Helsinki, 05 May 2020

Addressees
Registrants of butanone listed in the last Appendix of this decision (registrant(s)[1])

Decision/annotation number
[For the final decision] Please refer to the REACH-IT message which delivered this communication (in format SEV-D-XXXXXXXXXX-XX-XX/F)

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: Butanone
EC number: 201-159-0
CAS number: 78-93-3

DECISION ON SUBSTANCE EVALUATION

Based on Article 46(1) of Regulation (EC) No 1907/2006 (REACH), ECHA requests you to submit the following information on the Substance:

Developmental neurotoxicity study in rats, via inhalation route; test method OECD TG 426; including a Morris Water Maze test, as specified in Appendix 1.

Deadline to submit the requested information

Appendix 1: Section B.1 provides further details of how the deadlines were derived.

You have to provide an update of the registration dossier(s) containing the requested information, including robust study summary and, where relevant, an update of the chemical safety report by the deadline indicated below. In addition to the robust study summaries, you must submit the full study report for the developmental neurotoxicity study by the same deadline, by attaching it to the relevant endpoint study record in IUCLID.

The information required must be generated and provided by **15 May 2023** .

Appendices

The reasons of this decision and any further test specifications of the requirements are set out in Appendix 1. The procedural history is described in Appendix 2. Further information, observations and technical guidance as appropriate are provided in Appendix 3. Appendix 4 contains a list of registration numbers for the addressees of this decision. This appendix is confidential and not included in the public version of this decision.

[1] The terms registrant(s), dossier(s) or registration(s) are used throughout the decision, irrespective of the number of registrants addressed by the decision.

Who performs the testing?

Based on Article 53 of the REACH Regulation, you are requested to inform ECHA who will carry out the study/ies on behalf of all registrant(s) within 90 days. Instructions on how to do this are provided in Appendix 3.

Appeal

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, has to be submitted to ECHA in writing. An appeal has a suspensive effect and is subject to a fee. Further details are described under: http://echa.europa.eu/regulations/appeals

Authorised[2] by Christel Schilliger-Musset, Director of Hazard Assessment

[2] As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.

Appendix 1: Reasons

Based on the evaluation of all relevant information submitted on butanone and other relevant available information, ECHA concludes that further information is required to enable the evaluating Member State competent authority (MSCA) to complete the evaluation of whether the Substance constitutes a risk to human health.

The evaluating MSCA will subsequently review the information submitted by you and evaluate if further information should be requested in another decision to clarify the concern, according to Article 46(3) of REACH.

A.1 The potential risk – human health

The identification of a potential risk is based on a combination of exposure and hazard information.

According to the information in the registrations and publicly available information, the Substance is used as solvent in industrial processes, for extraction, manufacture of rubber and plastic and in products such as coatings, paints, paint removers, lacquers, cleaning agents, adhesives, lubricants and fuel. Significant exposure to workers and consumers cannot be excluded. Exposure may occur at the workplace or by using consumer products, via both inhalation and dermal route. Butanone has also been reported to be found in volatile release from building materials and consumer products and it has been detected in indoor and outdoor air and in drinking water and soil near waste sites (US EPA 2003A and 1990).

Based on information in the registration dossier(s) and information from the published literature as detailed below, there is a concern that the Substance may be a developmental neurotoxicant, according to the CLP Regulation (EC) No 1272/2008.

Based on this exposure and hazard information, there is a potential risk for workers and consumers. As the available information is not sufficient to conclude on the potential for developmental neurotoxicity, further information is needed, as explained below.

A.2 The possible risk management measures – human health

The results of the developmental neurotoxicity study will, amongst other relevant and available information, be used by the evaluating MSCA to assess whether the Substance should be classified as reproductive toxicant for development, Repr. Category 1B or 2, as defined in the CLP Regulation (EC) No 1272/2008. The evaluating MSCA will also assess whether the Substance should be proposed for identification as a substance of very high concern (SVHC) under Article 57(c) of REACH, which would lead to stricter risk management measures than those currently in place. The results could also lead to a lower DNEL.

The potential classification as Repr. Cat. 1B, would also have consequences for the classification of mixtures containing the Substance due to this classification's lower generic concentration limits for products and will have several effects according to EU downstream

legislation[3], leading to improved protection of workers and the public.

A.3 The concern(s) identified

Similar to several other aliphatic mono-ketones, butanone is a neurotoxicant. It has a harmonised classification as STOT SE3, H336 (may cause drowsiness or dizziness). Reported effects of butanone on the nervous system range from headaches, dizziness and anaesthetic effects following acute exposure, to a more complex pattern of toxicity, including cognitive and psychological impairment, subsequent to longer-term exposures (reviewed in Thompson, 2010 and 2011). The available information on neurotoxicity of butanone raises a substantial concern for developmental neurotoxicity (DNT). The physiology of brain development and experimental evidence suggest that developmental neurotoxicity is likely for most neurotoxicants (Grandjean 2006). Although intermittent, low level exposure to butanone seems to cause reversible effects in adults, foetal exposure effects can be qualitatively different and lead to permanent neurotoxicity at lower exposures, as shown for other neurotoxicants (Giordano and Costa, 2012; White and Proctor, 1997).

Placental transfer of butanone is supported by developmental toxicity studies, which show that it can interfere with the foetal development. In rodents in utero exposure to butanone is associated with developmental effects (Deacon et al., 1981). Further, higher concentrations of butanone have been found in the cord blood compared to the maternal blood, indicating a possible one-way transfer of the Substance to the foetus in human (Dowty et al., 1976).

The concern for developmental neurotoxicity of butanone is based on:

-Human data

Case reports and Epidemiological studies

-Animal data

Rat and zebrafish studies

Human data

Human data on butanone neurotoxicity is mainly from exposure via inhalation. Short-term exposure is generally considered to cause reversible Central Nervous System (CNS) depression, also referred to as a narcotic effect. Inhalation exposure to butanone causes headache at about 300 ppm and weakness and paraesthesia at 300-600 ppm. Exposure to higher levels leads to greater degree of nervous system depression, e.g. confusion and loss of coordination (Thompson 2011). A number of case reports and occupational studies indicate a more complex pattern of toxicity, with possible structural and functional impairment of the nervous system, subsequent to chronic exposure to butanone.

[3] ECHA guidance, Introductory Guidance on the CLP Regulation, v 3.0, section 21, p. 78-79, January 2019
https://echa.europa.eu/documents/10162/23036412/clp_introductory_en.pdf/b65a97b4-8ef7-4599-b122-7575f6956027

Case reports and Epidemiological studies

Available human information on butanone neurotoxicity has been reviewed previously, e.g. in the U.S. EPA toxicological assessment (U.S. EPA, 2003A) and it will only be summarised shortly here. A case report of exposure to butanone via both dermal and inhalation route, 2-3 h/day for 12 years described slurred speech, cerebral ataxia, sensory loss in arms and face and severe cerebellar and brainstem atrophy. A survey of the work area revealed peak butanone concentrations about 1695 ppm (5000 mg/m³) during some operations and 10-minute concentrations of approximately 305 ppm (900 mg/m³) (Seaton et al., 1992). In another report 7-month daily exposure to butanone and fumes from burning fiberglass material caused symptoms including severe chronic headaches, dizziness, memory loss, tremors and visual disturbances. The exposed person was diagnosed with chronic toxic encephalopathy and peripheral neuropathy (Callender et al., 1995). Information concerning the exposure levels and subsequent possible progression or regression of these conditions was not provided. In a third study a man developed multifocal myoclonus, ataxia and postural tremor after inhalation and dermal exposure over a 2-year period to solvents containing 100% butanone (Orti-Pareja et al., 1996). The actual exposure levels are unknown. The patient reported symptoms of dizziness, anorexia and involuntary muscle movement, beginning about 1 month prior to admission. Symptoms disappeared after one month of cessation of exposure and treatment.

Occupational studies are also available that have assessed workers chronically exposed to butanone (Freddi et al., 1982; Oleru and Onyekwere 1992; Mitran et al., 1997). Symptoms such as headache, muscular hypotrophy, decreased nerve conduction velocities, sleep disorders, memory difficulties and behavioural changes were among the symptoms reported to be associated with long-term exposure to butanone. Data from these studies also indicate that in psychological tests, butanone-exposed workers showed behavioural changes, such as emotional lability and low stress tolerance.

In their assessment, the U.S. EPA concluded that, the available human data is limited and provides equivocal evidence that repeated exposure to butanone increases the hazard for persistent neurological impairment. The identified limitations in the data were inadequate characterization of exposure, multiple solvent exposure and study design problems. The evaluating MSCA acknowledges that the existing information is inconclusive to address permanent neurotoxicity in adults. However, permanent neurotoxic damage in the adult is not a prerequisite for irreversible effects in the developing offspring (Grandjean et al., 2006; Sokol et al., 2003). Thus, the existing data on butanone neurotoxicity raise a concern for adverse effects on the developing nervous system.

Animal data

Read-across: You have proposed read-across to 2-butanol (EC 201-158-5), methyl isobutyl ketone (MIBK) (EC 203-550-1) and acetone (EC 200-662-2). The evaluating MSCA notes that overall, the toxicity profiles of butanone, acetone and MIBK and the corresponding alcohols 2-butanol and 2-propanol seem similar, with the nervous system, liver and kidney as the main target organs. In rodents and human 2-butanol is mainly converted to butanone and subsequently to common down-stream metabolites. MIBK and acetone are metabolised to similar breakdown products as butanone (Dietz et al., 1981; DiVincenzo et al, 1976; US EPA 2003C).

No acute inhalation toxicity study with butanone is provided. Data on acute oral toxicity is from read across to 2-butanol. In rats 2-butanol was shown to have low acute oral toxicity

with an LD_{50} of about 2000 mg/kg bw. At doses above 2000 mg/kg bw rats were comatose or prostrate within a few hours of dosing, with some being unconscious for 24 hours or more (registration dossier, 1986).

The registration dossier(s) for the Substance contain an inhalation sub-chronic study in which rats were exposed to 1254, 2518 and 5041 ppm butanone vapour for 90 days (Cavender et al., 1983). A transient depression in body weight gain and increased relative liver weights was seen at the high dose. High dose females had significantly decreased brain weights (abs 5%, rel 9%) without histopathology. Neurological function examination included in this study were assessment of posture, gait, facial muscular tone/symmetry and extensor-thrust reflexes. Neuropathological tests were examination of the sections of the medulla, sciatic nerve and teased fibers of the tibial nerve. These tests revealed no abnormalities. The evaluating MSCA notes that the behavioural neurological examinations were limited. The observed reduction in brain weight in rats should not be disregarded, despite lack of histopathology. The reported reduction of brain weight adds to the concern for developmental neurotoxicity.

In the registration(s) several prenatal developmental toxicity studies (OECD TG 414) with the Substance are provided. In these studies rats or mice were exposed via inhalation to up to 3000 ppm, (about 9000 mg/m^3) during gestation. At 3000 ppm butanone caused fetotoxicity, indicated by decreased foetal body weights and increased incidence of malformations, in presence of mild maternal toxicity. Thus, developmental toxicity (teratogenicity) was observed only at high doses. The standard OECD TG 414 does not investigate developmental neurotoxicity. No long-term toxicity study with the Substance is available. An oral two-generation reproductive toxicity study with 2-butanol shows high sensitivity (to nervous system effects) and death in new-born/young pups, after exposure to doses above 1700 mg/kg bw/d (Cox et al., 1975). This study has substantial limitations and many of the parameters relevant to developmental (neuro)toxicity, including adult brain weights and pup organ weight/histopathology were not examined. Thus, animal data on the long-term toxicity of butanone is inconclusive.

Butanone was included in a study to investigate the developmental effects of organic solvents in Zebrafish embryo and larvae from the 2-4 cell to 7 day post fertilisation (dpf) stage (Maes et al., 2012). Butanone exposure at 1 dpf induced microcephaly. Induction of microcephaly in zebrafish adds to the concern for DNT.

Data on neurotoxicity of MIBK and acetone has also been reviewed by the U.S. EPA (US EPA 2003B and C). In the MIBK evaluation it is indicated that CNS effects are reported in rodent sub-chronic studies. Inhalation developmental toxicity studies suggest that MIBK crosses the placenta and causes developmental effects. No human studies to address the relative sensitivity of children and adults or potential age-related differences in susceptibility to MIBK are available. Since no neurotoxicity studies of young animal are available and as the developing CNS can be more sensitive, there is a concern for developmental neurotoxicity (US EPA 2003B). Similarly, in the assessment of acetone it is stated that human and animal studies indicate neurotoxic effects that raise concern for DNT.

A recent review of the published literature on developmental neurotoxicity of butanols, including 2-butanol, concludes that available mechanistic data for the butanols support developmental neurotoxicity that has been observed in some rodent studies. However, further studies of the neurobehavior of developing pups in sensitive strains, as well as characterising the mechanisms involved, is needed to elucidate the neurodevelopmental

effects for risk assessment (Bale and Lee, 2016). The review indicates that unlike the more characterised shorter chain alcohols such as ethanol (generally accepted to cause developmental neurotoxicity following in utero exposure), the information on developmental neurotoxicity of butanols is extremely limited and there are no studies in humans that examine the potential for DNT.

A.4 Why new information is needed

Existing information for butanone and its similar substances is not sufficient to allow any definite conclusion on the specific hazard or dose response relation for developmental neurotoxicity. Compiled evidence suggests that the developing nervous system may be more and/or differentially susceptible to toxic insult, compared to the fully developed nervous system, e.g. exposure during certain time windows of development may be more critical than the total duration of the exposure for determining developmental outcome (Grandjean et al., 2006; Gennaro et al., 2012).

Based on the assessment of all available data, it is concluded that the information is not conclusive for classification as reproductive toxicant, for developmental neurotoxicity, category 1 or 2 and for proper risk management. Examinations of the structure and function of the nervous system in the neonatal and young pups, exposed during development would provide information to clarify the concern for DNT.

A.5 Considerations on the test method (OECD TG 426)

The study must be performed according to the OECD TG 426. The study must provide data on the potential functional and morphological effects on the developing nervous system. The evaluation must contain observations to detect neurologic and behavioural abnormalities, including the assessment of physical and sexual development, behavioural ontogeny, motor activity, motor and sensory function, learning and memory, brain weights and neuropathology. As the available information on neurotoxicity of butanone indicates a broad range of effects, sufficient examinations must be included to adequately cover a wide spectrum of structural and functional assessment of the nervous system during the entire developmental period.

For evaluating learning and memory the Morris Water Maze test must be performed to assess spatial learning, reference memory and cognitive flexibility (Vorhees et al., 2018). Additional available animals may be used for specific tests, e.g. neurobehavioral or neuropathological procedures, based on mechanism/mode-of-action (MoA). The MoA for neurotoxicity of butanone is not fully known. Butanone has been shown *in vitro* to disrupt the lipid micro-environment of cell membranes and thereby change the activity of membrane-bound proteins, such as receptors and signalling proteins (Huang et al., 1993). Due to its lipophilic nature the Substance can easily enter the lipid rich nervous tissue and cause damage. However, the MoA(s) for the effects caused by chronic exposure to butanone is not clear. Recent data suggests interaction with the cell adhesion molecule L1 CAM and Phospholipase D (PLD) and inhibition of fetal brain astroglial cell proliferation as potential mechanisms underlying developmental neurotoxicity of related substances (Bale and Lee 2016). However, the evidence and validated tests to assess these possible MoAs are currently limited.

Dosing

Because of the narcotic (CNS depressive) effects of the Substance, careful considerations

should be given to the study design, in particular selection of exposure route, dose and duration. Interruptions in the treatment should be avoided to the extent possible to obtain conclusive data.

Dose levels: dose levels should be set taking into account the existing data. Available data suggest that in particular neonatal pups may be more sensitive to the sedative effects of the Substance and that at doses where dam toxicity is observed pup mortality may occur (Cox et al., 1975). Therefore, to be able to conduct the study, doses should be set based on pup toxicity.

It is recommended to perform a range-finding study. According to the OECD TG 426, the range-finding study should determine the highest and lowest dose to be tested. The highest dose should not induce excessive offspring toxicity. The lowest dose should aim to not produce any developmental toxicity, including neurotoxicity. Dose levels should be selected to demonstrate any dose-related response and a No-Observed-Adverse Effect Level (NOAEL). It is proposed to include additional dose group(s) in the range finding study, if needed. The range-finding study should use the same type of inhalation exposure and administration conditions as those proposed for the main study.

In a prenatal-developmental toxicity study with butanone, decreased foetal body weight and/or malformation, in presence of mild maternal toxicity was reported at ≥3000 ppm. Data on long-term toxicity of butanone is limited. In an inhalation generational study with the analogue substance MIBK, signs of adult and neonatal CNS depression, occurring shortly after exposure, were reported at ≥1000 ppm. No pup mortality or other toxicity was reported at up to 2000 ppm until PND 21. The NOAEL for the neonatal and parental systemic effect in this study was 1000 ppm. However, signs of neonatal neurotoxicity was observed at about 500 ppm (lowest dose tested). Considering these data testing at up to about 2000 ppm is recommended.

Route of exposure: According to the OECD TG 426, the test substance should be administrated by the route most relevant to potential human exposure and based on available information on metabolism and distribution in the test animals. Accordingly, exposure via inhalation is requested based on the properties and the most relevant exposure route. Butanone is highly volatile. Human and animal data indicate that it is well absorbed following inhalation. Comparison of the concentrations in blood to alveolar air suggests rapid transfer from the lungs to the blood (Perbellini et al., 1984). Considering the possible human exposure patterns, exposure of both unborn (via mothers) and new-born offspring via inhalation is relevant and data is needed for proper risk assessment/management.

The main purpose of the study is determination and dose-response characterisation of effects on the developing nervous system of the offspring that may arise from exposure in utero and during early life, which are critical periods of nervous system development. Thus, ideally information on toxicity as a result of pre- and postnatal exposure should be obtained. Postnatal exposure, both direct via inhalation and "indirect" via lactation is considered relevant. In regard to classification, the purpose is primarily to clarify the hazard class reproductive toxicity for development, Repr, Category 1B, D or 2, d.

For the whole body inhalation studies the OECD Guidance Document 151 recommends simultaneous exposure of dams and pups. According to the OECD TG 426 if direct postnatal exposure of pups is not feasible, e.g. due to mortality, evidence of continuous (indirect) exposure shall be provided from e.g. pharmacokinetic information.

Duration of exposure: the test substance shall be administered daily from the time of implantation (GD 6) throughout lactation (PND 21). Dosing duration should ensure exposure during all early periods of brain development, i.e. equivalent to prenatal and early postnatal human brain growth.

In the reproductive toxicity studies with 2-butanol (oral) and MIBK (inhalation), young pups were shown to be highly sensitive to the sedative effects (Cox et al., 1975; Nemec et al., 2004). Decreased pup survival was reported during lactation in the study with 2-butanol (at ≥1700 mg/kg bw/d) and therefore treatment was interrupted to avoid mortality. In the study with MIBK pups at PND 22 (the first day of direct exposure) showed high sensitivity at ≥1000 ppm (exhibited signs of neurotoxicity, i.e. rocking while ambulating and being prostrate). Therefore, exposure was suspended through PND 27. Reasons for the higher sensitivity of young pups are unclear. As early post-natal exposure is critical for accurate assessment of effects on the nervous system development, treatment should be sustained during this period, but at doses that do not cause excessive toxicity. These dose levels shall be established in the dose range-finding study.

You must submit the full study report for the developmental neurotoxicity study as part of your dossier update. Considering the complexity of the case as described above, a complete rationale of test design and interpretation of results and access to all information available in the full study report with raw data collected, interpretations and calculations and consideration of uncertainties are needed. This will allow the evaluating MSCA to fully assess all the provided information and to efficiently clarify the concern.

A.6 Alternative approaches and proportionality of the request

The request for the developmental neurotoxicity test according to the OECD TG 426 is suitable and necessary to obtain information that will allow to clarify whether there is a potential risk for developmental neurotoxicity. More explicitly, there is no equally suitable alternative way available of obtaining this information.

It is noted that there is no experimental study available at this stage that will generate the necessary information and does not need to test on vertebrate animals.

A.7 Consideration of your comments on the original draft decision

You provided comments on the original draft decision. In your comments you agreed to perform the requested study and asked for further clarification on the design of the study, including clarification on the setting of dose levels and choice of the exposure route.

In regard to the dose level setting, you agreed to perform a range-finding study first. The decision has been revised to include information on the range-finding study, including clarification on the purpose of the study, e.g. to establish a NOAEL and that doses to be set based on pup (not dam) toxicity.

Regarding the route of exposure you considered "the whole-body inhalation would be an appropriate model for the potential exposure of workers and the general population and to establish if neurotoxicologial effects in pups are transient or irreversible". However, you raised the concern that exposing pups directly by inhalation, as well as via lactation would prevent separation of effects caused via lactation. Moreover, you indicated that pups are likely to receive a much higher dose than dams due to lower weight and thinner skin. You argued that the resulting NOAEL would be for total dose, not exposure via milk. Therefore

the result would not be useful for classification for effects via lactation. You requested clarification regarding the primary purpose of the study, to determine if the most appropriate exposure route is inhalation or oral and whether the main concern is effects of direct exposure of infants or effects on offspring due to parental exposure.

ECHA acknowledges your argument that the whole body exposure of neonatal pups may lead to excessive toxicity. To avoid this it is critical that a proper dose range is identified based on pup toxicity, in the range-finding study.

In regard to the purpose of the study, the decision has been revised to clarify. The main purpose is to detect any neurotoxicity as a result of *in-utero* or postnatal exposure (direct and indirect) and for hazard clarification for classification as a reproductive toxicant, for development, according to the CLH Guidance.

The evaluating MSCA does not agree with the alternative of performing the study via the oral route. Inhalation is relevant for human exposure, in particular for *in utero* exposure of the developing foetus (via pregnant mothers). There is no information to support that orally administrated substance would have the same kinetics as inhaled. Further, as direct exposure of pups can not be excluded, determining a NOAEL based on total exposure is more relevant than determining a NOAEL for lactation. Limiting the study to detect effects caused solely via lactation would not cover the critical period of *in utero* development.

The evaluating MSCA did not find the arguments to change the exposure route convincing to amend the request. The decision is however revised to clarify the reasoning for the choice of exposure route.

Additionally, you proposed inclusion of a group treated with another solvent that has demonstrated acute CNS effects and no indications of other neurotoxicity to "address concerns about link between acute CNS effects in dams and developmental neurotoxicity in pups".

The added value of including a group with another solvent is not clear. The requested study is *per se* insufficient to draw conclusions on mechanisms underlying toxicity, e.g. "links between acute CNS effects in dams and developmental neurotoxicity". Moreover, investigation of developmental neurotoxicity, in particular examination of functional outputs, e.g. behavioural effects is often complex. Unless tests to fully cover all potential effects are available for such a "control" solvent, limited conclusions can be drawn. Based on unclear added value and animal welfare considerations ECHA does not agree to inclusion of such a group.

B.1 Consideration of the time needed to perform the requested studies

The deadline for provision of the requested data takes into account the time that you may need to agree on which of the registrant(s) will perform the required tests (3 months is allocated for this) and include the time required for developing an analytical method, conduct of the study according to the OECD TG 426, preparation of the study report and reporting in IUCLID.

For the developmental neurotoxicity study, ECHA considers that 21 months is a sufficient time for conduct and reporting of the study.

In your comments to the original draft decision you requested an extension of 12 months to the 21 months deadline. You informed ECHA that you have identified one CRO that is able to conduct the OECD TG 426 test via inhalation. Based on the limited availability and capacity of the CRO you requested extension of the deadline. To justify your request you provided a certificate from the CRO with explanation of the situation and a time-plan, including a range-finding study. ECHA agrees to extend the deadline.

B.2 References

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Appendix 2: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of your registration after the end of the 12-month evaluation period.

On the basis of an opinion of the ECHA Member State Committee and due to initial grounds for concern relating to suspected reproductive toxicant, potential endocrine disruptor, wide dispersive use, consumer use, exposure of workers, exposure of environment, high (aggregated) tonnage and high RCR, butanone (CAS No 78-93-3, EC No 201-159-0) was included in the Community rolling action plan (CoRAP) for substance evaluation to be evaluated in 2018. The updated CoRAP was published on the ECHA website on 20 March 2018. The competent authority of Sweden (hereafter called the evaluating MSCA) was appointed to carry out the evaluation.

In accordance with Article 45(4) of the REACH Regulation, the evaluating MSCA carried out the evaluation of the above substance based on the information in your registration(s) and other relevant and available information.

In the course of the evaluation, the evaluating MSCA identified an additional concern regarding developmental neurotoxicty.

The evaluating MSCA considered that further information was required to clarify the concern for developmental neurotoxicity. Therefore, it prepared a draft decision under Article 46(1) of the REACH Regulation to request further information. It subsequently submitted the draft decision to ECHA on February 2019.

Registrant(s)' commenting phase

ECHA received comments from you and forwarded them to the evaluating MSCA without delay.

The evaluating MSCA took the comments from you, which were sent within the commenting period, into account and they are reflected in the reasons (Appendix 1). The request(s) and the deadline was amended.

Subsequently, the evaluating MSCA received proposal(s) for amendment to the draft decision and modified the draft decision. They are reflected in the reasons (Appendix 1).

ECHA referred the draft decision, together with your comments, to the Member State Committee.

ECHA invited you to comment on the proposed amendment(s).

Your comments on the proposals for amendment were taken into account by the Member State Committee.

MSC agreement seeking stage

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-69 written procedure and ECHA took the decision according to Article 51(6) of the REACH Regulation.

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EUROPEAN CHEMICALS AGENCY

Appendix 3: Further information, observations and technical guidance

1. This decision does not imply that the information provided by you in the registration(s) is in compliance with the REACH requirements. The decision neither prevents ECHA from initiating compliance checks on your dossier(s) at a later stage, nor does it prevent a subsequent decision under the current substance evaluation or a new substance evaluation process once the present substance evaluation has been completed.

2. Failure to comply with the request(s) in this decision, or to otherwise fulfil the information request(s) with a valid and documented adaptation, will result in a notification to the enforcement authorities of your Member State.

3. In relation to the required experimental study/ies, the sample of the substance to be used ('test material') has to have a composition that is within the specifications of the substance composition that are given by all registrant(s). It is the responsibility of all the registrant(s) to agree on the tested material to be subjected to the test(s) subject to this decision and to document the necessary information on the composition of the test material. The substance identity information of the Substance and of the sample tested must enable the evaluating MSCA and ECHA to confirm the relevance of the testing for the substance subject to substance evaluation.

4. In relation to the experimental stud(y/ies) the legal text foresees the sharing of information and costs between registrant(s) (Article 53 of the REACH Regulation). You are therefore required to make every effort to reach an agreement regarding each experimental study for every endpoint as to who will carry out the study on behalf of the other registrant(s) and to inform ECHA accordingly within 90 days from the date of this decision under Article 53(1) of the REACH Regulation. This information should be submitted to ECHA using the following form stating the decision number above at: https://comments.echa.europa.eu/comments_cms/SEDraftDecisionComments.aspxF
Further advice can be found at
http://echa.europa.eu/regulations/reach/registration/data-sharing
If ECHA is not informed of such agreement within 90 days, it will designate one of the registrants to perform the stud(y/ies) on behalf of all of them.