ppm, a longer mean gestation length was also noted and considered test substance-related but, since the value was within the range of historical control data, it was not considered as an adverse effect.

Statistically significantly lower pituitary weights (absolute and relative) were observed at 100 and 175 ppm in males and females but within historical control ranges.

Fertility, sperm measures, oestrus cycles, parturition, histopathology and gross pathology were unaffected by the treatment with 2-BTP.

In the IUCLID dossier, a NOAEC of 100 ppm was reported for female systemic and reproductive toxicity, based on the increase in mean water consumption, longer mean pre-coital interval and longer mean gestation length observed in the 175 ppm group. For male toxicity, the NOAEC was considered to be 175 ppm, based on the lack of adverse effects.

Table 9. Summary of the adverse effects on reproductive toxicity (Unnamed report, 2014)

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels, duration of exposure**	**Results**	**Reference**
Reproduction/ developmental inhalation toxicity screening test (OECD 421) GLP: Yes Rat/Sprague-Dawley 12 animals/sex/dose	BTP (no purity identified) Inhalation: vapour (Whole body) Concentrations: 0, 50, 100, 175 ppm Special acute exposure group: 10000 ppm Exposure: Males 14 days prior to mating and throughout the	**F0 - Parental generation** <u>Mortality and general clinical observations</u> No mortality at any exposure concentration. <u>Body weight and food consumption</u> *100 ppm and 175 ppm* Males: ↓ mean body weight gain on days 21-28 ($p < 0.05$). No changes in mean body weights therefore considered non adverse. <u>Water consumption</u> *175 ppm* ↑ Mean water consumption in females throughout gestation	Unnamed report, 2014

	mating period for a total of 28-29 days of exposure. Females 14 days prior to pairing and until gestation Day 20 (total of 35-46 days). Females that failed to deliver dosed through the day prior to euthanasia for a total of 52 days.	Reproductive performance *100 ppm* ↑ Mean gestation length. ↓ Pituitary weight. *175 ppm* ↑ Mean pre-coital interval and mean gestation length. ↓ Pituitary weight. *Acute exposure group (10000 ppm)* Hypoactivity, decreased respiration, completely shut eyelids, lacrimation in males and females only the first day of exposure. Salivation and red and/or clear material around the mouth and/or nose in males and females throughout 15 minutes and 1 hour post-exposure. Males: ↓ mean body weight gain throughout exposure period resulted in ↓ mean body weight on day 28. ↓ Mean food consumption on pre-mating period. Considered substance- related an adverse. **F1 – Offspring** Viability *100 ppm* ↓ Postnatal survival from birth to PND 4. Within the range of historical control data. *175 ppm* ↓ Postnatal survival from birth to PND 4. Below the range of historical control data Body weight *50, 100, 10000 ppm* ↑ Mean pup birth weights only on PND 1. No effects at 175 ppm. *175 ppm* Adverse increase in the incidence of interventricular septal defect. **NOAEC for systemic, fertility and reproductive effects was established at 100 ppm, based on increases in mean water consumption for females during gestation, longer mean pre-coital intervals and longer mean gestation length.** **NOAEC for the offspring was established at 100 ppm based on the reduced postnatal survival at 175 ppm.**	

Based on the information available, the eMSCA considers that several effects on sexual function and fertility were noted in the two screening toxicity studies. In the first study (Unnamed report, 2013c) longer oestrus cycles, longer pre-coital intervals, longer gestation lengths, abnormal sperm and decreases in weights of prostate, seminal vesicles and pituitary were observed, most of them at all doses tested. Systemic effects were clearly observed at the two highest doses. Although some similar effects were noted at the lowest dose, these occurred at much lower magnitude and were considered most likely not to be adverse. Furthermore, these slight effects at 198 ppm cannot account for the reproductive effects observed at this dose level.

On the other hand, some of the findings reported in the first OECD TG 421 were consistently observed in the second study (Unnamed report, 2014) at the two highest doses tested (only statistically significant at the high dose), i.e. lower pituitary weights, higher mean pre-coital interval and duration of gestation. In this case, no systemic effects were observed at any of the doses tested.

Consequently, the eMSCA concludes that there is a concern related to reproductive toxicity since common effects on both sexual function and fertility are noted in the two OECD TG 421 studies. These effects show dose-dependency (from low doses) and are considered to be substance specific and adverse in both male and female parental animals. In addition, the possibility of being a secondary non-specific consequence of generalised toxicity, although cannot be ruled out, does not seem likely, since reproductive effects were not always accompanied by generalized systemic toxicity.

7.9.7.2. Developmental toxicity

The developmental toxicity of 2-BTP was investigated in the screening tests mentioned above.

In the first inhalation reproduction/developmental toxicity screening test (Unnamed report, 2013c), F1 litters were indirectly exposed to the substance through their mothers who were dosed with aerosol concentrations of 198, 505 and 2900 ppm during pregnancy and until postnatal day (PND) 10.

At 2900 ppm, the mean number of implantations was reduced, compared to the control group (9.5 and 15.9, respectively). Only one female was able to produce a litter, showing low post-implantation survival (25%) and low birth index (33%), which led to only one pup being alive on PND 1. This pup was sacrificed due to poor condition. At 505 ppm, the mean number of implantations was slightly lower. Post-implantation survival, live birth index an viability index were lower, leading to a lower total and live litter size on PND 1 and lower litter size on PND 10, compared to the control group (8.3 vs. 14.7). In addition, a number of offspring was sacrificed due to poor condition (reduced activity and body temperature). Lower total and live litter size were also observed at 198 ppm, due to slightly lower mean number of implantations and post-implantation survival. Group mean survival from birth to PND 10 was also lower, primarily due to lower survival in two of nine litters.

Slight increase in pup weight was observed at 198 ppm only on PND 1. Nevertheless, body weight gain from PND 1 to PND 10 was slightly lower at 198 and 505 ppm, compared to controls. Only a slight difference in body weight was observed in the single female pup at 2900 ppm.

No macroscopic effects related to treatment were observed on the offspring sacrificed on PND 10. No milk in the stomach was frequently recorded in offspring which died or were sacrificed prior to PND 10, especially at 505 ppm.

A NOAEC below 198 ppm was established for developmental effects due to lower implantation rate, post-implantation survival and viability indices leading to lower litter size.

In the key screening study (Unnamed report, 2014) F1 pups were also indirectly exposed during gestation and lactation to doses of 50, 100, 175 and 10000 ppm of 2-BTP, until PND 4.

Lower postnatal survival was observed at 100 and 175 ppm from birth to PND 4, compared to the control group. Only at 175 ppm, values were below historical control data and for this reason, considered adverse.

Higher mean pup birth weights were noted for both sexes on PND 1 in the 50, 100 and 10000 ppm groups. However, pup body weights on PND 4 and mean body weight gains during PND 1-4 were similar to the control group. For this reason it was not considered as an adverse effect. Overall, no relevant effects were detected on body weights and body weight gains.

Mean number of pups born, pup sex ratio and live litter size were unaffected by 2-BTP exposure of parental animals.

Necropsy of pups that were found dead at 175 ppm, showed a substance-related and adverse increase in the incidence of an interventricular septal defect (1 or 2 mm in diameter opening in the anterior portion of the septum). At 100 ppm, this effect was also observed in a single pup eventhough postnatal survival was within the historical control ranges.

For developmental toxicity, a NOAEC of 100 ppm was established in this study based on the reduced postnatal survival noted in the 175 ppm group.

It has to be highlighted that a review of the available data was made by the US EPA New Chemical Programme (NCP). In this evaluation the appropriateness of the NOAEC of 100 ppm selected by the registrant was questioned, taking into account the reduced post-natal survival rates from birth to PND 4 observed at 175 ppm but also at 100 ppm, and considering the use of the study's concurrent controls versus the Testing Facility historical control. A peer review of the concerns raised by the US EPA NCP was conducted by an expert (Raymond D. York) and included in the IUCLID registration dossier. In the conclusion of this evaluation it was considered that the reduced post-natal survival rate at 100 ppm was not an adverse effect taking into account the lack of concordance between this effect and other developmental findings, the absence of statistically significance, and that this reduction was within the historical control data of the testing facility.

Based on this information, the eMSCA considers that a concern for development arises from the results obtained in the two screening toxicity studies. Both studies showed a reduction in post-natal survival with clear dose-dependency. In the first study (Unnamed report, 2013c), the effect was observed at the two highest doses, in the presence of generalized systemic toxicity, but not at the lowest dose. In the second study (Unnamed report, 2014), a statistically decrease in postnatal survival from birth to PND 4 was observed at 175 and 100 ppm in absence of systemic toxicity, although the values in the 100 ppm group were within historical control data.

Additionally, the increase in the incidence of interventricular septal defect reported at 175 ppm in the absence of systemic toxicity, may be an indication of a developmental effect of 2-BTP. This finding was only investigated in the second screening study, being observed in five pups of 33 examined (2/10 litters). Therefore, the biological relevance of this effect cannot be confirmed.

Taking into account the effects observed in the two OECD TG 421 studies (the reduction in post-natal survival and the increase in the incidence of interventricular septal defect, which is a severe malformation), the eMSCA considers that there is a concern for developmental toxicity. These effects show dose-dependency (from low doses) and are considered to be substance specific and adverse in both male and female parental animals. In addition, the possibility of being a secondary non-specific consequence of generalised toxicity, although

cannot be ruled out, does not seem likely, since reproductive effects were not always accompanied by systemic toxicity.

7.9.8. Hazard assessment of physico-chemical properties

There are some notifications in the C&L Inventory for the classification of 2-BTP because of its physico-chemical properties. Nevertheless, the substance is not self-classified in the registration dossier. Thus, it is considered that there are no indications for classification of 2-BTP with regard to physico-chemical properties. Therefore, the substance is considered of no concern for human health concerning physico-chemical properties.

7.9.9. Selection of the critical DNEL(s)/DMEL(s) and/or qualitative/semi-quantitative descriptors for critical health effects

For workers, long-term and acute (systemic and local for both cases) DNEL values have been derived by the registrant for the inhalation route of exposure. No DNELs have been derived for the dermal route on the basis that skin contact is not considered to present a hazard. DNEL values have been reassessed by the eMSCA.

A NOAEC of 100 ppm from the inhalation reproductive/developmental toxicity screening study is selected for the derivation of long-term, systemic effects DNEL value. A NOAEC of 0.49% (4900 ppm) from the cardiac sensitisation study has been used in the derivation of acute, systemic effects DNEL value. In addition a NOAEC of 199 ppm obtained from a sub-chronic inhalation study was used to derive the long-term and acute, local effects, DNEL values.

For the general population an acute, systemic DNEL for the inhalation route is derived based on Physiologically Based Pharmacokinetic Modelling (PBPK) using a LOAEC of 1% (10000 ppm) for cardiac sensitisation in dogs, equivalent to 71550 mg/m3.

Workers

Long-term, systemic effects

Occupational exposure to 2-BTP may occur via inhalation. Under normal working practices the oral and dermal routes would not be considered as significant routes of exposure, therefore, only DNELs for inhalation route has been derived.

Table 10

CRITICAL DNELS/DMELS - WORKERS					
Endpoint of concern	**Type of effect**	**Critical study(ies)**	**Corrected dose descriptor(s) (e.g. NOAEL, NOAEC)**	**DNEL/ DMEL**	**Justification/ Remarks**
Reproductive/ developmental toxicity study (Inhalation)	Systemic effects, long-term, inhalation	Reproductive/ developmental toxicity study (Inhalation)	NOAEC of 503.38 mg/m3	80.54 mg/m3	AF of 6.25 (other interspecies differences: 1.2; intraspecies differences: 5)

Acute/short-term, systemic effects

Based on the toxicological profile of 2-BTP, an acute DNEL for the inhalation route needs to be established. Acute, systemic effects were considered on the basis of a cardiac

sensitisation study rather than the available acute toxicity data, on the basis that the cardiac effects were seen at lower levels and following very brief exposure to 2-BTP.

Table 11

CRITICAL DNELS/DMELS - WORKERS					
Endpoint of concern	**Type of effect**	**Critical study(ies)**	**Corrected dose descriptor(s) (e.g. NOAEL, NOAEC)**	**DNEL/ DMEL**	**Justification/ Remarks**
Cardiac sensitisation study (inhalation)	Systemic effects, acute/short-term, inhalation	Cardiac sensitisation study (inhalation)	NOAEC of 23490.87 mg/m3	1879.27 mg/m3	AF of 12.5 (Intraspecies: 5; other interspecies: 2.5)

Long-term, local effects

Local effects following inhalation of 2-BTP were calculated on the basis of apparent respiratory irritation (histological changes in the nasal turbinates, larynx and teeth) seen even at relatively low levels in the 90-day repeated dose toxicity study by inhalation.

Table 12

CRITICAL DNELS/DMELS - WORKERS					
Endpoint of concern	**Type of effect**	**Critical study(ies)**	**Corrected dose descriptor(s) (e.g. NOAEL, NOAEC)**	**DNEL/ DMEL**	**Justification/ Remarks**
Repeated dose toxicity (inhalation)	Local effects, long -term, inhalation	Subchronic inhalation toxicity study	NOAEC of 954.68 mg/m^3	95.47 mg/m^3	AF of 10 (difference in the exposure duration: 2; Intrspecies: 5)

Acute/short-term, local effects

The starting point for derivation of the acute DNEL local effects following inhalation were the signs of respiratory irritation seen from the first exposure in the 90-day repeated dose inhalation study (therefore suggesting that the irritation may develop at this level, even over a short period of time such as a single exposure).

Table 13

CRITICAL DNELS/DMELS - WORKERS					
Endpoint of concern	**Type of effect**	**Critical study(ies)**	**Corrected dose descriptor(s) (e.g. NOAEL, NOAEC)**	**DNEL/ DMEL**	**Justification/ Remarks**
Repeated dose toxicity (inhalation)	Local effects,	Subchronic inhalation toxicity study	NOAEC of 954.68 mg/m^3	190.94 mg/m^3	AF of 5 (Intraspecies: 5)

	acute/short-term, inhalation				

General population

Acute/short-term, systemic effects

Consumer exposure to 2-BTP will be limited to the use of fire extinguishers, involving a single brief exposure by inhalation for up to five minutes. This acute/short-term exposure is expected to be an infrequent event and risk-related to long-term exposure is not expected.

No dermal exposure is considered because the end use of fire extinguishers involves the release of the substance as a liquid which rapidly evaporates and no significant skin contact is expected.

The hazard for acute systemic effects for 2-BTP is based on Physiologically Based Pharmacokinetic Modelling (PBPK) using measured arterial blood level concentration of 30.6 mg/L, to be the level at which cardiac sensitisation may be induced in dogs. These blood levels are reached at a concentration of 1% (10000 ppm) that is considered a LOAEC and is equivalent to 71550 mg/m^3. The limit acute exposure level for five-minute exposure was determined to be 0.95% by volume, equivalent to 67975 mg/m^3. See 7.12.1.2. for more detailed information on the PBPK modelling.

Table 14

CRITICAL DNELS/DMELS - GENERAL POPULATION					
Endpoint of concern	**Type of effect**	**Critical study(ies)**	**Corrected dose descriptor(s) (e.g. NOAEL, NOAEC)**	**DNEL/ DMEL**	**Justification/ Remarks**
Acute toxicity (inhalation)	Systemic effects, acute/short-term, inhalation	Cardiac sensitisation study (inhalation)	LOAEC 71550 mg/m^3	Other: 67975 mg/m^3	

7.9.10. Conclusions of the human health hazard assessment and related classification and labelling

After the evaluation of the information available on 2-BTP, it is concluded that the grounds for concern for human health are related to specific organ toxicity (single exposure), reproductive toxicity and potential endocrine disruption.

Exposure to 2-BTP appears to induce temporary depression of the central nervous system, noted by the decrease activity observed in the key acute toxicity study via the inhalation route (Unnamed report, 2004) at the highest concentration tested, and the temporary anesthesia seen in the supporting acute toxicity study by the same route (Unnamed report,1999). According to this, the registrant considered that a classification for specific target organ toxicity (single exposure), category 3 (H336: may cause drowsiness or dizziness) should be applied. The eMSCA considers these effects sufficient to meet the criteria for classification.

In addition, based on the irritation observed in the respiratory tract (nasal discharge, discolorations of the lungs, fluid in the lungs, bronchiolar/peribronchiolar acute/subacute inflammation) in the acute toxicity study (Unnamed report, 2004) additionally supported by those effects observed in the subchronic study (Unnamed report, 2013b) (histopathological treatment-related changes in the nasal turbinates and larynx) the substance is self-classified by the registrant as STOT SE 3 (H335: May cause respiratory irritation). The eMSCA considers these effects sufficient to meet the criteria for classification.

Based on the information available, the eMSCA considers that several effects on sexual function and fertility were noted in two screening OECD TG 421 studies (for details see Section 7.9.7. Toxicity to reproduction (effects on fertility and developmental toxicity)). In a first study (Unnamed report, 2013c) longer oestrus cycles, longer pre-coital intervals, longer gestation lengths, abnormal sperm and decreases in weights of prostate, seminal vesicles and pituitary were observed, most of them at all doses tested. Systemic effects were clearly observed at the two highest doses. Similar systemic effects were also noted at the lowest dose, but at much lower magnitude and, for this reason, they were considered most likely not to be adverse.

Some of these findings were consistently observed in a second study (Unnamed report, 2014) at the two highest doses tested (only statistically significant at the high dose), i.e. lower pituitary weights, higher mean pre-coital interval and duration of gestation. In this case, no systemic effects were observed at any of the doses tested.

Therefore, both studies showed common adverse effects on both sexual function and fertility and development. These effects show dose-dependency and are considered to be substance specific and adverse. In addition, the possibility of being a secondary non-specific consequence of generalised toxicity, although cannot be ruled out, does not seem likely, since reproductive effects were not always accompanied by systemic toxicity.

Consequently, the eMSCA concludes that these effects are considered sufficient to meet the criteria for classification as Repr. 2 (H361df) according to CLP Regulation and might fulfill Repr. 1B (H360FD).

2-BTP is neither self-classified nor has a harmonised classification for its reproductive effects. Therefore, in accordance with CLP Art. 36, CLH was identified as the regulatory follow-up action at EU level for this substance.

Thus, a CLH dossier should be prepared proposing a new entry in Annex VI to CLP Regulation.

7.10. Assessment of endocrine disrupting (ED) properties

7.10.1. Endocrine disruption – Environment

Not evaluated.

7.10.2. Endocrine disruption - Human health

The evaluation of the endocrine disrupting properties of the 2-BTP has been carried out considering all the available information for a weight-of-evidence analysis, in the context of the OECD Conceptual Framework (CF) for Testing and Assessment of Endocrine Disrupters (2012). This CF lists the OECD Test Guidelines and standardized test methods available that can be used to evaluate chemicals for endocrine disruption, establishing five appraisal levels:

Level 1: Existing data and non-test information.

Level 2: *In vitro* assays providing data about selected endocrine mechanism(s)/pathways(s).

Level 3: *In vivo* assays providing data about selected endocrine mechanism(s)/pathway(s).

Level 4: *In vivo* assays providing data on adverse effects on endocrine relevant endpoints.

Level 5: *In vivo* assays providing more comprehensive data on adverse effects on endocrine relevant endpoints over more extensive parts of the life cycle of the organism.

No information was available for the substance in the OECD QSAR toolbox. In addition, there are no OECD CF level 2 and 3 tests available. In this context, the registration dossier only includes studies corresponding to level 4, one subchronic inhalation toxicity study and two reproduction/developmental toxicity screening tests. These studies give limited but useful information on interaction with endocrine systems.

The subchronic inhalation toxicity study (OECD TG 413), although not validated for the detection of endocrine active substances, contains several endpoints suitable for the determination of endocrine effects. However, no effects related to endocrine-mediated endpoints were reported in this study (for more information see section 7.6).

On the other hand, although the OECD TG 421 is not designed to detect endocrine active substances, it includes endpoints relevant for the assessment of possible endocrine disruption. It has to be noted that this test guideline was updated in July 2016 to include some endocrine-relevant endpoints allowing a more comprehensive determination of endocrine effects. The screening tests available in the registration dossier were conducted before that date, so they do not include these extra parameters, such as anogenital distance and nipple retention. Even so, the original protocol is suitable for the determination of some endocrine effects.

Both screening tests available, extensively described in section 7.9.7, showed several adverse effects on fertility and development in rats, which could be related to the endocrine system. In the first one (Unnamed report, 2013c), higher pre-coital interval and gestation length was observed at the two highest doses tested. A shift to longer duration of gestation was also observed at the lowest dose. In addition, longer oestrus cycles, abnormal sperm, lower prostate and seminal vesicles weights, decreases in pituitary weight as well as lower postnatal survival and lower total and live litter size were also noted at all dose levels tested. In the second screening test (Unnamed report, 2014), common effects were observed at the two highest doses, i.e. higher pre-coital interval and gestation length, decreases in pituitary weight and lower postnatal survival, in absence of generalized systemic toxicity.

These findings give indications of endocrine-disrupting modes of action. However, due to the limitations of the OECD TG 421, no robust conclusions can be drawn to conclude about a concern for reproductive toxicity via endocrine disruption mechanism.

7.10.3. Conclusion on endocrine disrupting properties (combined/separate)

In the two reproduction/developmental toxicity screening tests, several adverse effects on fertility and development were reported, which could be related to an endocrine mode of action. However, the limited information provided by OECD TG 421 regarding the relatively small numbers of animals, the short duration of the study, and the selectivity of the endpoints do not allow to draw firm conclusions regarding the endocrine disrupting properties of the substance. In addition, the screening tests available in the registration dossier were performed in 2013 and 2014, according to the former OECD TG 421, and do not contain the sensitive endocrine endpoints included in the revised TG (2016).

7.11. PBT and vPvB assessment

2-BTP evaluation was targeted at human health and therefore no PBT/vPvB assessment has been carried out.

7.12. Exposure assessment

7.12.1. Human health

General

2-BTP is a clear liquid, with a faint yellow tint. It is a high volatile compound (vapour pressure of 82 kPa at 25 °C) with a boiling point of 34.4 °C at atmospheric pressure. It has a density of 1.65 g/cm^3 at 20 °C with moderate water solubility (1 g/L at 20 ºC). It is commercially available with purity higher than 97% (w/w).

It has been reported to be used as a fire protection agent. The international ban on the production of ozone-depleting halons has forced industry to search for new efficient fire suppressants with lower environmental impact (halon replacement agents). 2-BTP is considered as a new kind of halon replacement with application as a fire extinguishing agent in confined spaces (e.g. replacement of halon 1211). The substance has specific environmental properties (very short atmospheric lifetime and very low Ozone Depletion Potential (ODP) and Global Warming Potential (GWP) values). Accordingly, 2-BTP is not considered as a potentially significant contributor to stratospheric ozone depletion or global warming, or both.

2-BTP has been studied for several years as a streaming agent for possible development of aircraft portable extinguishers. Halotron BrX, which is the tradename for fire extinguishers containing stabilized 2-BTP, is described by industry to be an EN qualified and EASA certified product for use in aircraft cabins. 2-BTP is an EPA SNAP-approved extinguishing agent.

The substance is imported into the EU. The only use described that involves workers is filling of hand-held fire extinguisher units via a controlled closed systems at dedicated facilities. Consumer exposure may only happen in a rare emergency situation of discharge of the fire extinguishers within the aviation industry with short exposure duration.

Due to the high vapour pressure of 2-BTP, only the inhalation route has been considered by the registrant in the exposure assessment of the substance.

According to the registrant, no releases of 2-BTP to water, sediment, or soil are anticipated from the uses described, and the material is not released to Sewage Treatment Plants. The substance is highly volatile and any fugitive emissions or releases due to minor spillage during refilling and maintenance of extinguisher systems are expected to be airborne. On the other hand, end use of fire extinguishers involves the release of the substance as a liquid which rapidly evaporates so all expected emission at this stage is expected to be airborne as well. Additionally, the substance is not anticipated to present any hazard to predators on the basis that it has a low potential for bioaccumulation.

Therefore, indirect exposure through the environment is considered negligible.

The use areas described in the dossier are consistent with the information compiled during the literature search performed by the MSCA.

7.12.1.1. Worker

2-BTP is imported into the EU. Therefore, occupational exposure to the substance may potentially occur through inhalation during the use of the substance. According to the high vapour pressure of 2-BTP and its relatively high boiling point close to physiological temperatures, it is unlikely that significant dermal contact with the substance will occur. Oral exposure is assumed to be prevented by good hygiene practices.

According to the registration dossier, 2-BTP is only used by workers in activities involving the filling of fire extinguisher units via a controlled closed systems at dedicated facilities. Filling operations are described to occur from bulk containers to fire extinguishers in a filling station designed to control any trace of 2-BTP vapours released during the handling, through fitting connections/disconnections. On the other hand, filling of empty extinguishers requires additional steps (removal of any air or moisture contamination, helium pressurisation and leakage testing) prior to the introduction of 2-BTP. As the result of this testing stage, the registrant describes that the exposure to workers due to leakage from extinguishers will not occur under normal conditions of use. In addition, rigorous handling procedures including workers formally trained, wearing personal protective equipment and performing operations in controlled, well-ventilated areas are described.

The conditions of use described in the updated dossier are much more detailed and permit the refinement of the exposure assessment to a level significantly lower than the initial one. The Registrant have reported that there are only 'trace' exposures in filling operations. Modelled data have been reported by the registrant. Exposure has been estimated using ECETOC TRA v3 model. The new approach for exposure estimation results in a significant reduction of the highest RCR values (RCRs< 0.023).

External exposure by inhalation route has been reassessed in all scenarios by the Spanish evaluating MSCA. Exposure estimated values are similar to the ones calculated by the registrant.

7.12.1.2. Consumer

Fire extinguishers containing 2-BTP are considered high performance. Their use could be justified in areas where there are sensitive electronics, motors, and other high-value assets, such as in aviation. According to the information reported by the registrant, in Europe the primary current use is for aviation fire protection where discharge occurrences are very low, specifically on board aircraft from hand-held (portable) fire extinguishers.

The risk for consumers in case of emergency discharge of fire extinguishers has been estimated for acute exposures associated with potential hazard for cardiac sensitization.

The registrant uses a worst case EPA-approved PBPK model based on acute inhalation exposure to 2-BTP. This model was developed for halon alternatives used in fire suppression to determining safe egress times. A worst case scenario is used to determine the recommended conditions of use for a specific extinguisher (i.e. the minimum volume of an aircraft cabin or room in which an extinguisher may be safely used at 60 °C). These conditions for safe use are indicated in the label of the fire extinguisher. The exposure level derived from PBPK modelling is considered an acute exposure limit.

Regarding this consumer exposure scenario, we have to keep in mind that it may happen in a rare emergency situation of a fire within an aircraft and exposure duration would be as short as possible (not anticipated to last for more than five minutes). In this way, the registrant cited a study by Boeing showing that the probability of discharge of halon 1211 portables on any given flight is one in one million. On the other hand, during the use of 2-BTP to extinguish fires, the agent would interact with the fire producing combustion by-products with very little neat agent remaining out of 2-BTP originally discharged.

Due to no routine exposure is anticipated, long-term exposure is not expected

7.12.2. Environment

Not evaluated.

7.12.3. Combined exposure assessment

Not evaluated.

7.13. Risk characterisation

7.13.1. Human Health

2-BTP is only used by workers in activities involving the filling of fire extinguisher units via a controlled closed systems at dedicated facilities.

Consumer exposure is only considered in case of emergency discharge of the fire extinguishers within the aviation industry with short exposure duration.

Due to the high vapour pressure of 2-BTP, only the inhalation route has been considered by the registrant in the exposure assessment of the substance.

7.13.1.1. Workers

In the reported scenario, controlled closed systems complemented with rigorous handling procedures including workers formally trained, wearing personal protective equipment and performing operations in controlled, well-ventilated areas are described.

Exposure estimates and RCR provided in the updated CSR have been reassessed by the evaluating MSCA. In conclusion, under the conditions of use described by the registrant, exposure via inhalation is estimated to be very low and well below the respective DNELs.

7.13.1.2. Consumers

Consumers exposure may only happen in a rare emergency situation of discharge of the fire extinguishers within the aviation industry with short exposure duration. The risk in this case has been estimated for acute exposures associated with potential hazard for cardiac sensitization.

Due to no routine exposure is anticipated, long-term exposure is not expected.

7.13.1.3. Indirect exposure of humans via the environment

Indirect exposure through the environment is considered negligible.

7.13.2. Environment

7.13.3. Overall risk characterization

7.13.3.1. Human health (combined for all exposure routes)

Due to the high vapour pressure of 2-BTP, only the inhalation route has been considered by the registrant in the exposure assessment of the substance. Therefore, the same conclusions of section 7.13.1 are applied.

7.14. References

Battelle, Pacific Northwest Division, Battelle Project No. 64197 (2013). Determination of tissue to air partition coefficients for 2-bromo-3,3,3-trifluoropropene (Halotron BrX).

7.15. Abbreviations

AF	Assessment Factor
ALP	Alkaline phosphatase
AST	Aspartate amino transferase
BCF	Beat Cross Frequency
2-BTP	2-bromo-3,3,3-trifluoroprop-1-ene
bw	body weight / Bw, b.w.
CAS	Chemical Abstracts Service
CF	Conceptual Framework
CLP	Classification, Labelling and Packaging
CNS	Central Nervous System
CoRAP	Community Rolling Action Plan
CSR	Chemical Safety Report
DMEL	Derived Minimal Effect Level
DNEL	Derived No Effect Level
EASA	European Union Aviation Safety Agency
EC	European Communities
ECHA	European Chemicals Agency
ED	Endocrine disrupting
eMSCA	Evaluating Member State Competent Authority
EPA	Environmental Protection Agency
EU	European Union
GWP	Global Warming Potential
GLP	Good Laboratory Practice
HH	Human Health
IUCLID	International Uniform Chemical Information Database
IUPAC	International Union for Pure and Applied Chemistry
LC50	median Lethal Concentration
LD50	median Lethal Dose
LEV	Local Exhaust Ventilation
LOAEL	Lowest Observed Adverse Effect Level
MSC	Member State Committee
MSCA	Member State Competent Authority
NOAEC	No Observed Adverse Effect Concentration
NOAEL	No Observed Adverse Effect Level
OC	Operational conditions
OECD	Organisation for Economic Cooperation and Development
ODP	Ozone Depletion Potential
PBPK	Physiologically Based Pharmacokinetic Modelling
PBT	Persistent, Bioaccumulative and Toxic
PNEC	Predicted No Effect Concentration
PND	Postnatal day
PPE	Personal Protective Equipment
QSAR	Quantitative Structure Activity Relationship
RCR	Risk Characterisation Ratio
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RMM	Risk Management Measure
SEV	Substance evaluation
SNAP	Significant New Alternatives Policy
SVHC	Substances of very high concern
TG	Technical Guidance
UVCB	Unknown or variable composition, complex reaction products or of biological materials
vPvB	very Persistent and very Bioaccumulative
w/w	weight per weight ratio