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# 45th Meeting of Competent Authorities for REACH and CLP (CARACAL)

## Open session

## 5-6 July 2022

## Hybrid Meeting

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| **Concerns:** | **ECHA responses to comments on concerned substances for Annex VI of CLP (RAC opinions 2021 - preparation for 21th ATP)** |
| **Agenda Point:** | **CLP-6** |
| **Action Requested:** | **Competent Authorities and observers are invited to comment on the document and the discussion points put forward. Written comments should be sent by 31 August 2022 to:**<br>**GROW-CARACAL@ec.europa.eu**<br>**ENV-CARACAL@ec.europa.eu**<br>**CARACAL@echa.europa.eu** |

## 1. Introduction

In this document ECHA responds to issues raised in relation to specific proposed Annex VI entries based on opinions of the Committee for Risk Assessment which were adopted in 2021, on which comments have been provided to date. In addition to the summaries below, detailed responses are provided in the Annexes to this document.

## 2. Summaries

**Lead**

Summary

In comments received by COM via email on 10/03/2022 and 30/03/2022 (the latter including a position paper and study), representatives from industry (Ind) have indicated several reasons for their disagreement to RAC's opinion on the harmonised classification and labelling of lead for hazards to the aquatic environment. The perceived issues are various but include issues related to the derivation of the ERVs used in the classification and the assessment leading to classification of massive lead based on data for lead powder.

ECHA fully supports the RAC opinion and argues that the data assessed and concluded on by RAC in their opinion warrants classification as Aquatic Acute 1 (H400), M = 10 and Aquatic Chronic 1 (H410), M = 100 for all forms of lead, based on data for lead powder.

See Annex 1 for detailed response.

**DAPD**

Summary

In their position paper (March 2022), the DAPD Consortium argued that the opinion of the Committee for Risk Assessment (RAC) was not justified. They consider that the reproductive toxic effects were due to maternal toxicity, or were reversible, or that they could not be relevant to humans, thus overall only 'limited evidence' of reproductive toxicity was available for DAPD, which (it is argued) should have led to a classification in Category 2 and not in category 1B. In addition, the position paper stated that RAC arbitrary discarded available information and they were denied a possibility to adequately defend their position.

ECHA fully supports the RAC opinion, and considers the arguments brought forward by the DAPD Consortium in their March position paper (also included in a comment submitted during CLH dossier consultation (March – May 2021)), and in a letter addressed to the RAC Secretariat (September 2021)) as not substantiated.

Responses to the specific points raised are provided in the relevant Annex below.

See Annex 2 for detailed response.

**DBTO**

Summary

In their comments (dated 8 March 2022) Consortia Management, acting as Secretariat for the Global Organotin Stewardship Council (GOSC), disagrees with the classification for Reproductive toxicity (Repr. 1B; H360FD) in

the opinion of the Committee for Risk Assessment (RAC). It was argued that it is based on outdated studies as well as a flawed read across from other organotin compounds. It was also stated that further studies that could provide information giving a more accurate view of the toxic properties on reproduction of DBTO are ongoing, with results expected in 2022.

ECHA fully supports the RAC opinion and argues that the data assessed and concluded on by RAC in their opinion warrants classification as Repr. 1B; H360FD and also agrees with the read across approach used by RAC.

See Annex 3 for detailed response.

**Lithium**

Summary

In their opinion adopted on 16 September 2021, RAC concluded that classification as Repr. 1A H360FD was warranted for three lithium salts (lithium chloride, lithium carbonate and lithium hydroxide). A position paper (dated March, 2022) has been submitted by Albemarle, Livent, BCW and Eurometaux, another position paper (dated March 2022) by Atiel, Ueil, Elgi, and a third position paper (dated March 2022) by ILiA, as well as a fourth joint industry statement (dated March 2022). In these documents they have argued that the opinion of the Committee for Risk Assessment (RAC) was not justified. They disagree with RAC's evaluation of the data, e.g. that RAC took data from all relevant studies into account in a Weight of Evidence when concluding on the classification and not only the negative OECD and GLP compliant 2-generation study in rats, which according to these positions is the most relevant. Further, the positions disagree with RAC's and DSs assessment on read across, arguing that lithium hydroxide, due to its corrosivity, cannot be considered for classification as Repr. based on data available on another lithium salt.

Comments were submitted from DE, NL and SE, supporting the RAC opinion to classify all three lithium salts as Repr. 1A H360FD.

ECHA also fully supports the RAC opinion and considers weight of evidence assessment of RAC justified. In addition, the read across for reproductive toxicity between the three lithium salts is considered justified. Responses to the specific points raised are provided below.

See Annex 4 for detailed response.

**Methyl methacrylate**

Summary

The Committee for Risk Assessment (RAC) concluded in its 56$^{th}$ meeting in March 2021 that Methyl methacrylate (MMA, EC 201-297-1; CAS 80-62-6) should be classified as Resp. Sens 1; H334 based on evidence in humans.

In their position paper dated 21 March 2022, which was uploaded for CARACAL-44, the Methacrylates Sector Group (MSG) have argued that there is new scientific evidence which has become available since the adoption of the opinion on MMA, which relates to the 6 cases referred to in the RAC opinion as having asthma diagnoses following exposure to MMA confirmed by specific inhalation challenge (SIC). The individual

issues are addressed in detail in Annex 5. While taking note of the points made in the position paper, ECHA agrees with the conclusion and argumentation in the RAC opinion leading to the classification conclusion.

See Annex 5 for detailed response.

## Annex 1 ECHA responses to Ind comments on RAC's opinion on the aquatic hazards of lead.

**Ind email 10/03/22**

*We believe that the RAC opinion*

*(i)* ***Fails to uphold a fundamental principle of CLP that consistent criteria are applied between substances to derive a hazard classification.*** *This is evidenced by significantly different approaches being taken in ongoing metal ENV CLH cases being considered by RAC. The divergence includes, but not restricted to, the methodology for selection of critical studies to define the chronic ERV, and extrapolation of chronic T/dP to pH 5.5 and results in a much more stringent ENV classification for lead metal. As such the committee appears to have breached the principle of non-discrimination.*

ECHA response: CLH assessments are made by RAC on a case-by-case basis, using available information. Given the range of aspects to be assessed for a metal (pH banding, water quality parameters, assessment of the extensive nature of data sets etc) when determining the ERV and T/Dp values to be compared with the criteria, it is not realistic to expect an identical approach across metals, dissimilar cases do not warrant similar approaches. However, once the ERVs and T/Dp values and treatment of the various forms are determined, the criteria for deriving the classification in CLP guidance IV.5 are applied consistently. Extrapolating to pH 5.5 addresses concerns for acid lakes, in this case in relation to the properties of lead, based OECD Series on testing and assessment Number 29 (hereafter, the T/D protocol), where paragraph 8 states: "*As pH has a significant influence on transformation/dissolution both the screening test and the full test should in principle be carried out at a pH that maximises the concentration of the dissolved metal ions in solution. With reference to the conditions generally found in the environment a pH range of 6 to 8.5 must be used, except for the 28 day full test where the pH range of 5.5 to 8.5 should be used in order to take into consideration possible long term effects on acidic lakes.*"

*(ii)* ***Exceeded the mandate given by Commission in the REACH Article 77 3 (c) request.*** *The committee cannot draw opinions on aspects outside the request – this is the case for the Committee's consideration of aspects related to rapid transformation, bioaccumulation, and acute ERVs that are included in the opinion. Moreover, new toxicity and dissolution data was referenced in the opinion that was not in the existing dataset included in the CLH dossier of the original Dossier Submitter (DS) Denmark.*

ECHA response: The mandate from COM to ECHA asked for a reassessment of RACs opinion on the aquatic hazards of lead with a focus on the chronic ERV and the potential split/non-split classification for massive and powder, no elements were specifically omitted. Although the comment above does is not specific regarding the data to which it refers, additional T/Dp data was submitted by Ind during the Art. 77 consultation (comment 1) and the study providing the endpoint for the eventual RAC opinion was indicated by a national authority (present in the REACH dossier for lead), also during the consultation (comment 10). RAC is duty bound to take consultation comments in account during its assessment. Besides these, a great deal of information both solicited and unsolicited was submitted by Ind for RAC's deliberations. Again, RAC is duty bound to consider such information where relevant.

*(iii)* ***Breaches the principles of legal certainty and protection of legitimate expectations****. The Committee's re-interpretation of the reasons leading to the classification of the massive form by reference to the formation of particles <1mm in swarf's generated from processing of lead articles is not supported by the legal text of the CLP Regulation or by the applicable guidelines. The committee acted outside its competence by re-interpreting existing guidelines through development of a decision tree used to support its conclusions that powder and massive lead by classified identically.*

ECHA response: Without reference to the specific aspects of the CLP regulation being referred to here, it is difficult to address this point regarding the CLP regulation. However, this clearly refers

to Annex IV.5.5 of the CLP guidance on the application of the CLP criteria (version 5.0, July 2017). RAC interpreted Annex IV.5.5 of the CLP guidance taking into account all views expressed on its use and interpretation, including previous assessments made under Dir. 67/548/EEC (Dangerous Substances Directive). In Annex IV.5.5 of the CLP guidance, there is a lack of clarity regarding the treatment of particles < 1 mm generated from reasonable handling and use of the massive form as the precise intention of the guidance is not clear. However, although RAC's view is fully justifiable (RAC opinion section 5) an alternative interpretation and subsequent classification outcome is included in the opinion at COM's request (Annex II to the RAC opinion). It must be noted that RAC's opinion was adopted by consensus and that this alternative interpretation of Annex IV.5.5 of the CLP guidance does not represent a minority view.

(iv) ***Breaches the principle of proportionate regulation****. Basing the classification of lead metal massive on a case study involving machining lead articles that results in very small amounts of particles <1mm is not proportionate. The quantity of lead particles generated from lead sheet processing represents much less than 0.001% of the lead metal placed on the EU market. Most lead massive is in the form of 25-50kg ingots and classifying these as if they were 75µm powder lacks any sense of proportionality.*

ECHA response: The opinion outlines the reasoning behind using swarf from cutting of lead sheets. In essence, although lead sheet as an article itself is not subject to classification and labelling, swarf generated from cutting of such sheets is not precluded from an assessment determining the basis on which massive lead should be classified. On 'proportionality', the CLP Regulation Art 1(1) indicates that CLP's purpose is to ensure a high level of protection for human health and the environment. Furthermore, downstream or further consequences of classification and labelling are not relevant for assessments under CLP. Consequently, proportionality as outlined above is not relevant for classification and labelling and as such the relative amounts/proportions of powder and massive lead on the European market are not relevant. Furthermore, Annex IV.5.5 contains no guidance on the amount of generated particles < 1 mm from massive that is relevant for classification or whether mere presence is of particles < 1 mm is sufficient. RAC's opinion is that the documented generation of particles < 1 mm from reasonable handling and use that come under the general category of powders is sufficient to justify classifying massive based on data for powder. An alternative interpretation of Annex IV.5.5 of the CLP guidance is presented in the opinion at COM's request (see above).

**Ind email 30/03/22**

*Have you had the opportunity to reflect on the points I raised below in my previous e-mail and as such will consideration be given to postponing revising the CLP Annex VI entry for lead metal until RAC have provided opinions on the two other metal CLH cases currently under review (Cu and Ag)?*

ECHA response: Whilst this is matter from COM, ECHA considers that clarity on the agreed intention and use of CLP Guidance Annex IV.5.5 is something of a priority.

*We believe this is necessary to maintain the principle of non-discrimination as latest RAC deliberations for these two metals appear to be considering different approaches to ENV classification (for example neither apply the chronic T/dP test at pH 5.5, the copper opinion is based upon the Swedish CLH dossier that stated "although data for many species are available, only "standard" species and endpoints from standardised methods have been selected" and in neither case was chronic toxicity to juvenile snail data assessed as was the case for lead). In the situation of chronic toxicity to juvenile snail you will see from the paper I attach that Pb has higher EC50 for inhibition of growth (considered the most sensitive endpoint by RAC) than either Cu or Ag ! It is thus clearly not appropriate to include such data for Pb classification but omit in case of other metals and suggests an inherent bias.*

ECHA response: The difference in the relationship between pH and dissolution for lead and silver determined that different approaches were taken when assessing the T/Dp data. Toxicity data is assessed when available for a given substance. With reference to Cremazy *et al*. (2018), this paper is included in the RAC opinion for lead but was not included in the dossier for silver. The silver values in Cremazy *et al*. (2018) are above the value used for classification (probably due to the shorter experimental time) and so would not have influenced the outcome. As to the relative values between metals in Cremazy *et al*. (2018), RAC can only take studies into account on a case-by-case basis and Cremazy *et al*. (2018) was not available for silver. ECHA can only comment to extent that Cremazy *et al*. (2018) indicates that silver and copper could perhaps be classified more stringently than they otherwise have been should comparable data (> 14d time frame) be available (it is not for silver). It should be noted for silver that the ERV value used by RAC for chronic classification agrees with both the DS and the REACH registrant (at the time the opinion was adopted).

Although the copper proposals from SE are largely based on the RAC opinion for granulated copper, there is no RAC opinion for the copper dossier as assessment has only just begun. Therefore, it is not possible to comment on an assessment that is yet to be made.

**ILA position paper attached to Ind email of 30/03/2022**

*We have critical concerns with the latest RAC opinion on a harmonised ENV CLP classification of lead metal issued on 16th September 2021. It does not represent an objective review of the evidence available or follow the existing ECHA CLP guidance on metals. Importantly the methodology used by the committee for deriving the lead metal CLH opinion differs in several critical areas compared with other ongoing metal environmental CLH opinions and these have a significant bearing on the final hazard classification derived. Some aspects of the opinion even appear to go beyond the mandate given the Commission Article 77 (3) request.*

***As several metals ENV CLH opinions are currently being considered by RAC we would request that Commission considers postponing the inclusion of a revised lead metal CLH in Annex VI to CLP until these are complete. This is necessary to maintain the fundamental principle of CLP that consistent criteria are applied between substances to derive a hazard classification.***

***Assessment of the forms of lead:*** *RAC concluded that lead particles < 1 mm are present in swarf generated from industrial processing – cutting – of lead sheet (an article). This was seen as evidence that powders are formed during reasonably expected use of the substance lead [in massive form] which are relevant for hazard assessment and classification.* ***We challenge the conclusion that article releases can be used for the purpose of the hazard classification of the metal (a substance) which would set precedence for many substances even beyond the metal sector****.*

ECHA response: The opinion (section 5) outlines the reasoning behind using swarf from cutting of lead sheets. In essence, although lead sheet as an article itself is not subject to classification and labelling, swarf generated from cutting of such sheets is not precluded from an assessment determining the basis on which massive lead should be classified. An above answer (to email 30/03/22 point iv) addresses this in more detail.

*Notwithstanding this, the available evidence highlighted that the quantity of lead particles generated from lead sheet processing represents <0.001% of the lead metal placed on the EU market. RAC concluded that ANY quantity of such particles produced is relevant for classification, however small, and adopted a strategy whereby lead in massive form was classified for hazard based on the potential releases of lead ions into solution from a fine powder (75µm). After 28 days, lead ion releases from 75µm powder are 18x greater than a 1mm sphere (default for massive) at pH 5.5 and 200x times greater at pH 8. Given that most of the lead in massive form placed on the market is in the form of large ingots weighing between 25-50kg, significantly larger than 1mm (the default for massive used in T/dP testing), we believe* ***the RAC assessment clearly fails a test of proportionality****.*

ECHA response: Whilst the above does represent RAC's preferred opinion regarding the classification of massive lead, due to the potential to reach a different conclusion when considering the evidence in the context

of the CLP guidance (IV.5.5), the alternative conclusion is presented in Annex II to RAC's opinion. This approach was agreed with COM during the RAC discussions and made clear for all participants. On 'proportionality', the CLP Regulation Art 1(1) indicates that CLP's purpose is to ensure a high level of protection for human health and the environment. Furthermore, downstream or further consequences of classification and labelling are not relevant for assessments under CLP. Consequently, proportionality as outlined above is not relevant for classification and labelling and as such the relative amounts/proportions of powder and massive lead on the European market are not relevant. Furthermore, Annex IV.5.5 contains no guidance on the amount of generated particles < 1 mm from massive that is relevant for classification or whether mere presence is of particles < 1 mm is sufficient. RAC's opinion is that the documented generation of particles < 1 mm from reasonable handling and use that come under the general category of powders is sufficient to justify classifying massive based on data for powder. An alternative interpretation of Annex IV.5.5 of the CLP guidance is presented in the opinion at COM's request (see above).

***Assessment of solubility of the metal:*** *The new RAC opinion extends the pH range of the 28-day T/dP test (OECD TG 29) for the chronic assessment of release of lead ions into solution from pH 6 to pH 5.5. This* ***appears to go beyond the mandate provided to the committee by Commission in the Article 77(3) request*** *that only asked for an evaluation of the chronic Ecotoxicity Reference Value (ERV) for lead as well as a scientific opinion on how many entries are appropriate to appear in Annex VI to CLP.*

ECHA response: The mandate from COM to ECHA asked for a reassessment of RACs opinion on the aquatic hazards of lead with a focus on the chronic ERV and the potential split/non-split classification for massive and powder, no elements were specifically omitted.

*Moreover, we believe that assessing releases of metal ion into solution at pH 5.5 is not appropriate for CLP classification. Round Robin testing after publication of OECD TG 29 concluded that testing at pH 5.5 was highly unreliable and not feasible without modifying the speciation aspects of metals due to the pH modifiers used. The OECD Joint meeting agreed with this, and OECD has only validated the 28d T/dP test in the range 6.0-8.5.*

ECHA response: Although this is in essence correct, the concern for acid lakes in the T/D protocol does not preclude use of data at pH 5.5. Whilst the test method is indeed not validated at pH 5.5, RACs dissolution value for pH 5.5 is determined by extrapolating from data derived from testing at validated pHs and not from testing at pH 5.5. RAC concluded that the extrapolation was warranted and valid. It must also be further noted that the general pH range for consideration of aquatic hazards under CLP is pH 4-9.

*To date all previous metal ENV classifications only examined dissolution into solution down to pH 6, and furthermore the examples in the ECHA CLP Guidance on the Application of the CLP Criteria only use 28d T/dP data in this pH range****.***

ECHA response: Assessments are made on a case-by-case basis. Here, RAC felt it was valid to address concerns for acid lakes at pH 5.5 based on the properties of lead.

***To single out lead for examination of 28-day dissolution at pH 5.5 and no other metals appears to go against a fundamental principle of CLP that consistent criteria are applied****. It should be recognized that extending the pH range for 28-day T/dP tests would result in classification of many other metals in massive form, including iron, which was felt too precautionary.*

ECHA response: RAC concluded that due to the increase in lead release with decreasing pH, the concern for acid lakes (pH 5.5) indicated in the T/D protocol should be addressed for lead. Each metal is assessed on its own merits at a relevant pH range considering the properties of the metal in question. As noted above, the generic pH range for aquatic hazard assessment under CLP is pH 4-9.

*Applying the T/dP test in the range 6.0-8.5 is further supported by ecological evidence. Indeed, below pH 6, only species specifically adapted to this extremely stressful physiological condition would reasonably survive and it would therefore not be appropriate to compare dissolution/solubility of metals at this pH with toxicity observed in standard laboratory species. For example, sensitive invertebrate species such Ceriodaphnia dubia or Lymnaea stagnalis will not reproduce or thrive at pH 5.5 irrespective of presence of test chemical.*

ECHA response: Whilst this might be a valid concern for a risk assessment of any given organisms, this is not relevant for hazard assessment under CLP.

***Lack of recognition for ecotoxicity data quality**: The CLP Regulation states that "for the purposes of CLP classification preference should be given to studies conducted in accordance with the EU test methods (Reg. (EC) 440/2008) or other international test methods validated according to international procedures such as those of the OECD." The chronic Environmental Reference Value (ERV) for lead was however derived by RAC using the single lowest value from a large data set. The critical study selected was from a sensitive life stage of a non-standard species (Lymnaea stagnalis, the pond snail) using a protocol that was not conducted in accordance with international test methods validated according to international procedures. This is not an approach taken previously by RAC for other metal harmonized environmental classifications that have typically been restricted to use of "standard species and endpoints from standardised method". **Again, a fundamental principle of CLP appears to have been neglected in that consistent criteria have not be applied**.*

ECHA response: RAC considers and assesses any relevant data included in the CLH process on a case-by-case basis. In this case, RAC conducted an analysis (opinion section 8.4) which concluded that the deterministic approach using the lowest ERV values is warranted. Here, the *Lymnea stagnalis* study providing the chronic ERV (Munley *et al*., 2013) used in the classification was assessed extensively by RAC during the assessment (RAC opinion section 8.8.2). It should also be pointed out that at the time the RAC opinion was adopted, this study was rated as reliable in the lead REACH registration dossier.

***Comparison of toxicity and dissolution at different pH bands:** The ECHA Guidance on the Application of CLP Criteria, Version 5, section IV.2.3 Comparison of aquatic toxicity data and solubility data, states "When a more extensive toxicity/dissolution dataset is available, a split of the acute and chronic ecotoxicity reference values can be performed according to their pH used during T/D test. Meaning that toxicity data and transformation data are in this case always compared at the same pH."*

*While the above approach following pH banding of ecotoxicity and solubility data has typically been applied by RAC for other metals, the committee's opinion was that the classification for lead should be determined by comparison of the highest toxicity and maximal solubility across the entire pH range - the most precautionary approach possible and a situation that in practice cannot occur in nature as a water body cannot simultaneously have two pH values.*

*The rationale for taking this approach equally applies to other metals but has not been applied for lead in practice. **Again, a fundamental principle of CLP appears to have been neglected in that consistent criteria have not be applied.***

ECHA response: The above text is not an accurate representation of the CLP guidance IV.2.3 in that it only includes IV.2.3(2) and ignores IV.2.3(1). IV.2.3(1) states "*When only a limited dataset is available existing data should be taken together irrespective of whether the toxicity and dissolution data are at the same pH and the lowest data point should give the basis for classification (this should be used as the default approach). This default approach may lead to the lowest toxicity data point compared with the highest Transformation Dissolution result each derived at different pH levels used for the purpose of classification*." The guidance clearly anticipates that classification may be derived using ERV and T/Dp data at different pHs. Furthermore, as IV.2.3(1) is the default approach, taking the approach outlined in IV.2.3(2) should be the result of an assessment justifying doing so (in this context, what constitutes 'extensive' is a matter of assessment). For lead, RAC made an assessment as outlined in the opinion (section 8.4) and concluded that IV.2.3(2) was not justified, the consequence being that the default approach in IV.2.3(1) was followed.

While IV.2.3(2) has been used for copper forms and substances, it is far from certain that it's use can be described as 'typical' across metals (for example, RAC has previously only assessed two forms of copper and lead metal (original 2018 opinion) for aquatic hazards), especially as it is not the default approach. It is also worth noting that IV.2.3(1) has been followed for silver, an approach with which Ind firmly agreed.

**Annex 2 - ECHA response to the position paper on the proposal for the classification of DAPD by the DAPD consortium**

In November 2021, the Committee for Risk Assessment (RAC) adopted an opinion concluding that for 1,4-Benzenediamine, *N,N'*-mixed Ph and tolyl derivs.; Reaction mass of *N*-phenyl,*N'-o*-tolyl-phenylene diamine, *N,N'*-diphenyl-p-phenylene diamine and *N,N'*-di-*o*-tolyl-phenylene diamine (DAPD, or BENPAT in the CLH dossier and RAC opinion) should be classified as a Reproductive toxicant in Category 1B for effects on sexual function and fertility and developmental effects (H360FD), and Skin Sensitiser in Category 1 (H317), with no subcategorisation.

In December 2020, an Access to Documents (ATD) request was submitted to ECHA by Fieldfisher.

The CLH dossier was submitted by Germany and underwent consultation between 15 March and 14 May 2021. The DAPD Consortium commented during this period, and both the DS and RAC replied extensively to all points raised by the DAPD Consortium, see the RCOM on ECHA website.

On 15 September 2021, the DAPD Consortium, via Fieldfisher, stated their concern in an email and its attached position paper provided to the RAC Secretariat. The arguments included in this position paper were already submitted as a comment during the consultation (as stated in their letter) and as such both the DS and the RAC considered them and replied to them in detail, see the RCOM on ECHA website. ECHA secretariat provided replies to the points raised in the letters and clarification on RAC procedures.

A DAPD Ind representative participated in the relevant RAC working group and plenary as a Cefic accompanying expert and commented on the developmental toxicity.

ECHA's responses to the specific comments made in their letter are provided below.

1. *Studies on DAPD clearly demonstrate toxic effects and thus doubts exist that the dystocia was not secondary to maternal toxicity*

   Based on the results of the 2 generation study, no unequivocal correlation between toxic effects and dystocia can be drawn: "*Not all F0 dams with dystocia showed necrotic lesions in liver and kidney, and these effects were observed to be minimal to mild. On the other hand, incidence of clinical signs (piloerection, vaginal bleeding) was higher in F0 dams that died or that were euthanised in the high dose group. This together suggests that the dystocia is not secondary to the effects in liver or kidney. It cannot be excluded, however, that these lesions in the liver and kidney are the result of dystocia instead*." See RAC opinion on page 10 for additional details on the findings.

   *"Exposure to BENPAT was associated with dystocia and increased gestational length in rat one-and two-generation studies. No marked maternal toxicity was observed in both studies. Clinical signs and histopathological changes (liver and kidney) observed were likely the result of dystocia and thus secondary to dystocia. This is supported by absence of marked toxicity in two repeated dose toxicity studies available for BENPAT; a one-year dietary repeated dose toxicity study (none-guideline; ca. 3.3, 20 and 120 mg/kg bw/d) and a 28-day oral repeated dose toxicity study (similar to OECD TG 407; ca. 7.5, 30, and 120 mg/kg bw/d) in F344 rat (AHF, 1994; AHF, 1996). Besides increased relative weights of liver and kidney in the mid and high dose groups, no substance related deaths or clinical findings and no histopathological changes in liver and kidney were reported in these repeated dose toxicity studies"* See RAC opinion on page 12.

2. *Data are available that clearly establish doubts for the presumption of the same effects in humans*
   - There are no human data available on exposure to DAPD.

- Concerning the differences between rat strains and possible differences between species, which in the opinion of the DAPD Consortium leads to the conclusion that "*the reproductive effective observed in Sprague Dawley rats would be relevant to humans is flawed and lacks justification*" [DAPD Consortium position paper to CARACAL].

  In toxicology, by definition effects observed in animals are relevant to humans, unless data clearly demonstrate non-relevance. Differences in strain sensitivity do not constitute sufficient data to doubt the human relevance. In addition, in the guidance on the application of the CLP criteria (CLP guidance) VI, 4.1 Species and Strain, indicates that the most sensitive species and strain should be used. Please note that both the DS and RAC provided their view in line also with the CLP guidance, see RCOM, RAC response to comment 2 point 4.2a.

- *DAPD dossier does not contain a Post Natal Development Toxicity study (OECD 414) in a second species (not rat).* [DAPD Consortium position paper to CARACAL].

  There is no need to conduct studies in a second (non-rodent) species to conclude on the classification. Classification is based on the available data, if these fulfil the criteria for classification no further investigation are needed. Please note, that all available information is taken into account therefore even if a negative study in a non-rodent species would be available, this result would not automatically negate the findings on the rat studies.

  In addition, post-natal developmental studies do not provide information on fertility effects, thus it is not relevant to list them as second reason under "Reproductive effects on fertility" on page 2 of the DAPD Consortium position paper.

- Data on "*non-steroidal anti- inflammatory drugs (NSAIDs) such as acetylsalicylic acid and a substance chemically related to DAPD - diphenyl-p-phenylenediamine (DPPD)*" were ignored [DAPD Consortium position paper to CARACL].

  The DAPD consortium view that DAPD causes the same effects as salicylic acid was submitted during the consultation. Both the dossier submitter and RAC considered it and provided their evaluation on this point. The DS replied: "*Regarding the comparison with SA and ASA, the DS noted that these chemicals present a different target profile in comparison to BENPAT (e.g. malformations (amongst which cranioschisis, and dose-related growth retardation). A different target profile is also observed in repeated dose studies*" (RAC opinion page 7, and RCOM reply to comment 2, point 4.3).

- DPPD mode of action proposal of prostaglandin inhibition.

  RAC considered this evidence and stated in the opinion: "*Other animal studies demonstrated similar effects on dystocia and prolonged parturition upon exposure to DPPD (a BENPAT constituent), which acts as prostaglandin inhibitor (Fujimoto et al., 1984; Marois, 1998). In humans, prostaglandins have an important role in various physiological mechanisms, such as pregnancy (Bakker et al., 2017; Mitchell et al., 1978; Reece et al., 1996; Romero et al., 1994). DPPD induced dystocia and prolonged parturition in animals is supportive evidence of a possible mode of action. However, it is noted that BENPAT consists of other constituents and impurities, with unknown toxicity/modes of action. As a consequence the effects observed for BENPAT cannot be solely attributed to DPPD. There is no mechanistic information indicating that the observed effects are not relevant for humans, therefore the adverse effects on sexual*

*function and fertility reported in rats are considered relevant for classification and these effects are considered relevant to humans*."

3. *Developmental effects are reversible and thus cannot be considered developmental, and are species/strain specific thus presumption of relevant to humans is lacks justification.*

   RAC conclusion on developmental toxicity is the following: "*The consistent and dose-related post-implantation loss is key for classification for development. Polycystic kidneys in weanlings are considered as supportive evidence for this conclusion, because the effects are considered as permanent and serious, but it is not clear whether this is due to in utero exposure only.*" Post-implantation losses are not reversible. The effect on the kidneys were considered by RAC as supportive evidence.

4. *RAC has not taken into account, carefully and impartially, all the relevant and available information on DAPD provided by the registrants in support of the classification of DAPD as Repr 2, rather than Repr. 1B.*

   All information provided during the consultation was taken into account and scientifically evaluated by RAC and replies were provided in the RCOM and in some cases in the opinion itself even if not formulated as direct replies. See RCOM reply to comment 2.

5. *RAC arbitrarily discarded the information available, thus precautionarily concluding on a Repr. 1B classification.*

   RAC considered all information available and evaluated it scientifically to formulate the opinion.

6. *During the CLH process, the DAPD Consortium has been asked to prove the impossible and has been therefore denied a real opportunity to adequately defend its position.*

   No requests were made by RAC to DAPD Consortium during the CLH process.

7. *DAPD has been shown to degrade in the environment and thus would not present any risk to humans via the environment at all life cycle stages. Within the manufacturing and down-stream use phases, exposure risks are already controlled as a result of the existing Repr. Cat. 2 self-classification. The CLH proposal would therefore achieve no further control of risk against the current self-classification.*

   The CLH classification process is hazard based, therefore no consideration of exposure or risk are taken into account.

## Annex 3 ECHA response to points raised on the adopted RAC opinion for dibutyltin oxide (DBTO)

**Background**

On 16 September 2021, RAC adopted, by consensus, the classification of DBTO as Repr. 1B; H360FD. Consortia Management, acting as Secretariat for the Global Organotin Stewardship Council (GOSC), has provided comments on the agreed classification, questioning the basis for the RAC opinion as well as requesting the inclusion of the substance into an ATP to be postponed due to new data being generated. Below are ECHA's detailed responses to the arguments provided by Consortia Management.

**Comments by Consortia Management, acting as Secretariat for the Global Organotin Stewardship Council (GOSC) and ECHA responses**

**1. Classification by RAC was based on outdated studies and a flawed read across**

Consortia Management states in their comments that RAC based the classification on outdated studies, that the read across is flawed and that it relies heavily on old assumptions that DBTC is the main hydrolysis product of DBTP. This is not correct.

RAC recognised that in the initial hydrolytic studies, referred to as outdated by Consortia Management, an indirect detection method was used that could not determine the exact tin species that was formed.

RAC also noted that recent *in vitro* hydrolysis studies which used 119Sn-NMR spectroscopy [ECHA note: the method referred to as being more direct and selective by Consortia Management] showed that both DBTC and the related compounds DBTP and DBTM form the distannoxane ClBu2SnOSnBu2Cl.

The CLH dossier for DBTO includes one in vitro gastric simulation study, performed with GC-FPD, which showed a conversion under simulated gastric conditions to DBTC. It was noted by RAC that this detection method cannot distinguish whether the distannoxane ClBu2SnOSnBu2Cl is formed; however, considering the behaviour of the other category members, RAC concluded that this is highly likely.

The OECD TG 414 (prenatal developmental toxicity study; PNDT) study with DBTO, as well as a comparative study with DBTO and other dibutyltins (see details below), showed similar effects as observed for other category members. In addition, the immune system has been identified as a target organ for several other category members, mainly based on data for DBTC, and similar effects were seen also for DBTO. RAC considered this similar toxicological profile, together with the metabolism studies, to provide further support for the read across approach.

Consortia Management argues that the PNDT study with DBTO does not show effects justifying classification. ECHA, in agreement with RAC, disagrees with this. On the contrary, effects justifying classification were seen, e.g.; an increase in post-implantation loss, including several dams with total litter loss, also seen in the absence of maternal toxicity. In addition, there were effects on thymus weight, in line with what has been seen with e.g.; DBTC. In the additional, comparative study with DBTO, DBTC, DBTA, DBTM, and DBTL (Noda *et al*., 1993), exposure to DBTO lead to external and skeletal malformations. Treatment showed a comparable type of foetal malformations for all tested substances. The effects in these studies, as well as studies with other category members (DBTC and DBTA), support the RAC conclusion for Category 1B for development.

In addition, it should be noted that comments arguing against the read across were provided by industry representatives already during the CLH process, and these were taken into account by RAC.

**2. Chemical properties of DBTC and DBTO are different**

Consortia Management argues that the chemical properties of DBTC and DBTO are different, in contrast to what is stated in the CLH dossier.

ECHA considers, in agreement with RAC, that the toxicokinetic and hydrolytic behaviour of the substances clearly shows that the category approach is justified. In addition, the substances have similar toxicological profiles, giving further support to the applied read across.
For further arguments supporting the read across agreed by RAC, see reply to point 1.

**3. New OECD TG 416 (two-generation study) with DBTO to be performed**

ECHA is of the opinion that new data, even if negative, would not negate the findings in the already available studies, which clearly justify classification of DBTO as Repr. 1B; H360FD. Thus, ECHA does not support waiting for additional data to be generated before including the classification of DBTO in Annex VI of the CLP Regulation.

## Annex 4. ECHA comments on Albemarle, Livent, BCW and Eurometaux joint document Implications of the potential inappropriate classifications of lithium chloride, carbonate, and hydroxide, March 2022, 44th Meeting of Competent Authorities for REACH and CLP, AP 6

ECHA thanks for the opportunity to provide a view on the document provided by stakeholders on Lithium classification. In their position paper (dated March, 2022) Albemarle, Livent, BCW and Eurometaux, in another position paper (dated March 2022) Atiel, Ueil, Elgi, in a third position paper (dated March 2022) ILiA, and in a fourth joint industry statement (dated March 2022) they have argued that the opinion of the Committee for Risk Assessment (RAC) was not justified. They disagree with RAC's evaluation of the data, e.g. that RAC took data from all relevant studies into account in a Weight of Evidence when concluding on the classification and not only the negative OECD TG and GLP compliant 2-generation study in rats, which according to these position papers is the most relevant. Further, the positions presented disagree with RAC's and DSs assessment on read across, arguing that lithium hydroxide, due to its corrosivity, cannot be considered for classification as Repr. based on data available on another lithium salt.

Comments were also submitted from DE, NL and SE, all supporting the RAC opinion to classify all three lithium salts as Repr. 1A H360FD. SE raised an issue concerning using the word "weak" in the opinion, which is also further clarified in this ECHA response.

ECHA is of the view that the opinion adopted by RAC for all three lithium salts as Repr. 1A H360FD was well justified. The detailed reasons are provided below. The sections below addressing the issues raised are in the same order as they are in the joint document by Albemarle, Livent, BCW and Eurometaux. ECHA reactions are presented below to the issues raised in the stakeholder's document.

Issue 1- *Inappropriate classification of the three lithium salts would create business and legal uncertainty on future risk management options, deterring investments in Europe at a crucial time for the entire lithium value chain*

For classification, only the intrinsic toxic properties of substances are assessed against the CLP criteria and it does not take into consideration potential downstream consequences.

Issue 2- *The RAC opinion on the classification of the three lithium salts does not meet the criteria for classification as Cat 1A under Regulation (EC) No 1272/2008*

Classification as Repr 1A based on Developmental effects in humans

There were several epidemiological studies in humans showing concern for rare and severe cardiac malformations. However, the older studies, as explained in the opinion, which showed much stronger effects, were not considered in the WoE since the possibility of confounding factors could not be ruled out with sufficient confidence. RAC considered carefully the reliability and results / magnitude of the effects from the epidemiological studies in its assessment. The concern for developmental toxicity is due to a severe and very rare malformation which poses particular methodological challenges for the human studies. In the RAC opinion, the intention behind the references to the word "weak" was that the association in the epidemiological data for this malformation was not particularly high since the malformation is so rare, but there was nevertheless a risk which could not be ignored and thus this was considered to be reliable evidence. Similarly, very rare but severe malformations in animals are

considered for classification for Repr. 1, even if the incidence is very low. Consequently, when considering the weight of evidence, appropriate consideration was given to those studies with a sufficient number of pregnancies to be able to assess whether there is a dose-response relationship, use of appropriate control subjects, a balanced assessment, and due consideration of bias or confounding factors. Overall, the data supported classification for effects on development based on human data alone.

In addition, there were some animal studies which supported classification for developmental effects and some studies which were either inconclusive e.g. due to too low top dose (Van Deun et al. 2021) or did not show developmental effects. RAC concluded that a classification for developmental toxicity is supported by experimental animal studies where some concerns for neurodevelopmental effects in rats and mice as well as decreased pup body weight and litter size were reported. According to CLP, Annex I, 1.1.1.4:

"*Where evidence is available from both humans and animals and there is a conflict between the findings, the quality and reliability of the evidence from both sources shall be evaluated in order to resolve the question of classification. Generally, adequate, reliable and representative data on humans (including epidemiological studies, scientifically valid case studies as specified in this Annex or statistically backed experience) shall have precedence over other data*." Weight of evidence and expert judgement, according to CLP Annex I, 1.1.1. are based on data quality and conclusiveness, without needing to be further justified. RAC has a high level of experience and expertise to conduct this WoE, based on their expert judgement.

<u>Reasons why low weight was given for OECD TG 416 animal study for both sexual function and fertility and developmental toxicity classification</u>

According to the CLP Regulation, (CLP Annex I, 3.7.2.2.3) there must be reliable evidence of an adverse effect on humans in order to classify a substance in Category 1A.

RAC considered the quality and reliability of evidence from humans and animals. There were several factors why lower weight was given to the OECD TG 416 GLP 2-generation reproductive toxicity study (Anonymous, 2012, reviewed by the industry in public literature, see Van Deun et al. 2021, e-published only weeks before the second RAC meeting where Lithium was discussed) in this overall weight of evidence assessment. The documents related to this study made available for RAC during the process were a summary of the study by Anonymous (2012) provided in the CLH report by the DS and Van Deun et al. (2021). Another, important reason why this study was not given much weight by RAC was that the top dose used was not sufficiently high to allow a conclusion to be drawn on the tested parameters (relating to reproductive and developmental toxicity) in rats for classification and labelling.

As shown below, it is clear that in the 2-generation study (Anonymous, 2012) there was no effect on the maternal body weight at any dose including the top dose, or any other sufficiently severe toxicity that would have made the study conclusive for the tested parameters on reproduction in rats. In CLP there is no specific limit dose given above which classification and labelling for reproductive toxicity is not warranted, but the CLP regulation (CLP Annex I, 3.7.2.5.9) refers to an upper dose of 1000 mg/kg bw/day given in some OECD TGs unless expected human exposure indicates a need for a higher dose

level. The top dose of 45 mg/kg bw/day (8.6 mg/kg bw/day of $Li^+$) is far below 1000 mg/kg bw/day and it is not justified by the severity of co-occurring maternal toxicity that would not have allowed higher doses to be tested and assessed for classification and labelling. Therefore reproductive effects at higher doses cannot be excluded and the study is inconclusive for the tested parameters.

It is to be noted that the importance of a sufficiently high top dose is now also highlighted in the current ECHA guidance. This is to ensure that sufficiently high top doses are tested in reproductive toxicity studies to allow conclusions to be drawn on classification and labelling. The principles behind this guidance document are based on the CLP criteria and they are in line with the OECD test guidelines for testing reproductive toxicity, and have been available for concerned parties already at the time when the study was performed. The guidance emphasises that "For the highest dose level, it should be demonstrated that the aim is that it is the highest possible dose level without severe suffering or death, or the limit dose concept shall be used" (See https://echa.europa.eu/documents/10162/17220/211221_echa_advice_dose__repro_en.pdf/27159fb1-c31c-78a2-bdef-8f423f2b6568?t=1640082455275)

When looking at the detailed results of parental toxicity in Van Deun et al. 2021 2-generation reproductive toxicity study (detailed tables not included in the opinion), they show that that the top dose was not sufficiently high and therefore, in the absence of reproductive or developmental toxicity suggesting Cat 1 classification, the study is considered inconclusive for classification and labelling. In Supplementary Table 3. *Parental findings two-generation toxicity study in Wistar rats* Van Deun et al. 2021 it is shown that there we no decreases in body weight or food consumption in parental P0 or P1 animals during pregnancy or premating period.

Further, Table 5. *Statistically significant organ weight changes of the P0 generation* of Van Deun et al. 2021 illustrates that in females, there were no treatment related adverse effects on organ weights representing general toxicity and higher doses should have been tested and assessed for potential effects on reproduction.

Some histopathological findings were observed in kidney and liver in some parental animals, which were all graded as minimal or mild severity, suggesting that the top dose was not even close to the highest possible dose level without causing severe suffering or death. Histopathological changes from figures 1 and 2 of van Deun et al. (2021) are shown below to clearly demonstrate the parental toxicity (total number of animals 25/group):

Liver:

| **P0 generation** | **Males** | | | | **Females** | | | |
|---|---|---|---|---|---|---|---|---|
| **dose (mg/kgbw/d)** | **0** | **5** | **15** | **45** | **0** | **5** | **15** | **45** |
| **dose (mg Li+/kg bw/d)** | **0** | **(0.95)** | **(2.9)** | **(8.6)** | **0** | **(0.95)** | **(2.9)** | **(8.6)** |
| cytoplasmatic rarefaction | 1 | 0 | 0 | 12 | 0 | 0 | 0 | 0 |
| basophilic hepatocytes | 0 | 0 | 0 | 0 | 1 | 1 | 2 | 6 |
| hepatocellular hypertrophy | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 7 |
| **P1 generation** | **Males** | | | | **Females** | | | |
| **dose (mg/kgbw/d)** | **0** | **5** | **15** | **45** | **0** | **5** | **15** | **45** |
| **dose (mg Li+/kg bw/d)** | **0** | **(0.95)** | **(2.9)** | **(8.6)** | **0** | **(0.95)** | **(2.9)** | **(8.6)** |
| cytoplasmatic rarefaction | 2 | 2 | 4 | 11 | 0 | 1 | 2 | 0 |
| basophilic hepatocytes | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 5 |
| hepatocellular hypertrophy | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

Kidney:

| P0 generation | Males | | | | Females | | | |
|---|---|---|---|---|---|---|---|---|
| dose (mg/kgbw/d) | 0 | 5 | 15 | 45 | 0 | 5 | 15 | 45 |
| dose (mg Li+/kg bw/d) | 0 | (0.95) | (2.9) | (8.6) | 0 | (0.95) | (2.9) | (8.6) |
| minimal dilated tubuli | 4 | 1 | 11 | 12 | 0 | 1 | 3 | 7 |
| mild diliated tubuli | 0 | 0 | 0 | 10 | 0 | 0 | 0 | 13 |
| **P1 generation** | **Males** | | | | **Females** | | | |
| dose (mg/kgbw/d) | 0 | 5 | 15 | 45 | 0 | 5 | 15 | 45 |
| dose (mg Li+/kg bw/d) | 0 | (0.95) | (2.9) | (8.6) | 0 | (0.95) | (2.9) | (8.6) |
| minimal dilated tubuli | 2 | 1 | 6 | 19 | 1 | 1 | 8 | 16 |
| mild diliated tubuli | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 |

In the RAC background document, an assessment of systemic toxicity for this study in females for instance, shows that RAC was aware of the level of severity of general parental toxicity which was described in detail in van Deun et al. (2021) (RAC's assessment on male parental toxicity is not reported here but can be found in the RAC opinion). RAC noted in its opinion that in both P and F1 generations premating females showed higher net body weight gains. In the P0 (parental) females, a significant increase in the relative liver weight was observed. In the F1 generation, the terminal body weight was not affected in any of the female and male dose groups. Microscopic analysis of the P0 generation animals in the highest dose group revealed hepatocellular hypertrophy of minimal severity and focal basophilic hepatocytes in females. Thyroid follicles of females showed increased colloids. The test item related microscopic changes observed in thyroid of females in the parental generation were not evident in F1 generation parental animals. F1 parental animals also revealed increased focal basophilic hepatocytes in the liver of females. Pronounced and severely dilated tubules of kidneys were observed in both generations. Dilated tubules of kidneys were discussed by the authors to be an adaptation to the pharmacological effect of lithium carbonate (vasopressin-downregulation) and therefore not considered as a toxicological effect. No test item related microscopic findings were observed in both male and female pups of F1 and F2 litters.

Based on the above, the maternal toxicity cannot be considered sufficiently severe to allow the study to be considered conclusive and therefore was given low weight in the assessment for classification and labelling for Reproductive toxicity.

There are several studies which support classification as Repr. 1B. Some of these are performed at doses similar to those in the Anonymous (2012) study. It should be noted that the dose which triggers effects commonly varies depending on e.g. the study type, set up, laboratory, animal strain used and other factors and thus exact dose levels cannot be given much weight in comparison of the studies, particularly from different laboratories.

It is thus appropriate to assess effects seen in a particular study rather than to compare effects or lack thereof at a particular dose level. Thus studies where effects are seen in the absence of excessive maternal toxicity are given greater weight than a study where the top dose was not sufficiently high to allow a conclusion on classification to be drawn.

Effects on or via lactation

The effect on or via lactation was very thoroughly assessed and there were sufficient data supporting the classification. ECHA agrees with RAC opinion on effects on or via lactation.

*Issue 3- Contradictory statements and incoherencies in the RAC opinion*

Regarding the industry statement on contradictory statements in the RAC opinion, ECHA agrees with the remark from DE in their comment where two of the quotes reflect IND and MSCA comments, not the RAC view. The quotes on Munk-Olsen et al. and Patorno et al. studies, where a lower association of such malformations compared to "old" studies is observed, is not in contradiction, neither are the results of these two studies when compared to each other.

Regarding read across justification, the arguments presented by IND are not considered relevant to dismiss lithium hydroxide from the read across. It is irrelevant if a study cannot be performed due to corrosivity, since exposure after use of the substance is not always to the substance itself and exposures are often prolonged as compared to a gavage study. There was a small group of RAC experts established as an outcome of the July RAC CLH WG meeting (see the minutes of the RAC WG meeting) from the field of chemistry and toxicology to discuss carefully the applicability of the read across. The issue was thus deeply assessed by RAC. All the documents provided by industry were considered by RAC. The group supported the RAC in forming its opinion on read across.

RAC has therefore written a 2 page analysis of read across in the RAC opinion. In particular, RAC notes that corrosivity of the hydroxide anion does not prevent exposure to lithium cation from mixtures, especially if they have a lower pH. Further, some relevant points from the RAC read across statement in the opinion: "*According to the REACH Guidance R.7.6.2.3.2 (v6.0), corrosive or highly irritating substances should be tested preferentially via 5 the oral route; however, it must be noted that in vivo testing with corrosive substances at concentration/dose levels causing corrosivity must be avoided. However, a vehicle with buffering capacity should be chosen to minimise gastrointestinal irritation, indicating that substances with corrosive properties are not excluded from testing for reproductive toxicity.*

*RAC notes that even very diluted solutions of lithium hydroxide have a high pH around 13.0 but that due to a very low alkaline reserved they are easily neutralised. This indicates that concentrations and pH values of lithium hydroxide solution can be obtained at which systemic effects, but not corrosive effects are observed, see table below.*

*RAC notes that the use of lithium hydroxide or conditions for exposure are not relevant for hazard classification, which is based on the intrinsic properties of the substance. In general, all routes and sources of exposure are considered relevant for lithium compounds and may contribute to lithium toxicity.*

*Overall, the read across approach between lithium carbonate, lithium chloride and lithium hydroxide based on the analogue approach proposed by the DS is supported by RAC. The compounds dissociate to lithium cation (Li+) and the corresponding anions, carbonate (CO3 2- ), chloride (Cl- ) or hydroxide (OH- ), in aqueous solutions. The anions are rapidly integrated into the physiological pool of anions or neutralised in the body. Systemic toxicity is considered to be determined by the lithium cation and is not influenced by the anions. The lithium cation remains unchanged in the body, and due to similarities with sodium and potassium cations it uses the sodium ion channels to reach target organs. The*

*corrosivity of lithium hydroxide would not prevent inclusion of this substance in the read across assessment from lithium carbonate and lithium chloride for the reproductive toxicity hazard class. Likewise, the corrosive nature of lithium hydroxide leading to low exposure to lithium cannot be used as an argument for excluding lithium hydroxide from read across since this would be related to risk assessment rather than hazard evaluation. RAC noted that no sub-acute or sub-chronic toxicity study with lithium hydroxide was included in the REACH registration or included in the CLH report by the DS, with which to compare potentially corrosive concentrations of lithium hydroxide. An oral acute toxicity study with lithium hydroxide monohydrate was included in the REACH registration (Bio-test, 1976). Due to questionable reliability, this study was not used for comparison of effects of lithium salts."*

ECHA further notes that the RAC Rapporteurs made an analysis using available data to estimate whether systemic toxicity could be reached due to corrosivity of lithium hydroxide. In rats exposed to lithium hydroxide monohydrate up to 80 mg/kg bw d no severe corrosion in the gastrointestinal tract was reported, indicating the possibility to expose rats to lithium hydroxide monohydrate up to this dose level (corresponding to 13 mg/kg bw/d Li). This dose level of 80 mg lithium hydroxide/kg bw/d is shown to be below the corresponding levels of lithium exposure inducing systemic toxicity:

| **Effects:** | **Lithium carbonate** | **Lithium hydroxide monohydrate** | **Lithium hydroxide anhydrous** |
|---|---|---|---|
| Kidney (Anonymous, 2012) | 45 mg/kg bw/d (8.6 mg/kg bw/d Lithium)* | 52 mg/kg bw/d (8.6 mg/kg bw/d Lithium)* | 30 mg/kg bw/d (8.6 mg/kg bw/d Lithium)* |
| Fertility, male reproductive organ (Thakur et al., 2003) | 44 mg/kg bw/d (8.3 mg/kg bw/d Lithium)** | 51 mg/kg bw/d (8.5 mg/kg bw/d Lithium) ** | 29 mg/kg bw/d (8.5 mg/kg bw/d Lithium)** |
| Sperm (Zarnescu and Zamfirescu, 2006) | 35 mg/kg bw/d (6.6 mg/kg bw/d Lithium)** | 40 mg/kg bw/d (6.6 mg/kg bw/d Lithium)** | 23 mg/kg bw/d (6.7 mg/kg bw/d Lithium)** |
| Testis, sperm (Toghiani et al., 2012) | 30 mg/kg bw/d (5.6 mg/kg bw/d Lithium)** | 35 mg/kg bw/d (5.8 mg/kg bw/d Lithium) ** | 20 mg/kg bw/d (5.8 mg/kg bw/d Lithium)** |

*Calculated by Industry

**Calculated by Rapporteurs

**Conclusion**

ECHA considers the RAC opinion for Repr. 1A H360FD was justified for all three lithium salts.

## Annex 5 ECHA response to the Methacrylates Sector Group (MSG) concerning Methyl Methacrylate

The Committee for Risk Assessment (RAC) concluded in its 56th meeting in March 2021 that Methyl methacrylate (MMA, EC 201-297-1; CAS 80-62-6) should be classified as Resp. Sens 1; H334 based on evidence in humans.

In their position paper dated 21 March 2022, which was uploaded for CARACAL-44, the Methacrylates Sector Group (MSG) have argued that there is new scientific evidence which has become available since the adoption of the opinion on MMA, and which was therefore not considered by RAC to date. This new evidence relates to the 6 cases referred to in the RAC opinion as having asthma diagnoses following exposure to MMA confirmed by specific inhalation challenge (SIC). The individual issues are addressed below. While taking note of the points made in the position paper, ECHA agrees with the conclusion and argumentation in the RAC opinion leading to the classification conclusion.

The MSG has argued that contrary to CLP requirements, in relation to these 6 SIC tests

1. They "*were not made with the substance but instead products that we now know likely contain other chemicals that are already classified, or are the subject of a CLH proposal as Resp. Sens., thereby making the claim that MMA was solely responsible unreliable*"

ECHA Response: Item 3.4.2.1.2.3 of the CLP Regulation states that "*The evidence referred to above could be:* […] *(b) data from one or more positive bronchial challenge tests with the substance conducted according to accepted guidelines for the determination of a specific hypersensitivity reaction*".

During the CLH process, RAC sought additional information on the number of cases (in Suojalehto et al, 2019) where specifically MMA could be determined as the likely causative agent for respiratory sensitisation in the cohort by specific inhalation challenge (SIC) as opposed to other acrylates, and how this was determined (Annex 5 to the CLH report, now available from 1584ac0b-07ab-f64d-4c3f-d6f4145147d1 (europa.eu)). In the response it was noted that "*In the series by Suojalehto et al. 2019, six patients had been both predominantly exposed to MMA and also tested positive specifically for this substance in the SIC. This was judged based on the information on workplace agent that was also used in the respective SIC. During the study period, two-component, self-curing methacrylate products used in e.g. dental and other prosthetic work as well as in preparing nails by the "acryl technique", have typically contained MMA as their main ingredient. In the FIOH cases we were able to verify from the original product information that this was indeed the case"* (underlining ours).

They also noted concerning the three cases from other centres that "*Based on the product information provided by the respective centres we concluded that they had used two-component MMA products to make prostheses*" and provided a description of the way the SIC had been performed.

If MMA was the predominant substance and it was indeed the case (as argued by the MSG) that other chemicals in the product may equally have been responsible for the responses observed, the other substances must have a higher potency for respiratory sensitisation than MMA.

2. They "*did not follow accepted guidelines in that they failed to measure the levels of MMA exposure thereby avoiding irritation, a recognised property of MMA and the other substances now known to be present the products used*".

ECHA Response: Concerning the argument that that in these tests they failed to measure the levels of MMA exposure, in the opinion it is noted that "*In the SICs, the exposures were kept well below known respiratory irritant concentrations and relevant OELs, but MMA concentrations were not measured in any of the SICs included in Suojalehto et al. (2020). However, 3/6 of the MMA-cases in this publication were diagnosed at the Finnish Institute of Occupational Health, where a stable SIC protocol for two-component MMA-based methacrylate products has been used since 2000, and detailed information on the exposure levels in SICs exist".* The opinion then refers to exposure level data from Annex 5 to the RAC opinion which indicates that it is extremely unlikely that any of the three Finnish MMA cases in Suojalehto et al. (2019) were exposed to more than the highest measured level (13 mg/m3) during the SIC. The opinion further states that "*Due to similar products and SIC protocols, it is likely that the exposure levels in two further MMA cases, diagnosed in other units, were comparable to those from which the measured concentration data were available*".

Concerning differentiating respiratory irritation from respiratory sensitisation, RAC took into account the fact that the substance has an existing classification for respiratory irritation (STOT SE 3; H335), noting in the opinion (among others) that "*RAC acknowledges the fact that methyl methacrylate is a respiratory irritant that can provoke asthmatic reactions due to its irritant effects and has an existing harmonised classification as STOT SE 3; H335*".

Therefore, in the opinion the issue of differentiating between respiratory irritation and respiratory sensitisation was considered in detail. In relation to this, it is stated in the opinion, in relation to early vs late or biphasic reactions that "*Three of these six subjects had a delayed reaction in the SIC, two had a bi-phasic reaction (meaning both early and delayed), and one had an early reaction. While irritant effects cannot always be ruled out in early reactions, late and bi-phasic reactions in adequately performed SICs are considered by experts a hallmark of an immunological response*". In addition, according to the opinion "*Regarding the differentiation between irritating and sensitising effects of MMA, it is important to note that also negative responses (i.e. no asthmatic response) in the SIC are seen in asthmatics tested for MMA*". After considering the evidence (described in the opinion) it is stated that "*RAC considers this information to demonstrate that it is not plausible that MMA induces reactions in asthmatics purely due to irritation*".

In contrast to the argument from the MSG that "*these short peak exposures cause irritation that, according to accepted guidelines, would have confounded the interpretation of the tests*", it is argued in the opinion that "*the measurement data available for the SICs were average levels, and therefore the presence of MMA-peaks could not be excluded. However, RAC considers it unlikely that peaks would have been of paramount importance in the cases described in Suojalehto et al. (2020)".*

The MSG have referred to "*a new publication and other documented evidence show that the measurement method used by FIOH could not detect short peak exposures that are now reliably known to occur when handling these types of products*".

Therefore at least five of the six subjects referred to had late or biphasic reactions which were considered to have been attributable to an immunological response to MMA at concentrations lower than what would be associated with irritation.

3. *that the claim of involvement of an immunological mechanism based upon observation of late asthmatic responses is not supported by the current science and recent literature, thereby not satisfying the requirement to demonstrate specificity to MMA*;

ECHA Response: In appendix 3 to the document submitted by MSG, a further positive SIC case with MMA is referred to as having been identified, from a "personal communication" with BG ETEM (March 2021), who "*had strong non-specific bronchial hyperreactivity and gave an early reaction in SIC making it unlikely that his OA was caused by MMA*". It is noted that insufficient detail on the case has been provided for a conclusion to be drawn and the role of MMA could not be ruled out.

The details of the reference to Pemberton and Kimber (2021) were not provided in the document, but it is assumed that this refers to the following paper (for which the Methacrylate Producers Association were listed as the sponsors):

Pemberton MA, Kimber I (2021). Classification of chemicals as respiratory allergens based on human data: Requirements and practical considerations. Regulatory Toxicology and Pharmacology, 123;104925 https://doi.org/10.1016/J.YRTPH.2021.104925

The arguments provided by MSG, including questioning the that "*late and bi-phasic reactions in adequately performed SICs are considered by experts a hallmark of an immunological response*" are from this paper. The paper indeed suggests, as cited in the MSG paper, that based on a study (Sastre et al, 2011) with bleach chlorine, "*it would be inappropriate to regard elicitation of a LAR in a challenge test as providing firm evidence of an allergic mechanism*". On the other hand, the RAC opinion included supplementary data to Suojalehto et al. (2020, received from the authors) from "*55 acrylate occupational asthma subjects, of which 24 had asthma considered by the authors to be ascertained as methacrylate induced. Of these, 20/24 had either late or bi-phasic positive SIC reactions. Apart from the six subjects that had specifically used MMA, most of these 24 were occupationally exposed to mixtures of methacrylates*". This contrasts with the 3/13 seen with chlorine in Sastre et al (2011).

Hence RAC had sufficient confidence that the evidence provided related to the involvement of immunologic mechanisms in the SIC tests with MMA to conclude on the classification as Resp sens 1.

4. *"that as a result of the lack of transparency of these undocumented SIC tests, and absence of critical information necessary to exclude non-specific hyperreactivity, it is not possible to confirm their reliability and good quality as required by CLP"*

ECHA Response: In this section the MSG have not quoted the CLP text correctly. There is in fact no sub-section 3.4.2.1.2.2 (c). The text which they have quoted is from Section 3.4.2.1.2.3, which states that "*the evidence referred to above could be:*" (a) clinical history …

Section 3.4.2.1.2.3 (b) states (as quoted elsewhere in the document) that "*data from one or more positive bronchial challenge tests with the substance conducted according to accepted guidelines for the determination of a specific hypersensitivity reaction*".

Clinical history and bronchial challenge tests are considered separately in the CLP Regulation.

5. *that new independent studies raise doubt as to the robustness of the RAC conclusion since they came to a conclusion that the evidence does not support classification as Resp. Sens*.

ECHA Response: ECHA notes that there are documents submitted or prepared for publication. The recently published review article by Sadekar et al (2022) does not include references to the more recent key studies used in the assessment of methyl methacrylate by RAC, and in fact includes a link to a list of respiratory sensitisers (referenced as ECHA 2021) which is in fact not an ECHA document, but appears to be part of Appendix VI to an EC report from 2009 (https://ec.europa.eu/health/scientific_committees/docs/vito_study_allergy_en.pdf).