MSC/M/57/2017
Adopted at MSC-58

Minutes
of the 57th Meeting of the Member State Committee (MSC-57)
11-15 December 2017

I. Summary Record of the Proceedings

Item 1 - Welcome and Apologies

The Chairman of the Committee, Mr Watze de Wolf, opened the meeting and welcomed the participants to the 57th meeting of the Member State Committee (MSC) (for the full list of attendees and further details see Part II of the minutes).

Item 2 - Adoption of the Agenda

The Agenda was adopted as provided for the meeting by the MSC Secretariat without further changes (final Agenda is attached to these minutes as Section III). One suggestion for an AOB item was made but it was finally dealt with under the update on appeals and court cases.

Item 3 - Declarations of conflicts of interest to the items on the Agenda

No potential conflicts of interests were declared by any members, experts or advisers with any item on the agenda of MSC-57.

Item 4 - Administrative issues

The Chairman reminded MSC that plenary meetings are organised in Secure WebEX and the remote participants should register well in advance. The Chairman also informed MSC that preparatory WebEX are not organised in Secure WebEX, however, the participants are still required to register in advance and all experts must be announced by the member. In case of unclarities the Chairman reserves the right to expel a participant to ensure that confidentiality is maintained.

The Chairman informed MSC of a new registration system which is in place in ECHA for all its meetings requiring everyone to register as a participant, including members. The participants were encouraged to join a demo to make the registrations for the next meeting easier.

The Chairman also informed MSC that the '2018 workplan' has been included as an information document to MSC-57. The document indicates that in 2018 two Rapporteurs will have to be appointed, one for the draft CoRAP update 2019-2021 and one for the 9th draft Recommendation to include priority substances in Annex XIV. The Chairman expects that each MSC member will discuss with their hierarchy their personal objectives for the year 2018, and consider volunteering as one of the Rapporteurs.

The Chairman informed MSC that the 'Report on other ECHA bodies' which had been distributed as information document to MSC was not produced for this meeting and the Committee's Secretariats plan to discontinue it for 2018 onwards. The Secretariat felt that as the information provided is easily available electronically via the ECHA website the added value of the report is less than when the Committees and Forum were first founded.

SECR informed MSC that the new MSC Rules of Procedure are available on ECHA website and S-CIRCABC with links to new templates for different declarations. As one of the updates, the declaration of commitment and declaration of interest have been combined. In addition, the forms do not have to be signed any more. Instead the email will be used as a record of the form being submitted from the person in question.

SECR informed MSC that for dossier and substance evaluation RCOMs SECR will discontinue making annexes separately available since embedding documents seems not to pose problems to the members anymore. One member who had experienced problems with embedded documents confirmed that this issue has been resolved.

- Outlook for MSC-58

The Chairman presented an estimation on the potential length of the next meeting which is expected to require approximately three and a half plenary days.

Item 5 – Minutes of the MSC-56 meeting

The minutes of MSC-56 were adopted as modified at the meeting.

Item 6 – Substance evaluation

1. Community Rolling Action Plan (CoRAP) & MSC opinion development

The Rapporteur introduced the working group (WG) members and explained how the work was organised to assess the draft CoRAP and prepare the draft MSC opinion. MSC was invited to send comments to the Rapporteur on the Annex and draft opinion by 17 January 2018 and to remind their eMSCA to update the justification documents of the substances they are evaluating latest by 10 January 2018.

2. Decision making process

a. Written procedure report on seeking agreement on draft decisions on substance evaluation

SECR introduced the report on the outcome of the written procedure (WP) for agreement seeking on one substance evaluation case (see Appendix to the final agenda in Section III for more detailed identification of the case). WP was launched on 16 November 2017 and closed on 27 November 2017. By the closing date, unanimous agreement was reached on the draft decision (DD).

b. Introduction to and preliminary discussion on draft decisions on substance evaluation after MS-CA's/ECHA reactions *(Session 1, open session)*

c. Seeking agreement on draft decisions when amendments were proposed by MS-CA's/ECHA *(Session 2, closed)*

SEV-DK-010/2012 Ziram (EC No. 205-288-3)

Session 1 (open)

One representative of the Registrants participated in the initial discussion. In absence of specific confidentiality concerns in draft decisions (DDs), an open session was held.

The eMSCA from Denmark (DK-CA) presented the SEv outcome of the above-mentioned substance. The initial grounds for concern as placed on the Community Rolling Action Plan (CoRAP) were that of possible endocrine disrupting properties, and risk characterisation ratios (RCRs) in the close vicinity of 1 (workers), which indicates a need of clarification and possible reduction of exposure. A DD tackling these concerns was sent for the first Registrants' comments in 2013. The Registrants updated the registration dossier with supplementary data on exposure. The data provided was sufficient for the eMSCA to withdraw the initial requests based on the concerns related to human exposure. Thus the concern on the exposure was clarified and the RCR consequently reduced. Furthermore, a study on developmental neurotoxicity study, OECD 426 had already been performed, and the Registrants included it in the updated registration dossier.

Based on the information in the updated dossier the eMSCA concluded, that ziram may cause adverse effects on the developing nervous system manifested as increased activity before weaning and in adulthood, but no final conclusions could be drawn based on the available studies. In addition, in the course of the evaluation the eMSCA identified specific concerns regarding involvement of ziram in the development of parkinsonian disorders in papers from the public literature. Consequently the eMSCA considered that a revised testing strategy was required to clarify the concerns for developmental neurotoxicity and parkinsionian disorders.

The DD consulted with the MSCAs and ECHA requested for a combined developmental neurotoxicity study (OECD TG 426) and neurotoxicity study in rats (OECD TG 424), oral route of administration via feed, including additional endpoints to investigate effects linked to development of Parkinson's Disease in the OECD TG 424 part of the study.

MSC was guided by the expert from the eMSCA through the information on the substance including four proposal for amendments (PfAs) received from four MSCAs, the Registrants' comments on the PfAs and the eMSCA's response to them.

The first PfA proposed to broaden the investigation of effects to neurodegeneration in general rather than limiting it to Parkinson's disease alone. The second PfA proposed to investigate effects on the nervous system more broadly, while highlighting similarities to pathways identified in Parkinson's disease. The third PfA proposed to remove the requested study. They were of the view that any new testing should be conditional on a

thorough evaluation of the lifetime rodent studies for clinical signs consistent with Parkinson's disease. They believed that there is sufficient data already available to make a robust assessment of the developmental neurotoxicity potential of ziram. In their opinion, these studies did not provide any convincing evidence that ziram is a developmental neurotoxicant. Furthermore, they did not agree that there was a concern for the development of Parkinson's disease. In their view, even if *in vitro* mechanistic data suggested that it is biologically plausible that ziram could be implicated in the development of Parkinson's disease, this did not appear to be borne out by the available animal data. Furthermore, given the concerns expressed by EFSA regarding the utility of the rat as a reliable model for investigation of Parkinson's disease, this PfA submitter asked the eMSCA to further justify the requested investigations. The fourth PfA proposed some edits to clarify the text throughout the DD.

The Registrants submitted written comments on the PfAs. They did not agree with the requested study. They submitted a position paper that lists the available data on these endpoints and concluded that ziram does not cause relevant neurodegenerative effects. At the meeting the Registrants' representative went through some of these highlighting that each study did not show any effect for parkinsonian disorders. The behavioural effects collected did not show any parkinsonian signs. He argued that the *in vivo* models did not have metabolic capacity to simulate ziram metabolism and did not have a blood brain barrier to mitigate the effects of parkinsonian disease on the brain. Since all studies were carried out according to current standards it was not clear to the Registrants what else needed to be done to improve their quality. The studies started in the young adults covering also the later stages in their life span. The Registrants' representative expressed his surprise that instead of the eMSCA asking the Registrants for the full study report of the neurotoxicity study, the eMSCA was requesting for an extensive set of testing which he described as unjustifiable. He continued by explaining that investigation of effects on rotarod performance were included in the 90-day neurotoxicity study and the rats showed no effects. Ziram has been evaluated a number of times and developmental neurotoxicity and neurodegeneration have never been raised as a concern. The representative of the Registrants linked the delayed development of the offspring seen in the 90-day neurotoxicity study at the highest dose with the maternal toxicity evidenced by low body weight and an increase of locomotive activity in the offspring. This lack of body weight gain correlated with lack of habituation which did not correlate to neurotoxicity. Hence in his view the request seemed to be based on epidemiological studies alone.

During the meeting discussion the PfA submitter that did not agree with the request, explained in detail their PfA saying that Parkinson's disease has been linked to pesticides in general but not to any particular substance. The only evidence the request is based on, is that of increased motor activity which in the view of the PfA submitter is not evidence of Parkinson's disease. The Registrants' representative complemented by saying that the study did not have any specific mention of any abnormal findings in the mid-brain sections. Ziram never reached the brain since it was not detected in the tissue. One NGO stakeholder representative expressed the view that epidemiological data should be used together with other non *in vivo* data to address concerns and since rats do not capture parkinsonian effects in humans, they think that the study should not be requested.

Regarding the epidemiological studies used in the weight of evidence, the eMSCA expert explained that they agree that they cannot show causation between ziram exposure and development of Parkinsonian disorders but these studies show an association between the two, which raises a concern together with the mechanistic results available.

Regarding the mechanistic studies (*in vivo* and *ex vivo* studies with neurons prepared from rats) and the comment made by the Registrants' representative that metabolic activation was absent and there was no blood brain barrier, the eMSCA expert explained that they still could not conclude that the brain was not exposed to ziram based on the available data. The current data showed that there was no accumulation in the brain but it did not show that there was no exposure. The observation of effects in the pups showed that there were effects on the brain. The eMSCA expert further explained that even though the results from the *in vivo* and *ex vivo* studies might seem contradictory yet in their view

they are not since ziram may act through more than one mode of action leading to several types of effects during the development and lifetime of an organism.

Regarding the lack of effect seen with regular staining in the mid-brain of the animals in the 90-day neurotoxicity study, the eMSCA expert explained that the animals have been exposed for too short time and at too early age to investigate the parkinsonian effects. Furthermore, the currently used guideline studies and the 90-day neurotoxicity study available, do not include the proper sectioning and staining of the brain to detect parkinsonian disorders described in the EFSA scientific opinion from 2017[1]. Hence, the available study did not remove the concern that ziram reached and may cause adverse effects in the brain.

Regarding the rat as the right model to investigate these parkinsonian disorder effects, eMSCA expert acknowledged that the rat does not measure all the symptoms seen in humans. During their evaluation they consulted a member from the EFSA PPPR panel who was part of the discussions in the drafting of the EFSA 2017 scientific opinion and verified to them that the rat study as requested in the SEv DD was adequate to investigate this concern since the investigations requested are in line with the adverse outcome pathway (AOP) developed by the EFSA PPPR panel for parkinsonian motor deficit.

Regarding the comment made by the Registrants' representative on requesting a totally new study instead of the full study report of an existing study, the eMSCA explained that the Registrants had time to provide the full study reports of Lamb 1993 and Lamb 1994 since 2012, yet this was not done. Even the robust study summaries in the updated registration dossier did not refer to the neurotoxicity data brought forward by the Registrants in writing when commenting on the PfAs and at the meeting. The Registrants' representative replied that the robust study summary for the 90-d neurotoxicity study clearly mentions the absence of behavioural and neuropathological findings. The neurodegeneration issue was not raised by the eMSCA before until very recently. The full study report is of course available, but this was never requested. There is no way for registrants to submit unsolicited dossier updates during evaluation. Another MSC member reminded the Registrants' representative of the general obligation under REACH to include any new studies once they become available. The Registrants' representative explained that the new studies were not available to them for submission under REACH, but were part of the obligations for one of the Registrants under the Plant Protection Products Regulation.

Session 2 (closed)

All the arguments raised in the open sessions were re-discussed in the closed session. Special focus was given on the information that is available to the Registrants which was not made available in the registration dossier and on how to better reflect the neurotoxic (neurodegenerative effects) concern without linking ziram to parkinson's disease since there are over 100 neurodegenerative diseases. The term 'Parkinson's disease' was considered to be too specific and 'Neurodegenerative effects' was considered to be too general hence reference to Parkinsonian disorders was instead to be considered.

Regarding the information available on ziram especially in the context of the plant protection products legislation, MSC agreed unanimously to keep the request for a combined developmental neurotoxicity study (OECD TG 426) and neurotoxicity study in rats (OECD TG 424), oral route of administration via feed since the data that the Registrants' representative was referring to at the meeting was not available to the eMSCA and could not have been evaluated. MSC also unanimously agreed that even if the eMSCA had access to the full study reports for Lamb 1993 and Lamb 1994, this would not have changed the request, since specific sectioning of the brain and staining of special areas with relevant staining methods were not included in those studies.

[1] EFSA 2017. Scientific Opinion. EFSA Panel on Plant Protection Products and their residues (PPR). Investigation into experimental toxicological properties of plant protection products having a potential link to Parkinson's disease and childhood leukaemia. EFSA Journal 2017; 15(3):4691 http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2017.4691/epdf

Regarding the better reflection of the neurotoxic (neurodegenerative effects) concern in the DD, MSC agreed unanimously to reword slightly the request by referring to Annex 3 of the decision for the additional investigations in the OECD TG 424 part of the study, without referring to neurodegenerative effects linked to Parkinson's disease. Instead MSC unanimously agreed to refer to parkinsonian disorders as defined in the scientific opinion of the PPPR Panel (EFSA 2017).

The MSC unanimously agreed on the decision as amended in the meeting. The member from UK abstained from voting.

SEV-2-DK-005/2013 4,4'-methylenebis[N,N-bis(2,3- epoxypropyl)aniline (EC No 249-204-3)

Session 1 (open)

One representative of the Registrants participated in the initial discussion. In absence of specific confidentiality concerns in DD, an open session was held.

The eMSCA from Denmark (DK-CA) presented the SEv outcome of the above-mentioned substance. The initial grounds for concern as placed on the CoRAP were that of mutagenicity, carcinogenicity and wide dispersive use. The substance evaluation was carried out in 2013 and a decision unanimously agreed by MSC was sent to the Registrant tackling these concerns. Following receipt of an update to the registration dossier, including the result of an in vivo mammalian alkaline comet assay in rat by oral gavage (OECD 489), the eMSCA considered that further information was required to clarify the concern from germ cell mutagenicity, hence a second decision was drafted by the eMSCA as a follow-up.

The DD consulted with the MSCAs and ECHA requested for a transgenic rodent (TGR) somatic and germ cell gene mutation assays in mouse or rat by oral gavage (EU TM B.58./OECD TG 488) following a 28-day exposure with a subsequent 3 days sampling period for somatic tissue, and 49 days (mouse), or 70 days (rat) sampling period for germ cells. It is requested to sample and analyse male germ cells from the vas deferens/cauda epididymis.

MSC was guided by the expert from the eMSCA through the information on the substance including seven PfAs received from four MSCAs, the Registrants' comments on the PfAs and the eMSCA's response to them.

The four PfA submitters agreed with the mutagenicity concern. In their view the positive result of the in vivo comet assay confirms the concern regarding induction of mutagenic effects of the test substance or its metabolites at least for somatic cells. Furthermore, it increases the concern for a possible induction of mutagenic effects on germ cells, which makes an in vivo mammalian germ cell mutagenicity test necessary. Due to the already seen positive mutagenic effects in somatic cells, all four PfA submitters propose not to sample the somatic cells (after 3 days) but to sample only for the germ cells. In the view of all PfA submitters it can be expected that there is already enough information from *in vitro* and *in vivo* studies to conclude that the substance is a somatic cell mutagen and can be classified as Muta 2. PfAs proposing different sampling time for germ cells after exposure were received. Two MSCAs proposed to sample germ cells 7 weeks (mouse) or 10 weeks (rat) after the end of the 28-day treatment, whilst a third MSCA proposed to sample germ cells 28 days after the 28-day exposure regime.

The latter's proposal was based on the latest scientific knowledge, according to current expert discussions in an ILSI-HESI working group, showing that the highest sensitivity is obtained with the sampling of germ cells from the seminiferous tubules 28 days after the end of the treatment. However, this PfA mentioned that this outcome from the expert discussions was not yet documented in a report or in the OECD TG 488. If the scientific community ultimately did not accept the 28+28 days setup and the germ cells from the seminiferous tubules sampled and analysed at 28 + 28 days yield a negative result then a request for other studies, for example to sample germ cells from the vas deferens/cauda epididymis at 28 + 49/70 days, may be made in a subsequent decision. This third MSCA therefore, proposed to sample germ cells 28 days after the 28-day exposure and provided

two options for sampling of somatic cells in case the eMSCA still wanted to sample the somatic cells. If the 28 + 28 days in germ cells yields a negative result a request for other studies may be made in a subsequent decision.

The fourth MSCA noticed the ongoing TGR notification in the updated registration dossier of April 2017. In fact, during the consultation on the first draft of the follow-up DD, the Registrants proposed to conduct the TGR with an exposure of 28 days and sampling after three days for germ cells from the vas deferens/ cauda epididymis, liver, glandular stomach and duodenum, and a conditional follow-up study with a 10-week post exposure period in the event the 3-day assay is negative. The Registrants started the test with the design they proposed in April 2017 without waiting for the formal REACH decision making process which ensures the unanimous agreement of the authorities on the appropriate design of the TGR assay.

Even though the fourth MSCA normally would support the approach proposed by the eMSCA, they suggested to acknowledge the ongoing testing which would inform on the need for the requested study. They proposed that to protect animal welfare, eMSCA was to agree with the strategy proposed by the Registrants in their comments on the first follow-up DD. If this in respect to germ cell mutagenicity resulted in an unequivocal positive outcome, the appropriate classification and risk management measures should be adopted. If this in respect to germ cell mutagenicity resulted in a negative or equivocal outcome a TGR with 28 days exposure + 10 week sampling time would be needed to be initiated without delay.

The Registrants submitted written comments on the received PfAs. In response to the PfA from the fourth MSCA the Registrant/his representative confirmed both in writing and at the meeting that they have initiated a TGR study (28+3 days) and that the in-life phase of the study has been completed by the time of the meeting. He further stated that mutation analysis had not been started and that the complete results of the study were expected to be available in February 2018. As the TGR study was currently underway the Registrant disagreed with the PfAs to conduct the study with the 28-day exposure + 10 week sampling. This may be reconsidered once the current (28+3 day) study was complete. The Registrant representative further commented that duodenum, stomach and liver have already been sampled for analysis. The Registrant representative explained that the test design was established following discussion with the labs which are also members of the ILSE-HESI working group. He also highlighted that the analysis of these samples will either i) confirm mutagenicity in somatic cells or ii) provide opposing results to those observed in the comet assay and thereby, in their view, indicate that the comet assay is not valid for epoxy based substances and therefore it would be unwarranted to classify the substance as a Cat.2 mutagen.

During the discussion the eMSCA expert explained that the Registrant reached out to the eMSCA on the test design in March 2017. The eMSCA however, informed him to wait for the MSC decision before starting the test. In response to the comment by the Registrant representative that they have a negative micronucleus test (MNT), the eMSCA representative explained that it is possible for a substance to be positive for gene mutations (detected by TGR) but not for chromosomal aberrations (detected by MNT).

When further clarification on the early start of the test was requested, the Registrant representative explained that the test was started out of their own initiative and their sense of responsibility towards worker protection, without receiving any formal request for such testing from any authority. However, MSC explained that time is needed before testing is approved and test results are available. In case of safety concerns, the Registrants should try to prevent the exposure to the substance as if the substance would have an adverse effect. A precautionary approach in the use of the substance is strongly advised if not expected. It was also explained that the final decision that would be sent to the Registrant might not request for testing of somatic cells, even if such testing had started already. The premature starting of the test, denied MSC the possibility to influence the design and minimise animal testing. This is definitely not the approach other Registrants should adopt, and Registrants shall await the decision before starting the test. It was again stressed that wherever the Registrants have any concern the proper risk

management measures should be put in place. To this the Registrant representative explained that the risk management measures in place are based on Muta. 2 classification.

The PfA submitter that proposed to sample germ cells after 28 + 28 days, informed MSC that they accepted the arguments made by the eMSCA in the updated DD for not accepting their PfA and agreed with the suggestion from eMSCA to sample the germ cells after 28 + 70 days in rat.

Session 2 (closed)

When discussing the best way forward, that is, if to proceed with the test that was started by the Registrant or to keep the request for the test design as proposed by the eMSCA, the MSC acknowledged that a negative result in germ cells using the 28 + 3 days testing strategy as carried out by the Registrant would not be sufficient for clarifying the concern. More specifically, this sampling time may give false negative results in germ cells because the most sensitive (mitotically active) cell population has not been adequately exposed to the test material. However, if the Registrant reports data showing that the 28 + 3 days testing strategy yielded an unequivocally positive result in germ cells, this would normally be expected to be sufficient for harmonised classification in Muta, cat. 1B and no further testing (TGR 28 + 49/70 days) would be needed.

MSC agreed unanimously to not request the sampling of somatic cells, to keep the request for sampling of germ cells at 49 days (mouse) or 70 days (rat) after the 28-day exposure regime, and to sample male germ cells from cauda epididymis and not from vas deferens**.**

Item 7 – Dossier evaluation

a. Written procedure report on seeking agreement on draft decisions on dossier evaluation

SECR introduced the report on the outcome of the written procedure (WP) for agreement seeking on ten dossier evaluation cases (see "Appendix to the MSC-57 agenda" in Section III *Final agenda* for more detailed identification of the cases). WP was launched on 16 November 2017. By the closing date 27 November 2017, MSC reached unanimous agreement on eight DDs. For two DDs, MSC Chairman terminated the WP on the basis of Article 20(6) of the MSC Rules of Procedure.

b. Introduction to and preliminary discussion on draft decisions on compliance checks and testing proposals when amendments were proposed by MS-CA's (Session 1, open session)

c. Seeking agreement on draft decisions on compliance checks and testing proposal examinations when amendments were proposed by MS-CA's *(Session 2, closed)*

CCH-106/2017 2-ethylhexyl salicylate (EC No. 204-263-4)

Session 1 (open)

Exceptionally three representatives of the Registrant participated in the initial discussion (same representatives as for CCH-107/2017). In absence of specific confidentiality concerns in the DD, an open session was held.

SECR presented the seven PfAs received from two MSCAs, the Registrants' comments on the PfAs and SECR responses to them.

In one PfA on read-across it was agreed that the approach should be rejected, however it was proposed to include a reference on an existing Risk Assessment Committee (RAC) opinion on the harmonised classification of salicylic acid, which includes additional information (e.g. on toxicokinetics).

Two PfAs on Long term toxicity testing on fish (OECD TG 210 or OECD TG 234) were submitted. One suggested to remove all references to require examination of endocrine disrupting (ED) potential, even as a "testing alternative" via OECD TG 234, because the ED concern may be best addressed in substance evaluation. The other suggested to request

only OECD TG 234 to adequately cover information requirement and address potential ED properties and drop OECD TG 210.

Another PfA on Long-term toxicity testing on invertebrates (OECD TG 211) suggested to remove examination of sex ratio changes in Daphnia long-term reproductive toxicity test because of unclear grounds and possible premature conclusion on ED potential. Furthermore any results may be difficult to relate specifically to an ED cause and effect, and ED would be best considered in SEv.

One PfA on Sub-chronic toxicity study (90-day) suggested to remove the request because there is no justification to request the study at dose levels higher than the dose levels found in the existing 90-day study (OECD TG 408). Also a new 90-day study would not lead to a more stringent classification or DNEL derivation. Alternatively, the PfA suggested that if the study is kept, then alignment to the sequential testing text with EOGRTS would be required.

Another PfA suggested to delete the request for Pre-natal developmental toxicity study (PNDT) because 2-ethylhexanoic acid (a metabolite of the hydrolysis product 2-ethylhexanol) has a harmonised classification for developmental toxicity (Category 2; H361d) and RAC used a read across approach to conclude on classification of the hydrolysis product salicylic acid as a category 2 developmental toxicant. If shown to rapidly hydrolyse, information on toxicologically significant metabolites could be used for classification and risk characterisation.

In another PfA on Extended one-generation reproductive toxicity study (EOGRTS) it was suggested to a) remove the test if no new 90-day study is requested because the existing 90-day study does not indicate adverse effects on reproductive organs or tissues, nor concerns on reproductive toxicity; and because a non-statistically significant effect (prolonged gestation length from OECD TG 421) should not be used to trigger the study; b) if EOGRTS is kept it suggested to remove the inclusion of F2 and DNT/DIT cohorts; and c) if EOGRTS is kept, then to align with the sequential testing text to include another deadline, that is to request a deadline of 12 months for submitting results from the 90-day study before commencing the EOGRTS

SECR did not amend the DD in advance of the meeting based on the PfAs.

The Registrant had provided written comments on the DD (not reflected here) and on the PfAs.

The Registrant's representative highlighted in the meeting that both substances, 2-ethylhexyl salicylate and Homosalate (CCH-107/2017), are used in cosmetic products, for this reason the Registrant's representative considered that the potential consumer exposure is out of the scope of REACH. In their view ECHA's request for a new Sub-chronic toxicity study (90-day) based only on slight effects in the existing study (e.g. effects on food consumption or changes in body weight) is scientifically not justified. They stressed that the data provided in the dossier on developmental toxicity studies and systemic toxicity can be interpreted because of the hydrolysis of the substance, however the full set of results on the effects caused by the hydrolysis products in relation to systemic toxicity are not yet available. The Registrant's representatives stressed that relevant effects occur at higher doses in other studies and though justified the dose setting for the existing 90 day study. Consequently guidance documents and the interest of animal welfare do not sustain additional animal testing.

With regards to the requests for EOGRTS the Registrants representatives explained that the substance is imported and formulated in EU and at present is listed in the CoRAP list for substance evaluation (due to ED concern). For this reasons, the Registrants' representatives considered that the entire ED discussion is premature and not justified at this stage.

With regards to the requests for aquatic toxicity testing the representatives of the Registrants highlighted that they are committed to perform Long-term toxicity testing on aquatic invertebrates (*Daphnia magna* reproduction test, OECD TG 211, standard design) and agrees with the PfA requesting to remove examination of sex ratio changes in *Daphnia*

magna. Referring to the requested fish study, in their view it is premature to assess and conclude on ED potential (see above) and the additional parameters requested are disproportionate and goes beyond the scheme of dossier evaluation. The representatives of the Registrants also highlighted that the OECD 234 is not mentioned in the current ECHA Guidance on Information Requirements R7b Version 2017.

SECR reiterated that in the ECHA guidance, the draft of FSDT was already mentioned.

During the discussion the Chairman reminded that MSC as a dynamic scientific committee in the decision making process can go beyond guidance documents to take into account the latest scientific developments, and the same possibility to go beyond the guidance, if scientifically justified, is available to the Registrants.

The MSC thoroughly discussed the issues raised in the PfAs, Registrants' comments and the way they have been addressed in the revised DD. One MSC member supported the view of Registrant's representatives that for aquatic toxicity testing only OECD TG 210 should be requested, while some other MSC members supported the request for only OECD TG 234. One MSC mentioned that at least a limited OECD TG 210 may be needed for a proper concentration setting of OECD TG 234.

The MSC member supporting the option of the OECD 210 noted a number of issues with requesting the FSDT at CCH and considered that the choice of ED test should be made under substance evaluation, where fuller evaluation (and consultation with the ED EG could occur) to ensure the most appropriate information is obtained. They cited the points that they had raised in their RCOM and in the more general consultation on the use of the FSDT in Dossier evaluation.

An MSC member highlighted that ECHA's guidance from 2009 on ecotoxicity, persistency and bioaccumulation was not thoroughly updated, and in particular updates made available for the aquatic toxicity section occurred when no standards for investigating ED existed, supporting ECHA's request for OECD TG 234. He agreed with ECHA's view on EOGRTS design as requested, and supported the PfA on removing examination of sex ratio changes in Daphnia.

SECR clarified that according to the guidance the doses used in Sub-chronic toxicity study (90-day) have to be set at levels which induce toxicity but not death, and that in this respect the provided data was not acceptable, hence there is a data gap. The Registrant did not agree that OECD TG 422 provide sufficient triggers for DNT and DIT. The Registrant supports that the OECD 422 can not trigger DNT and DIT.

Regarding the different details of information given in the CSR in the dossier of 2-ethylhexyl salicylate in comparison with the data provided for homosalate, the Registrant's representatives indicated that the two dossiers were prepared at different times.

Session 2 (closed)

With regards to testing strategy for 90 day sub-chronic toxicity study and EOGRTS study design SECR presented to MSC three options: 1) to request an EOGRTS including cohorts 2A, 2B and 3, and not to request a 90 day sub-chronic toxicity study; 2) to request an EOGRTS including cohorts 2A, 2B and 3, and to request a 90 day sub-chronic toxicity study; and 3) to request an EOGRTS but not to include cohorts 2A, 2B and 3, and to request a 90 day sub-chronic toxicity study. In all three options SECR indicated that the EOGRTS, if requested, would exclude the extension of Cohort 1B.

Some MSC members were also concerned on the most appropriate test(s) to be requested, taking into account that the safe use of the substance in cosmetics products has been assessed under the Cosmetic Products Regulation (EC) No 1223/2009. It was clarified that no animal testing should be performed to meet the information requirements of the REACH human health endpoints, with substances which are only exposing humans due to the use exclusively in cosmetic products. If occupational exposure, however, also occur testing may be required to assess the hazards for workers in industrial settings. Furthermore, one MSC member referred to an ECHA decision for a substance with cosmetic uses which had been appealed and where the Board of Appeal decided to annul the Contested Decision because it should have expressly referred to ECHA's factsheet on the relationship between

REACH Regulation and the Cosmetics Regulation, which would have enabled the Registrant to rely on the fact sheet[2] or to contest it.

With regards to long term toxicity to fish SECR presented to MSC the following options: 1) to request only OECD TG 210, which may not be ideal option because of the possible duplication of animal studies (as the substance is listed in draft CoRAP[3] SEv and if the OECD TG 234 was requested); 2) to request only OECD TG 234, however extensive preliminary studies on fish might be needed anyway for dose setting; and 3) to allow option between OECD TG 234 or OECD TG 210, taking into account that Registrant may perform only OECD TG 210.

Some MSC members considered that to clarify ED concern and to provide the best possible information for risk assessment (including the likely most sensitive endpoints for the specific substance) with potential ED" identified as the initial ground for concern the decision should request only OECD TG 234, and pointed out that, in line with animal welfare considerations, a stronger justification in the decision for this request should be provided. Other MSC members motivated their support for the request of OECD TG 210 because of difficulties to establish concentration range to be administered in the test OECD TG 234, and that such a test may not be sufficient to fully clarify the ED concern. One adviser explained that it would be preferable to evaluate the data in more detail under substance evaluation to determine the appropriate ED testing, including consideration of data for other salicylates, as well as the requested mammalian test. In his view the request for the FSDT based on the likely need under substance evaluation appears to pre-judge the outcome of that assessment. SECR stressed that according to REACH Regulation and guidance documents triggering one test or another is possible, once that is justified to address a concern and then to ask specifically the test which addresses it. SECR also clarified that giving the Registrants a choice between the two tests, possibly the Registrant would perform OECD TG 210, as they declared in open session. Further testing (under SEv) would then be needed to address the concern raised which would then extend the timelines.

It was further considered that the OECD TG 234 should be performed such that data for risk assessment would be provided. Hence 5 test concentrations have to be selected.

One MSC member explained that in the test guideline it is specified that the concentration of the substance to be administered should not be higher than 10 mg/l, or 1:10 of LC 50 if available. Another MSC member highlighted that in the decision the highest concentration should not be indicated, however, there could in addition be a recommendation depending on weight gain and that the, highest test concentration, should be at a concentration level which would not cause significant mortality.

Based on all these considerations, MSC concluded to amend the draft decision as follows: to delete the request for Sub-chronic toxicity study (90-day) (OECD TG 408) and to include a note for consideration to the Registrant under the EOGRTS request concerning the dose level selection and on the use of the information generated to (re)evaluate the general toxicity of the substance; to keep the request for EOGRTS with inclusion of DNT and DIT cohorts however without the inclusion of the extension of the Cohort 1B (because the consumer use of this substance is outside the scope of the REACH and thus not a relevant trigger to request extension of Cohort 1B, see the discussion for CCH-107/2017); to keep the request for Long-term toxicity testing on fish (OECD TG 234); and to delete the option between OECD TG 234 and OECD TG 210 for long-term toxicity testing on fish by removing the request for a Fish, early-life stage toxicity test OECD TG 210, and to remove request for examination of additional optional parameters (sex ratio change) from the long-term toxicity study with *Daphnia magna* (OECD TG 211). With regards to the exclusive use of the substance in cosmetic products MSC agreed to introduce a note to explain why the studies have been requested, that is to assess the hazard of workers.

[2] http://echa.europa.eu/documents/10162/13628/reach_cosmetics_factsheet_en.pdf/2fbcf6bf-cc78-4a2c-83fa-43ca87cfb314

[3] https://echa.europa.eu/documents/10162/13628/corap_list_2018- 2020_en.pdf/3be44b84-5d72-01fe-f8d7-3a5a9c27951e

MSC agreed unanimously to the DD as amended during the meeting. The MSC member from UK abstained from voting.

CCH-107/2017 Homosalate (EC No. 204-260-8)

Exceptionally, three representatives of the Registrant participated in the initial discussion (same representatives as for CCH-106/2017). In absence of specific confidentiality concerns in the DD, an open session was held.

SECR presented the three PfAs received from one MSCA, the Registrants' comments on the PfAs and SECR responses to them.

In one PfA on read-across it was agreed that the approach should be rejected however it was proposed to include a reference on an existing Risk Assessment Committee (RAC) opinion on the harmonised classification of salicylic acid to be considered in a risk assessment together with toxicokinetic data.

A PfA on sub-chronic toxicity study (90-day) (identical to a PfA submitted for CCH-106/2017) suggested to remove the request because there is no justification to request the study at dose levels higher than the dose levels found in the existing 90-day study (OECD TG 408). Also, a new 90-day study would not lead to a more stringent classification or DNEL derivation. Alternatively, the PfA suggested that if the study is kept, then alignment to the sequential testing text with EOGRTS would be required.

With regards to Extended one-generation reproductive toxicity study (EOGRTS) the PfA suggested to remove the request, regardless of whether or not a robust read across justification is provided, because in the view of the PfA submitter a) the results of OECD TG 422 screening study used for triggering EOGRTS are unacceptable for regulatory decision-making due to the unconventional photoperiod applied during the study resulted in reproductive toxicity and unreliable data, and because b) the *in vitro* androgen receptor binding assay alone does not provide a sufficient trigger. It was also requested (in the same way as for CCH-106/2017) that if EOGRTS is kept a) to remove the inclusion of F2 and DNT/DIT cohorts; and b) if EOGRTS is kept, then to align with the sequential testing text to include another deadline, that is to request a deadline of 12 months for submitting results from the 90-day study before commencing the EOGRTS.

In another PfA on EOGRTS it was suggested to a) remove the test if no new 90-day study is requested because existing 90-day study does not indicate adverse effects on reproductive organs or tissues, nor concerns on reproductive toxicity; and because a non-statistically significant effect (prolonged gestation length from OECD TG 421) should not be used to trigger the study; b) if EOGRTS is kept it suggested to remove the inclusion of F2 and DNT/DIT cohorts; and c) if EOGRTS is kept, then to align with the sequential testing text to include the two deadlines, that is to request a deadline of 12 months for submitting results from 90-day study.SECR did not amend the DD in advance of the meeting based on the PfAs.

The Registrants had provided written comments on the DD (not reflected here) and on the PfAs.

They highlighted in the meeting that both substances, homosalate and 2-ethylhexyl salicylate (CCH-106/2017) are used exclusively in cosmetic products, for this reason the Registrant considered that the potential consumer exposure is out of the scope of REACH. The Registrant's representatives reiterated that they agreed with the PfA to provide the option to strengthen the read-across with additional mechanistic studies. However additional from ongoing studies forming the basis for predicting the properties of the registered substance cannot be generated in short time, so additional time is needed to strenghten the read-across. The Registrant's representative also stressed that it is difficult to consider the same study (OECD 422, permanent light exposure) as Klimisch 2 for systemic toxicity and on the same time as Klimisch 3 for reproductive toxicity (with artificial findings) Therefore the Registrant has choosen Klimisch 2 for the complete study, but used an weight of evidence approach for the reproductive part.

The Registrant's representatives provided a detailed time schedule for the proposed tests. They highlighted that that based on feedback from CROs the lack of capacity mainly comes

from the need to have animals and analytics at the same time, hence they asked for the possibility of extending the timeline.

During the discussion several MSC members encouraged strengthening the read-across. They put questions marks around the reliability of the data provided within the OECD 422 study, e.g. body weight gain/loss and other changes especially with regards to reproductive toxicity which could depend on the photoperiod deviations during the test.

Moreover one stakeholder representative, referring to the Court of Justice of the European Union[4] and to the European Ombudsman opinion from 2017, highlighted that it is not proportionate to ask for animal tests for HH assessment for chemicals used in cosmetics, as it is specified in the Cosmetic Products Regulation (EC) No 1223/2009, and that the requests should be waived unless there are serious health concerns. The Registrants considered it essential that the option to strengthen the read across is stated in the final decision.

SECR specified that the Registrant has the possibility to adapt and strengthen the read-across, however, there is no guarantee that an improved read-across justification would be sufficient completely remove the concern.

Registrant's representatives explained that the substance is imported and formulated in EU under strictly controlled conditions and only for cosmetic use, hence they considered that there is no exposure to workers.

One MSC member informed that the Norwegian authorities performed a screening study which indicated that the two substances can be found in the environment, thus suggesting significant exposure or widespread use.

Another member considered that the effects observed in the OECD TG 422 study suggested as the trigger for generation of the F2 cohort should be confirmed within the EOGRTS. However, ECHA-S considered that the interim results from the EOGRTS are not needed to maintain the request for F2.

Session 2 (closed)

MSC discussed the proper level of justification needed with regards to exposure based triggering to include the extension of Cohort 1B to produce the F2 generation in the EOGRTS design, confirming the points raised in the ECHA Factsheet on the relationship between REACH and Cosmetics Regulations. One MSC member's expert stressed that literature data and the results from their national strategy of *in vitro* tests performed to determine ED estrogenic and antiandrogenic effects of this substance support the extension of Cohort 1B in EOGRTS design. Moreover some MSC members considered that significant environmental exposure and the high tonnage could justify the extension of Cohort 1B.

SECR clarified that in this particular case, according to REACH and cosmetics regulation, the triggers to include the F2 in EOGRTS design, is not necessarily supported by worker exposure but that it could be supported by non-cosmetic, professional and mixed uses which may result in exposure to consumers and the environment. A member noted that regarding the OECD TG 422 test results, the difference in effects in the control and dosed groups are still there irrespective of the continuous lighting indicating that the effects reflect the treatment with the substance.

SECR proposed to amend the draft decision and to remove the request for including the extension of Cohort 1B animals to produce the F2 generation in the EOGRTS study design. Moreover, a note was added to further clarify the exclusive use of the substance in cosmetic products and to explain why the human health studies have been requested, that is to assess the hazard of workers. Additionally MSC considered that the timeline has been set to allow for sequential testing therefore agreed not to modify the deadline. Other main aspects of the decision remained unchanged.

Based on the discussion MSC agreed unanimously to the DD as amended at the meeting.

[4] Court of Justice of the European Union case C592/14

CCH-113/2017 Reaction mass of 4-tert-butylphenol and 1,3-phenylene-dimethanamine and 2-({[3-(aminomethyl) benzyl]amino}methyl)-4-tert-butylphenol (List No. 939-071-6)

Session 1 (open)

One representative of the Registrant participated in the initial discussion. In absence of specific confidentiality concerns in the DD, an open session was held.

SECR explained that one PfA was received to the ECHA's DD. The PfA on extended one-generation reproductive toxicity study (EOGRTS) suggested including developmental neurotoxicity (DNT) cohorts 2A and 2B in the study. According to the PfA, the major constituent and close structural analogue of the substance (4-tert-butylphenol, hereinafter PTBP) has been identified as an endocrine disruptor (ED) in the environment and it disrupts the sex hormone balance in rats based on available data. The justification for inclusion of DNT in the PfA referred also to *in vivo* information on the UVCB substance from a 90-day study in rats showing lower mean, absolute, and relative uterus weights accompanied by treatment-related atrophy of the cervix, uterus, and vagina. These types of apical adverse effects are in accordance with the concern that such effects can be caused by an anti-estrogenic activity *in vivo* of the UVCB substance.

SECR had not modified the DD in advance of the meeting based on this PfA.

The Registrant had provided written comments on the DD (not reflected here) and on the PfA, disagreeing with this PfA. The representative of the Registrant provided details on the composition of the substance. He then confirmed his disagreement with the PfA, highlighting that the toxicity profile of PTBP had not raised particular concerns for DNT when reviewed in the substance evaluation process. He highlighted the interest in delaying the testing in this CCH until having conducted testing with PTBP, which was requested in substance evaluation decision, to utilise those to clarify needs for further testing and, if deemed necessary for this registered substance, to guide on the study design. The representative of the Registrant also made a note having submitted a 90-day study in dossier of another analogue substance. Finally, he emphasized that in the 90-day oral toxicity study with the registered substance itself there was no indication of estrogenic activity.

The expert representing the MSCA submitting PfA explained that their concern for DNT was based on signs of *in vivo* antiestrogenic activity, indicating that systemic effects cannot be excluded, and on PTBP effects on thyroid which cannot be excluded as indicated in SEv decision. Several MSC members supported the PfA.

Session 2 (closed)

SECR argued that in their view the potency of PTBP was not high enough to support a concern and that available data did not show effects with low doses. It emphasized that "absence of information", indicated in the SEv decision, cannot be used to trigger further investigations on DNT or to support a particular concern. It also considered that findings were related to reproductive toxicity, which is not the same as developmental neurotoxicity, and therefore not being a trigger for DNT.

An expert to MSC member questioned the link between in vitro effects and the mode of action. Another expert to MSC member counter-argued that available data indicate modulation of estrogen receptor activity *in vitro* and anti-estrogenic activity *in vivo*; further explaining that association of this mechanism/mode of action with sexual differentiation of the brain was established and that these *in vivo* findings further justified the specific concern for DNT effects and hence should trigger the DNT cohort; finally emphasizing, and that potency was neither mentioned in ECHA ED Guidance nor as part of ED criteria proposed by the Commission. In the concluding discussion, several MSC members supported the concerns presented in the PfA.

MSC did not reach unanimous agreement on the DD as provided for the meeting. Ten MSC members voted against the decision, including those from Austria, Croatia, Denmark, France, Italy, Lithuania, the Netherlands, Slovakia, Spain and Sweden. The Norwegian

member did not support the DD either. Four members abstained from voting, including those from Belgium, Bulgaria, Czech Republic and Portugal. The Chairman invited the disagreeing eleven MSC members to provide written justification for the disagreement (see Section V).

SECR will refer the DD to the Commission for further decision-making in accordance with the procedure of Article 133(3) of REACH.

CCH-108/2017 Reaction mass of Bis(1,2,2,6,6-pentamethyl-4-piperidyl) sebacate and Methyl 1,2,2,6,6-pentamethyl-4-piperidyl sebacate (List No. 915-687-0)

Session 2 (closed)

SECR explained that agreement was initially sought in written procedure. The written procedure was terminated by the Chairman of MSC in accordance with Article 20(6) of the MSC Rules of Procedure.

A MSC member requested stopping the written procedure to allow a discussion on the PfA requesting to include a risk assessment for the identified consumer uses of the substance in selected product categories regarding skin sensitising properties.

SECR had not modified the DD in advance of the written procedure based on this PfA.

The Registrant had not provided any comments on this PfA.

The MSC member who requested discussion in the meeting reiterated the discrepancies within the dossier and the gaps in the risk assessment, which were considered to be incompliant with the REACH regulation. The risk for consumers resulting from the identified uses should not be excluded, because the substance is a potent skin sensitizer.

Another MSC member supported this view and made a reference to an earlier, similar discussion in MSC-50, where it also considered the current CCH approach to be too restrictive for some dossiers. In its view, SECR should be able to address the limited number of clear data gaps in a chemical safety report (CSR) that are highlighted in PfAs. MSC-50 has suggested this to be part of the CCH workshop discussions.

SECR confirmed that this had indeed not been discussed in the workshop, but stated it had followed the compliance check approach agreed with Member States to focus on selected endpoints, excluding the assessment of the CSR, to make best use of its limited resources. Since the deadline to submit the information requested in the DD is 42 months, SECR suggested that this CSR issue could be solved quicker by opening another compliance check covering an assessment of the full CSR.

An expert to MSC member supported the current DD, while several MSC members shared the views of the PfA.

SECR reminded that currently MSC's scope of review was limited to the PfA on a specific consumer issue and not the full CSR. It agreed to pay particular attention to similar observations on the CSR at an earlier stage, and to open the CCH by year end.

MSC agreed unanimously to the DD as circulated for the written procedure. Two MSC members from Germany and the Netherlands abstained from voting. MSC took note that SECR was to start, by the end of 2017, a new compliance check on the CSR of the registered substance.

TPE-034/2017 Bis(α,α-dimethylbenzyl) peroxide (EC No. 201-279-3)

Session 2 (closed)

SECR explained that agreement was initially sought in written procedure. The written procedure was terminated by the Chairman of MSC in accordance with Article 20(6) of the MSC Rules of Procedure.

A MSC member requested stopping the written procedure to allow a discussion on the PfA requesting to drop the request for pre-natal developmental toxicity study (PNDT; OECD TG 414) for a second species. This substance was evaluated under SEv and the T criterion (for toxicity) was considered being fulfilled based on available data. Consequently, Norway has submitted a CLH proposal for Repr 2 earlier this year for this substance.

SECR had not modified the DD in advance of the written procedure based on this PfA.

The Registrant had not provided any comments on the PfA.

The member who requested the MSC discussion reiterated the consideration not to take decisions at this stage, as the information brought forward in the public consultation of the CLH proposal two Member states had argued that the substance could fulfil the criterion for a possible Repr 1B classification, which would fulfil a column 2 adaption.

SECR considered that a conclusion on possible Repr 1B classification cannot be based on future information, in this case the meeting of the Committee for Risk Assessment (RAC) which will assess information for the CLH proposal in June 2018, and thus PNDT for second species remains a data gap.

One MSC member supported to wait for RAC decision because there was some uncertainty of its outcome. Some other MSC members argued that waiting would not be appropriate, as the initial CLH proposal was made for Repr 2, which would not allow for a REACH information requirement adaptation.

MSC agreed unanimously to the DD as circulated for the written procedure. The MSC member from Norway abstained.

d. Decision making process - general topics

- Update from SECR on the proposal for using OECD TG 234 in dossier evaluation

SECR presented the feedback received on its proposal for use of OECD TG 234 (Fish Sexual Development Test, FSDT) in dossier evaluation which had been presented during the MSC meeting in September 2017. The proposal was that testing according to the FSDT could be requested when a concern for endocrine disruption (ED) is identified for a substance with a data gap for long-term fish toxicity testing but otherwise the preferred option is to request a long-term fish toxicity test OECD TG 210 (Fish early-life stage - FELS). The feedback received represented some opposite views as well as support and brought up further considerations on how and by which means the potential ED concern should be identified. In advance of the meeting SECR responded to the comments providing further clarifications and suggested alternatives for a way forward.
At the meeting several speakers highlighted the importance of choosing the right, most appropriate test for example whether the FSDT should be the default approach to address the concern. Some members emphasised that the aim of such testing is to get sufficient information for enabling to protect wildlife rather than simply looking at this issue from (laboratory) animal welfare point of view.
One advisor referred to comments provided in the meeting documents and reiterated their concerns on requesting the FSDT under dossier evaluation (including case CCH-106).
At least for complex cases there was a suggestion to use substance evaluation rather than compliance check, and some members suggested consultation of Endocrine Disruptor Expert Group (ED EG) on this topic. A stakeholder representative raised animal welfare, legal and scientific concerns, including the concern that more fish will be tested if the new approach is applied because far more substances will have OECD TG 234 requested under dossier evaluation than would otherwise go through the substance evaluation process. SECR indicated that it has to apply some (practical) triggers usable to address most of the cases while evaluating dossiers but whenever complexity of a case or data in the dossier is identified, it may need to consult expert groups as well.
Several speakers raised the concern about how to define the suitable test concentrations so that data for also risk assessment would be provided without the need to conducting an OECD TG 210 when no effects are detected at the highest concentration tested in the OECD 234. One member pointed out that validated *in vitro* data and use of appropriate QSAR estimates should also be sufficient for identifying an ED concern at least under certain conditions.

An advisor noted that OECD guidance document for ED does not indicate that a level 4 test is always required based on QSAR or in vitro data. He also noted that in his view, there should be a differentiation between CCH in advance of substance evaluation (where

environmental exposure, for example wide dispersive use, would exist) compared to normal CCH.

After some discussion the large majority of MSC clearly supported the possibility to use OECD TG 234 (FSDT) in dossier evaluation when, following the identification of a data gap, it is considered as the most appropriate method due to an ED concern. However, MSC identified the need to discuss further what level of information is needed for triggering FSDT as the most appropriate method in dossier evaluation. Therefore the Committee invited SECR to forward some open questions to the Endocrine Disruptor Expert Group (ED EG), including what specific ED data would trigger the concern for the FSDT to be requested and advice on the concentration range setting in the FSDT.
The Chairman concluded the discussion noting the value in MSC's inputs to this topic.

- Introduction to the examination of testing proposals for a group of substances *(closed session)*

SECR gave a presentation on the examination of testing proposals for a group of substances (silanes), which are planned to be submitted for the MSC-60 round. The Registrants of this group have suggested testing strategies, read-across and grouping approaches for selected substances, which are currently in the testing proposal process. Due to the complexity of the approach, SECR suggests to clarify details of this group approach prior to MSCA notification for the MSC-60 round.

MSC took note of the presentation and appreciated the proactive information given to MSC. The MSC members agreed to inform their Competent Authorities to send expressions of interest for a preparatory discussion.

Item 8 – SVHC identification - Seeking agreement on Annex XV proposals for identification of SVHC

a. Written procedure report on seeking agreement on identification of SVHCs

SECR gave a brief report on the outcome of the written procedure for SVHC agreement seeking on the identification of eight substances[5] proposed to be identified as SVHC based on Article 57 of Regulation (EC) 1907/2006, due to their hazardous properties for human health and/or for the environment.

On 28 November 2017, the MSC Chairman terminated the written procedure for agreement seeking on the SVHC proposal for *tricobalt tetraoxide (EC No. 215-157-2) containing ≥ 0.1% w/w nickel oxides: nickel monoxide (EC 215-215-7); nickel oxide (EC No. 234-323-5)* following a justified request of an MSC member and the case was brought for further discussion and agreement seeking in the MSC-57 meeting.

MSC agreed unanimously on identification of the other seven substances (see Appendix to the final agenda in Section III for more detailed identification of the cases) as SVHCs in the written procedure launched on 20 November 2017 and closed on 30 November 2017. SECR explained that the final documents will be made available on MSC S-CIRCABC and on the ECHA website and these substances will be included in the Candidate List of SVHCs mid-January 2018.

b. Seeking agreement on Annex XV proposals for identification of SVHC

4,4'-isopropylidenediphenol (bisphenol A, BPA) (EC No. 201-245-8)

The dossier submitter (DS) representative from the German CA presented to MSC the Annex XV proposal for identification of Bisphenol A (BPA) as an SVHC under Article 57 (f)

[5]"Dechlorane Plus" TM as an SVHC under Article 57 (e) of REACH; Benz[a]anthracene (EC No. 200-280-6) and Chrysene (EC No. 205-923-4) as SVHCs under Article 57 (a), (d) and (e) of REACH; Cadmium nitrate (EC No. 233-710-6), Cadmium carbonate (EC No. 208-168-9) and Cadmium hydroxide (EC No. 244-168-5) as SVHCs under Article 57 (a), (b) and (f) of REACH; Reaction products of 1,3,4-thiadiazolidine-2,5-dithione, formaldehyde and 4-heptylphenol, branched and linear (RP-HP) [with ≥0.1% w/w 4-heptylphenol, branched and linear] as an SVHC under Article 57 (f) of REACH and Tricobalt tetraoxide (EC No. 215-157-2) containing ≥ 0.1% w/w nickel oxides: nickel monoxide (EC No. 215-215-7); nickel oxide (EC No. 234-323-5), as an SVHC under Article 57 (a) of REACH.

of REACH due to its endocrine disrupting properties for which there is evidence of probable serious adverse effects to the environment giving rise to equivalent level of concern (ELoC) to CMR and PBT/vPvB substances under Article 57 (a)-(e). The DS explained the rationale for preparing the dossier and noted that BPA is already identified as SVHC with respect to human health according to Article 57(c) and 57(f) of REACH. Further, the DS pointed out that the assessment was based on the WHO/IPCS definition of endocrine disrupters as interpreted by the European Commission's Endocrine Disruptors Expert Advisory Group and the SVHC identification of BPA due to its endocrine disrupting properties with respect to the environment would complete the hazard assessment of this substance. The dossier focused primarily on the identified adverse effects of BPA in a high variety of species in different ecosystems, based on the available information *in vitro,* and information *in vivo* in fish, amphibians and a variety of invertebrates, and the biological plausible links between these effects and the oestrogen agonist and thyroidal modes of action (MoA) in fish and amphibian species. The DS outlined also the main comments received in the public consultation on the proposal and the DS's responses to them.

The DS also noted that a reference has been made in the Support document to the BPA conclusions of SVHC ED identification for human health and their relevance for wildlife mammals and non-mammalian vertebrates. It was highlighted that a weight of evidence approach has been used in this hazard assessment with careful consideration of the data quality and reliability when concluding on the substance's equivalent level of concern (ELoC).

In the following discussion, many MSC members expressed their support to this SVHC proposal and further exchanged views on data robustness and how to better structure and further strengthen the argumentation provided in the Support document, by distinguishing between the clear evidence for BPA activity as an oestrogen agonist in fish and as a thyroid antagonist in amphibians, the supporting evidence for BPA acting as a potential oestrogen agonist in amphibians and via a potential thyroid mode of action in fish and some further evidence for potential ED effects of BPA seen in molluscs and in arthropods.

Some further aspects regarding the data reliability and proper reflection of uncertainty, the prioritisation of data and the considered number of taxa, the relevance of the mammalian data used in the SVHC identification of BPA as an endocrine disruptor for human health at the population level, how to address properly the effects seen in invertebrates, as well as whether/how to consider BPA potency and environmental fate in the SVHC identification process have been considered.

An adviser to the MSC observer from CEFIC brought further clarification on some of the key studies and made valuable suggestions for proper addressing of uncertainty.

Members thoroughly discussed also the rapid degradability of BPA and its occurrence in the environment (as although having a low potential for bioaccumulation, BPA has been found in biota and eggs of different sea birds in remote areas) and suggested some further modifications in the Support document.

As a result, the agreement seeking documentation was further adjusted.

Further, MSC members agreed that the available evidence for the altered functions (i.e. development and reproduction) in fish and amphibians as a result of an oestrogenic respectively a thyroidal mode of action, as well as the supporting additional information for additional modes of action and adverse effects in other taxa, is sufficient to establish an equivalent level of concern for BPA due to its endocrine disrupting properties for the environment. One member expressed that in their view persistency, bioaccumulation and potency are highly relevant factors in deciding whether a substance is of equivalent level of concern, and they considered that the data for BPA are not sufficient for such identification.

MSC went through the text of the Support Document for BPA SVHC identification for the environment with amendments introduced at the meeting. MSC supported the text and the conclusion on identification of BPA as SVHC due to its endocrine disrupting properties under Article 57 (f) with regard to the environment and also unanimously acknowledged that there is scientific evidence on the endocrine disrupting activity of BPA and on the

plausible biological link between this activity and the adverse effects to organisms in the environment, such as fish and amphibians.

When the MSC agreement document and support document were brought to a vote, the members unanimously agreed to the identification of BPA as SVHC due to its endocrine disrupting properties in the environment under Article 57(f), i.e. the available information for BPA was sufficient to conclude that there is scientific evidence of probable serious effects giving rise to an equivalent level of concern in relation to the environment (i.e. to substances listed in points (a) to (e) in Article 57 of the REACH Regulation).

CZ, IT, MT and UK members abstained from the vote. One of them made a statement to the minutes (see Section VI).

The Chairman thanked the dossier submitter for this SVHC proposal and MSC for its deliberations on it and unanimous agreement reached.

Tricobalt tetraoxide (EC No. 215-157-2) containing ≥ 0.1% w/w nickel oxides: nickel monoxide (EC No. 215-215-7); nickel oxide (EC No. 234-323-5)

The dossier submitter (DS) representative from the Dutch CA presented to MSC the Annex XV proposal for identification of tricobalt tetraoxide (EC No. 215-157-2) containing ≥ 0.1% w/w nickel oxides: nickel monoxide (EC No. 215-215-7); nickel oxide (EC No. 234-323-5) as an SVHC under Article 57 (a) due to its carcinogenic properties when containing these nickel oxides above 0.1% w/w. He also outlined the main comments received in the public consultation on this proposal and the DS's responses to them. The DS noted that no comments challenging this SVHC proposal had been received, but more clarification on the substance identity had been provided, thus the case was addressed initially for MSC agreement seeking in written procedure.

The member who requested the written procedure be stopped in order to have an MSC discussion prior to the agreement seeking on this SVHC proposal clarified further the reasons for this request. She noted that the approach followed in this SVHC case deviated from the one discussed earlier in CARACAL within the scope of the Roadmap 2020 and RMOA preparation; therefore, there was a need for a further, more thorough discussion among MSCAs on the general approach to be followed when a substance is proposed for SVHC identification based on its hazardous impurity(ies), without the impurity itself in the Candidate List.

DS noted that the general paper discussed in RiME and CARACAL lays down a non-binding approach to assessing impurities of concern and was not explicitly developed to lay down criteria for SVHC identification. Furthermore, in this particular case the substance has specific characteristics allowing different conclusions from those in the general approach. In this case, an RMOA for the impurity itself was available which concluded that occupational exposure limit (OEL) setting may be a better RMM. This led the DS to the conclusion that it would not be prudent in this case to submit a SVHC proposal for the impurity. He also underlined that as the main impurities (nickel monoxide and nickel oxide) have a harmonised classification as Carc. 1A, if proposed for SVHC identification, they will be listed in the Candidate list. He expressed the view of his CA that removal of the substance with the impurity from the EU market would be a quick way to improve worker safety, and much faster than waiting for a restriction or OEL proposal to be submitted.

In addition, the MSC observer from EUROMETAUX provided a further update on the hazardous profile of the substance in its recently updated registration dossiers and its current volumes on the market that are to be further reduced in the following year. He expressed some doubts on the efficiency of the suggested regulatory measure i.e. SVHC identification of this substance and noted the complexity of the recycling processes and the efforts of the recycling industry in this regard in line with the circular economy objectives.

In the following discussion, several members expressed their views on the issues raised and expressed a preference to have a more in-depth discussion at the MSCA level on the way to identify SVHCs on the basis of the hazardous properties of impurities, prior to the identification of tricobalt tetraoxide as an SVHC based on the impurities contained in it.

Taking into consideration the members' views and the latest update provided by the industry concerned, the DS representative informed the committee of the decision of his MS to withdraw the current SVHC proposal for tricobalt tetraoxide with >0.1% w/w nickel oxides (nickel monoxide and nickel oxide) from this MSC agreement seeking process.

The Chair thanked the dossier submitter for providing the proposal to the SVHC identification process and MSC for the interesting discussion on the case.

Item 9 – Opinion of MSC on ECHA's draft 8th recommendation of priority substances to be included in Annex XIV

a) Update by SECR on further work done on the 8th recommendation of priority substances

SECR provided an update to MSC focusing on NMP mainly. Based on the analysis and comparisons made SECR confirmed that the supply chain for NMP seems the most complex one in this recommendation round, and hence it will move NMP to the last latest application date (LAD) slot of 24 months. A representative of SECR also referred to the oral interventions and the statement by one member at MSC-56 concerning the perceived inconsistencies in EU-wide legislation. SECR reflected that NMP is given as one example of a less hazardous solvent than phenol or furfural in one specific BAT reference document (i.e. the BREF on refining mineral oil and gas) under Industrial Emissions Directive (IED). This does not make the use of NMP a requirement. Nor does such BAT reference document contradict the identification of NMP as SVHC or ECHA's assessment of NMP's priority for inclusion in Annex XIV. SECR further clarified that the same conclusion applies also to the related Commission Implementing Decision 2014/738/EU.

In explaining the next steps SECR informed MSC that after the adoption of the opinion of MSC SECR will finalise its recommendation to COM by early February.

b) MSC opinion on ECHA's Draft 8th recommendation of priority substances to be included in Annex XIV

The MSC Rapporteur presented the draft opinion with small changes since the first discussion in October. MSC supported the opinion as drafted and supported ECHA's draft recommendation for all the seven substances that were subject to the public consultation for possible inclusion in Annex XIV, including the proposed transitional arrangements, review periods and other proposed Annex XIV entry specifications, except for NMP for which MSC was of the opinion that the latest application date should be 24 months instead of the originally proposed 18 months. Some members repeated their concerns that the authorisation route might not be the most appropriate way to regulate NMP properly, however agreeing that NMP meets the agreed prioritisation criteria. These members felt that it was a bit unfortunate to discuss prioritisation of this substance when a restriction on NMP is almost published. COM reminded that the restriction sets only exposure limit values. The member from the Czech Republic made also reference to the statement that they made during the MSC-56 meeting and called attention to the Commission Implementing Decision 2014/738/EU establishing best available techniques (BAT) conclusions, under Directive 2010/75/EU on industrial emissions, for the refining of mineral oil and gas. This Commission Implementing Decision is binding and in view of the Czech member requires the use of NMP as a less hazardous solvent in the BAT 22. The Czech Republic doubted about the proportionality and the regulatory consistency of inclusion of the NMP in Annex XIV and did not support this inclusion. MSC adopted the opinion by consensus. Four members (from the Czech Republic, Hungary, the Netherlands, and the United Kingdom) abstained from voting during the adoption of the opinion. On behalf of the Committee the Chairman thanked the Rapporteur, Co-Rapporteur and the Working group for preparing the draft opinion and its support document for the adoption at this meeting.

Item 10 – MSC Manual of decisions (MoD)

SECR presented a proposal for an entry for inclusion in the Manual of Decisions and Opinions (MoD). It comprised the approach for selecting tissues to be collected and analysed when requesting a TGR assay via oral route in dossier evaluation.

Generally, TGR information requests require to collect somatic cells from three tissues (liver, glandular stomach and duodenum) and to analyse two tissues (liver and glandular stomach). Duodenum shall be stored and analysed only if both liver and glandular stomach results are negative or inconclusive. Germ cells shall be collected at the same time and stored up to 5 years, considering the need to analyse them in case of a positive result is obtained in somatic cells. MSC had discussed the approach in its 56th meeting based on recent decisions on such cases and then agreed to consider a proposal for inclusion of an MoD entry at its next meeting.

MSC agreed to include this entry in section 3.1.10 of the MoD.

Item 11 – Any other business

- Implementation plans of MSC's priority actions regarding process changes

SECR informed MSC on the planned actions regarding process changes from 2018 onwards. One of them is that SECR will discontinue the practise of uploading the final ECHA decisions to MSC Circabc since the agreed decisions will systematically be made available to MSC already by the end of the meeting. SECR also informed MSC that small revision to the MSC working procedures, practically harmonisation of text in DEv and SEv working procedures is required and that is planned to be tabled for MSC adoption in MSC-58.

- Update on appeals and court cases *(Partly in closed session)*

SECR gave an overview of the status of recent appeals on evaluation cases submitted to ECHA's Board of Appeal, as well as on pending cases submitted to the European Court of Justice. MSC took note of the information received.

One member informed MSC about a court case in which its Member State has brought an action for annulment of a Board of Appeal decision partially annulling a substance evaluation decision. The case addresses the role of Member States in the evaluation process under REACH and the scope of review of ECHA's Board of Appeal of evaluation decisions.

- Update on ECHA premises

ECHA presented an overview on the planning of future ECHA premises providing information on the procurement procedure, location and functioning of the conference centre. ECHA informed MSC that the lease agreement has been signed and the commencement date is planned for 1 January 2020.

- Suggestions from members

One MSC member made one suggestion with regards additional information on appeals and court cases discussed under Item 11 - Update on appeals and court cases.

Item 12– Adoption of conclusions and action points

The conclusions and action points of the meeting were adopted at the meeting (see Section IV).

II. List of attendees

Members/Alternate members
ANDRIJEWSKI, Michal (PL)
COCKSHOTT, Amanda (UK)
CONWAY, Louise (IE)
DEIM, Szilvia (HU)
DIMITROVA, Rada (BG)
DUNAUSKIENE, Lina (LT)
FINDENEGG, Helene (DE)
FRANZ, Michel (FR)
HERMES, Joe (LU)
HORSKA, Alexandra (SK)
HUMAR-JURIC, Tatjana (SI)
KREKOVIĆ, Dubravka (HR)
KULHANKOVA, Pavlína(CZ)
LUNDBERGH, Ivar (SE)
MARTÍN, Esther (ES)
MENDONÇA, Elsa (PT)
MIHALCEA UDREA, Mariana (RO)
PALEOMILITOU, Maria (CY)
PISTOLESE, Pietro (IT)
REIERSON, Linda (NO)
RISSANEN, Eeva (FI)
TYLE, Henrik (DK)
VANDERSTEEN, Kelly (BE)
VESKIMÄE, Enda (EE)
WIJMENGA, Jan (NL)
Representatives of the Commission:
SCHUTTE, Katrin (DG ENV)
Observers
ANNYS, Erwin (Cefic)
BERNARD, Alice (ClientEarth)
CINGOTTI, Natacha (HEAL)
DROHMANN, Dieter (ORO)
FAßBENDER, Christopher (PETA)
KERÄNEN, Hannu (CONCAWE)
LENNQUIST, Anna (ChemSec)
WAETERSCHOOT, Hugo (Eurometaux)

ECHA staff
AHRENS, Birgit
AJAO, Charmaine
ANASTASI, Audrey Anne
BERCARU, Ofelia
BICHLMAIER, Ingo
BICHLMAIER SUCHANOVA, Bohumila
BROERE, William
CESNAITIS, Romanas
CALEY, Jane
CARLON, Claudio
CLENAGHAN, Conor
DE WOLF, Watze
DEYDIER, Laurence
DREVE, Simina
ERICSSON, Gunilla
GARALEVICIENE, Dalia
HAUTAMÄKI, Anne
HERBATSCHEK, Nicolas
HUUSKONEN, Hannele
JAAGUS, Triin
JOHANSSON, Matti
JUTILA, Arimatti
KARHU, Elina
KARJALAINEN, Anne-Mari
KOVARI, Agnes
KREUZER, Paul
LE CURIEUX, Frank
LEPPÄRANTA, Outi
NAUR, Liina
NYMAN, Anna-Maija
O'FARRELL, Norah
RÖNTY, Kaisu
SIMOES, Ricardo
SUMREIN, Abdelqader
TOLLOSA, Meskerem
TRNKA, Jan-Peter
VAHTERISTO, Liisa
VASILEVA, Katya
WICKHAM, John

Proxies

- HUMAR-JURIC, Tatjana (SI) also acting as proxy of STESSEL, Helmut (AT)
- PALEOMILITOU, Maria (CY) also acting as proxy of KOUTSODIMOU, Aglaia (EL) during the whole meeting except on 12 December at 15:00-17:00
- PISTOLESE, Pietro (IT) also acting as proxy of BORG, Ingrid (MT)
- VESKIMÄE, Enda (EE) also acting as proxy of JANTONE, Anta (LV)
- HUMAR-JURIC, Tatjana (SI) also acting as proxy of PALEOMILITOU, Maria (CY) for 12 and 15 December
- KULHANKOVA, Pavlina (CZ) also acting as proxy of MIHALCEA UDREA, Mariana (RO) on 15 December from 11:00 onwards
- PALEOMILITOU, Maria (CY) also acting as proxy of HUMAR-JURIC, Tatjana (SI) on 12 December at 15:00-17:00
- PALEOMILITOU, Maria (CY) also acting as proxy of STESSEL, Helmut (AT) on 12 December at 15:00-17:00

- TYLE, Henrik (DK) and LØFSTEDT, Magnus (DK) also acting as proxy of DUNAUSKIENE, Lina (LT) for short periods during the meeting.

Experts and advisers to MSC members
ATTIAS, Leonello (IT) (expert to PISTOLESE, Pietro)
BARTHELEMY-BERNERON, Johanna (FR) (expert to FRANZ, Michel)
CIESLA, Jacek (PL) (expert to ANDRIJEWSKI, Michal)
COPOIU, Oana (RO) (expert to MIHALCEA UDREA, Mariana)
DE KNECHT, Joop (NL) (expert to WIJMENGA, Jan)
DOYLE, Ian (UK) (adviser to COCKSHOTT, Amanda)
EINOLA, Juha (FI) (adviser to RISSANEN, Eeva)
GRINCEVICIUTE, Otilija (LT) (expert to DUNAUSKIENE, Lina)
INDANS, Ian (UK) (expert to COCKSHOTT, Amanda)
KAßNER, Franziska (DE) (adviser to FINDENEGG, Helene)
KOZMIKOVA, Jana (CZ) (expert to KULHANKOVA, Pavlina)
KUROVA, Martina (SK) (expert to HORSKA, Alexandra)
LE, Elisa (FR) (expert to FRANZ, Michel)
LØFSTEDT, Magnus (DK) (expert to TYLE, Henrik)
MALKIEWICZ, Katarzyna (SE) (expert to LUNDBERGH, Ivar)
NYGREEN, Beryl C. (NO) (expert to REIERSON, Linda)
NYITRAI, Viktor (HU) (expert to DEIM, Szilvia)
PASQUIER, Elodie (FR) (adviser to FRANZ, Michel)
ROSENTHAL, Esther (DE) (expert to FINDENEGG, Helene)
SAKSA, Jana (EE) (expert to VESKIMÄE, Enda)
ZELJEZIC, Davor (HR) (expert to KREKOVIC, Dubravka)

MSCA experts for SEv cases:
HOLMER, Marie Louise (DK)
ZENNER BOISEN, Anne Mette (DK)

MSCA expert for SVHC case:
HASSOLD, Enken (DE)

Advisers to the regular observers:
WÖLZ, Jan (Cefic)

By WEBEX/phone connection:

During the whole meeting:
Hristina FILIPOVA (BG)
Kerstin HEESCHE-WAGNER (DE)
Christian UNKELBACH (DE)
Michel FRANZ (FR) (on 13-15 December)
Cécile MICHEL (FR)
Cécile BLOM (NO)

During the Agenda Item 6:
Agnieszka DOBRAK-VAN BERLO (BE)

During the Agenda Items 6.2 b+c:
Simone MÜHLEGGER (AT)
Jens VANSELOW (DE)
Sebastian SCHMEISSER (DE)
Ana-Maria FLOREA (DE)
Marta AXELSTAD PETERSEN (DK)
Susanne HOUGAARD (DK)
Jana SAKSA (EE)

During the Agenda item 7:

Simone MÜHLEGGER (AT)

During the Agenda Items 7 b+c:
Annemarie LOSERT (AT)
Michal WIECKO (DE)
Jana SAKSA (EE)
Sandrine CHARLES (FR)

During the Agenda Item 7 d:
Els BOEL (BE)
Martine RÖHL (BE)

During the Agenda items 8 a+b:
Eva STOCKER (AT)
Simone MÜHLEGGER (AT)
Jürgen ARNING (DE)
Jana SAKSA (EE)
Stéphanie ALEXANDRE (FR)
Samantha GUICHELAAR (NL)

During the Agenda item 9:
Eva STOCKER (AT)
Jana SAKSA (EE)

During the Agenda item 11:
Simone MÜHLEGGER (AT)

From DG GROW during the whole meeting:
Enrique GARCIA-JOHN
Jacek ROZWADOWSKI
Georg STRECK

Case owners:
Representatives of the Registrants were attending under the Agenda Item 6.2 b for SEV-DK-010/2012 and SEV-DK-005/2013; under the Agenda Item 7 b for CCH-106/2017 and CCH-107/2017.

Apologies:
ALMEIDA, Inês (PT)
BORG, Ingrid (MT)
JANTONE, Anta (LV)
KOUTSODIMOU, Aglaia (EL)
STESSEL, Helmut (AT)
WAGENER, Alex (LU)

III. Final Agenda

MSC/A/057/2017

Agenda

57th meeting of the Member State Committee

11-15 December 2017
ECHA Conference Centre
Annankatu 18, in Helsinki, Finland

11 December: starts at 9 am
15 December: ends at 1 pm

Item 1 – Welcome and Apologies

Item 2 – Adoption of the Agenda

MSC/A/057/2017
For adoption

Item 3 – Declarations of conflicts of interest to items on the Agenda

Item 4 – Administrative issues

- Outlook for MSC-58

For information

Item 5 – Minutes of the MSC-56

- Draft minutes of MSC-56

MSC/M/56/2017
For adoption

Item 6 – Substance evaluation

Timing for start of 6.1 is Day 4 and of 6.2b is Day 1
Closed session for 6.2c

3. Community Rolling Action Plan (CoRAP) & MSC opinion development

Preparations for the MSC opinion on the draft update of Community Rolling Action Plan (CoRAP)

- Report by the Rapporteur and discussion on the first draft opinion of MSC

ECHA/MSC-57/2017/009
For discussion

4. Decision making process

a. Written procedure report on seeking agreement on draft decisions on substance evaluation[6]

ECHA/MSC-57/2017/010
For information

b. Introduction to and preliminary discussion on draft decisions on substance evaluation after MS-CA's/ECHA reactions *(Session 1, open session)*:
For discussion followed by agreement seeking under 6.2c:

ECHA/MSC-57/2017/011

MSC code	Substance name	EC No./ Document
SEV-DK-010/2012	Ziram	205-288-3/ ECHA/MSC-57/2017/012-13
SEV-2-DK-005/2013	4,4'-methylenebis[N,N-bis(2,3-epoxypropyl)aniline	249-204-3/ ECHA/MSC-57/2017/014-15

For discussion

c. Seeking agreement on draft decisions when amendments were proposed by MS-CA's/ECHA *(Session 2, closed)*

Cases as listed above under **6.2b**

For agreement

Item 7 – Dossier evaluation

Timing for item 7b is Day 2
Closed session for 7c and partly for 7d

a. Written procedure report on seeking agreement on draft decisions on dossier evaluation[1]

ECHA/MSC-57/2017/001
For information

b. Introduction to and preliminary discussion on draft decisions on compliance checks and testing proposals when amendments were proposed by MS-CA's *(Session 1, open session)*

ECHA/MSC-57/2017/002

For discussion followed by agreement seeking under 7c:

Compliance checks

MSC code	Substance name	EC/List No./ Documents
CCH-106/2017	2-ethylhexyl salicylate	204-263-4 / ECHA/MSC-57/2017/003-4
CCH-107/2017	Homosalate	204-260-8/ ECHA/MSC-57/2017/005-6
CCH-113/2017	Reaction mass of 4-tert-butylphenol and 1,3-phenylenedimethanamine and 2-({[3-(aminomethyl) benzyl]amino}methyl)-4-tert-butylphenol	939-071-6/

[6] Please see the Appendix at the end to see the list of cases agreed in MSC written procedure in advance of the meeting.

For discussion

c. Seeking agreement on draft decisions on compliance checks and testing proposal examinations when amendments were proposed by MS-CA's *(Session 2, closed)*

Cases as listed above under **7b** and the cases returned from written procedure for agreement seeking in the meeting

CCH-108/2017	Reaction mass of Bis(1,2,2,6,6-pentamethyl-4-piperidyl) sebacate and Methyl 1,2,2,6,6-pentamethyl-4-piperidyl sebacate	915-687-0
TPE-034/2017	Bis(α,α-dimethylbenzyl) peroxide	201-279-3

For agreement

d. Decision making process - general topics

- Update from SECR on the proposal for using OECD TG 234 in dossier evaluation

ECHA/MSC-57/2017/025

- Introduction to the examination of testing proposals for a group of substances *(Closed session)*

For information

Item 8 – SVHC identification - Seeking agreement on Annex XV proposals for identification of SVHC

Tentative timing for start of item 8 is Day 1

a. Written procedure report on seeking agreement on identification of SVHCs[7]

ECHA/MSC-57/2017/020
For information

b. Seeking agreement on Annex XV proposals for identification of SVHC

Substance name	**EC No./Documents**
4,4'-isopropylidenediphenol (bisphenol A, BPA)	201-245-8 ECHA/MSC-57/2017/021-023
Tricobalt tetraoxide containing ≥ 0.1% w/w nickel oxides: nickel monoxide (EC 215-215-7); nickel oxide (EC 234-323-5) *(case returned from written procedure)*	215-157-2 ECHA/MSC/D/2017/215-217

For discussion and agreement

Item 9 – Opinion of MSC on ECHA's draft 8th recommendation of priority substances to be included in Annex XIV

Tentative timing: Day 1

[7] Please see the Appendix at the end to see the list of cases agreed in MSC written procedure in advance of the meeting.

a) Update by SECR on further work done on the 8th recommendation of priority substances

ECHA/MSC-57/2017/016
For information

b) MSC opinion on ECHA's Draft 8th recommendation of priority substances to be included in Annex XIV

- Discussion on the draft MSC opinion
- Adoption of MSC opinion

ECHA/MSC-57/2017/017
For discussion and adoption

Item 10 – MSC Manual of decisions (MoD)

- Suggestion for possible new entries to the MoD

ECHA/MSC-57/2017/018
For discussion and possible decision

Item 11 – Any other business

- Implementation plans of MSC's priority actions regarding process changes

ECHA/MSC-57/2017/024 (room document)
For information

- Update on appeals and court cases *(Partly in closed session)*
- Update on ECHA premises
- Suggestions from members

For information

Item 12 – Adoption of main conclusions and action points

- Table with conclusions and action points from MSC-57

For adoption

Information documents:

Information documents are not allocated a specific agenda time but the documents are available on MSC CIRCABC before the meeting. Based on the listed documents and the meeting agenda, if any MSC member considers that information documents may merit a discussion under any agenda point, they should inform MSC Secretariat

- Status report on-ongoing substance evaluation work
- Status report on on-going dossier evaluation work (Presentation slides)
- Guidance updates (Presentation slides)
- Work plan of MSC for 2018 (ECHA/MSC-57/2017/019)

APPENDIX to the MSC-57 agenda:

List of evaluation cases agreed by MSC in written procedure in advance of the MSC-57 meeting:

Substance evaluation

SEV-DK-003/2016	2,3-epoxypropyl o-tolyl ether EC No. 218-645-3

Dossier evaluation

Compliance checks

CCH-109/2017	Bis(2,2,6,6-tetramethyl-4-piperidyl) sebacate EC No. 258-207-9
CCH-112/2017	Boron orthophosphate EC No. 236-337-7
CCH-114/2017	Zinc dibenzyldithiocarbamate EC No. 238-778-0
CCH-121/2017	Poly[oxy(methyl-1,2-ethanediyl)], a-hydro-omega-hydroxy-, ether with 2,6 bis{[(2-hydroxyethyl)amino]methyl}-4-nonylphenol EC No. 614-668-1
CCH-124/2017	Reaction mass of 1-(3-((c12-18-(even numbered))-alkyl-amino)propyl)guanidine acetate salt and 1-(c12-18-(even numbered))-alkyl-1-(3-guanidinopropyl)guanidine acetate salt and 1-(c12-18-(even numbered))-alkyl-tetrahydropyrimidin-2(1h)-imine acetate salt List No. 939-650-3
CCH-126/2017	2-(dimethylamino)-2-[(4-methylphenyl)methyl]-1-[4-(morpholin-4-yl)phenyl]-butan-1-one EC No. 438-340-0

Testing proposal examinations

TPE-036/2017	3-(Trimethoxysilyl)propyl (2E,4E)-hexa-2,4-dienoate List No. 642-902-2
TPE-037/2017	Methyl [3-(trimethoxysilyl)propyl]carbamate EC No. 245-659-7

List of SVHC proposals agreed by MSC in written procedure in advance of the MSC-57 meeting:

Reaction products of 1,3,4-thiadiazolidine-2,5-dithione, formaldehyde and 4-heptylphenol, branched and linear (RP-HP) [with ≥0.1% w/w 4-heptylphenol, branched and linear] EC No. -

1,6,7,8,9,14,15,16,17,17,18,18-Dodecachloropentacyclo-[12.2.1.16,9.02,13.05,10]octa-deca-7,15-diene ("Dechlorane Plus"™) [covering any of its individual anti- and syn-isomers or any combination thereof] EC No. -

Benz[a]anthracene	EC No. 200-280-6
Chrysene	EC No. 205-923-4
Cadmium nitrate	EC No. 233-710-6
Cadmium carbonate	EC No. 208-168-9
Cadmium hydroxide	EC No. 244-168-5

IV. Main Conclusions and Action Points

Main conclusions and action points
MSC-57, 11-15 December 2017
(adopted at MSC-57)

CONCLUSIONS / DECISIONS / MINORITY OPINIONS	ACTIONS REQUESTED
Item 5 – Minutes of the MSC-56	
MSC adopted the draft minutes as modified at the meeting.	**MSC-S** to upload final version of the minutes on MSC S-CIRCABC by 18 December 2017 and on ECHA website without undue delay.
Item 6.1 – Community Rolling Action Plan (CoRAP) & MSC opinion development Preparations for the MSC opinion on the draft update of Community Rolling Action Plan (CoRAP) • Report by the Rapporteur and discussion on the first draft opinion of MSC	
MSC took note of the update.	**MSC members** to send comments to Rapporteur on the draft CoRAP opinion by 17 January 2018.
Item 6.2 – Substance evaluation - Decision making process **a. Written procedure report on seeking agreement on draft decisions on substance evaluation**	
	MSC-S to upload on MSC S-CIRCABC the final ECHA decision agreed in written procedure.
Item 6.2 – Substance evaluation - Decision making process ***b.*** **Introduction to and preliminary discussion on draft decisions on substance evaluation after MS-CA's/ECHA reactions *(Session 1, open session)*** **c. Seeking agreement on a draft decision when amendments were proposed by MS-CA's/ECHA *(Session 2, closed)***	
MSC reached unanimous agreement on the following ECHA draft decisions as modified in the meeting: SEV-DK-010/2012 Ziram (EC No. 205-288-3) SEV-2-DK-005/2013 4,4'-methylenebis[N,N-bis(2,3-epoxypropyl)aniline (EC No. 249-204-3)	**MSC-S** to upload on MSC S-CIRCABC the agreed decisions [in the meetings folder]. **SECR** to present at MSC-58 the ongoing discussions on the TGR germ cell sampling time. **MSC members** to inform MSC-S by 17 January 2018 if their experts wish to contribute to the preparation of the TGR update discussion for MSC.
Item 7 – Dossier evaluation **a. Written procedure report on seeking agreement on draft decisions on dossier evaluation**	
MSC took note of the report.	**MSC-S** to upload on MSC S-CIRCABC the final ECHA decisions agreed in written procedure.
Item 7 – Dossier evaluation **b. Introduction to and preliminary discussion on draft decisions on testing proposals and compliance checks after MS-CA reactions *(Session 1, open session)*** **c. Seeking agreement on draft decisions on compliance checks and testing proposal examinations when amendments were proposed by MS-CA's *(Session 2, closed)***	
MSC reached unanimous agreement on the following ECHA draft	**MSC-S** to upload on MSC S-CIRCABC the

CONCLUSIONS / DECISIONS / MINORITY OPINIONS	ACTIONS REQUESTED
decisions (as modified in the meeting): **<u>Compliance checks</u>** CCH-106/2017 2-ethylhexyl salicylate (EC No. 204-263-4) CCH-107/2017 Homosalate (EC No. 204-260-8) CCH-108/2017 Reaction mass of Bis(1,2,2,6,6-pentamethyl-4-piperidyl) sebacate and Methyl 1,2,2,6,6-pentamethyl-4-piperidyl sebacate (EC No. 915-687-0) **<u>Testing proposal examination</u>** TPE-034/2017 Bis(α,α-dimethylbenzyl) peroxide (EC No. 201-279-3)	agreed decisions [in the meetings folder]. **SECR** to start by the end of 2017 a new compliance check on the full chemical safety report (CSR) of the registered substance of CCH-108/2017.
MSC could not reach unanimous agreement on the following draft decision, as submitted to the meeting: CCH-113/2017 Reaction mass of 4-tert-butylphenol and 1,3-phenylenedimethanamine and 2-({[3-(aminomethyl) benzyl]amino}methyl)-4-tert-butylphenol (EC No. 939-071-6)	**MSC members who voted against** the draft decision to provide their finalised justification(s) in writing to the MSC-S by 18 December 2017; otherwise, the draft justification(s) as provided at the time of the vote will be considered as the final justification. **MSC-S** to refer the decision to the Commission for further decision making, without undue delay once minutes of MSC-57 are agreed.
Item 7d. Dossier evaluation decision making process -General topics • Update from SECR on the proposal for using OECD TG 234 in dossier evaluation	
MSC took note of the responses and supported the possibility to use OECD TG 234 (FSDT) in dossier evaluation when it is considered as the most appropriate method.	**MSC** welcomes having further discussion on the necessary information level for identifying or triggering OECD TG 234 as the most appropriate method in dossier evaluation. **MSC-S** to forward to the ED Expert Group questions on these necessary information levels and also on concentration range setting in the FSDT.
Item 7d. Dossier evaluation decision making process -General topics • Introduction to the examination of testing proposals for a group of substances	
MSC took note of the presentation.	**MSC members** to inform their CAs to send expressions of interest for a preparatory discussion prior to MSCA notification to the Evaluation Functional Mailbox by 8 January 2018.
Item 8 – SVHC identification - Seeking agreement on Annex XV proposals for identification of SVHC **a. Written procedure report on seeking agreement on identification of SVHCs**	
MSC took note of the report.	**MSC-S** to upload on MSC S-CIRCABC the final MSC documents on the substances identified as SVHCs in written procedure. **SECR** to add the newly identified SVHCs to the Candidate List (update foreseen by mid-January 2018).
Item 8 – SVHC identification - Seeking agreement on Annex XV proposals for identification of SVHC **b. Seeking agreement on Annex XV proposals for identification of SVHC**	

CONCLUSIONS / DECISIONS / MINORITY OPINIONS	ACTIONS REQUESTED
MSC unanimously agreed to identify the following substance as an SVHC (and unanimously agreed on its SD and agreement): • 4,4'-isopropylidenediphenol (bisphenol A, BPA) (EC No. 201-245-8)	**MSC-S** to upload the MSC agreement for BPA, as well as its support document and RCOM, on MSC S-CIRCABC and to publish them on the ECHA website. **SECR** to update the entry for BPA in the Candidate List (update foreseen by mid-January 2018). Those abstaining **MSC members who made statements** and **requested for their attachment to the minutes** to provide these statements in writing to MSC-S by 19 December 2017.
MSC considered the Annex XV proposal for SVHC identification of • Tricobalt tetraoxide (EC No. 234-323-5) containing ≥ 0.1% w/w nickel oxides: nickel monoxide (EC 215-215-7); nickel oxide (EC 234-323-5) *(case returned from written procedure)* and noted that further discussion seems necessary on the general approach to be followed when proposing for SVHC identification a substance based on the hazard properties of its impurity(ies). The dossier submitter informed MSC that they withdrew the above-mentioned SVHC proposal from this MSC agreement seeking process.	**SECR** to facilitate any further discussion on this topic in RiME and CARACAL, as appropriate. **SECR** to consider a proper way for debriefing MSC on issues discussed in RiME and CARACAL of relevance to the MSC work and *vice versa*.
Item 9 – Opinion of MSC on ECHA's draft recommendation of priority substances to be included in Annex XIV b) MSC opinion on ECHA's Draft 8th recommendation of priority substances to be included in Annex XIV • Discussion on the draft MSC opinion • Adoption of MSC opinion	
MSC discussed the 8th ECHA's draft recommendation for inclusion of priority substances in Annex XIV. MSC in its opinion supported recommending the seven substances that were subject of the public consultation for inclusion in Annex XIV. MSC adopted the opinion on ECHA's 8th draft recommendation.	**MSC-S** to inform SECR and publish the final MSC opinion on MSC S-CIRCABC and on ECHA website after the meeting. **SECR** to take into account the MSC opinion when finalising ECHA's 8th recommendation for inclusion of substances in Annex XIV and to submit it to the Commission.
Item 10 – MSC Manual of decisions (MoD) • Suggestion for possible new entries to the MoD	
MSC agreed to include a new entry on TGR (under 3.1.10) in the MSC Manual of Decisions and Opinions (MoD) and mandated MSC-S to make an editorial specification that the entry applies to oral route.	**MSC-S** to update on MSC S-CIRCABC the MoD, as revised at the meeting, in early 2018.
Item 11 – Any other business • Implementation plans of MSC's priority actions regarding process changes • Update on appeals and court cases (Partly in closed session) • Update on ECHA premises • Suggestions from members	
MSC took note of the planned actions regarding process changes.	**MSC-S** to report back to MSC on the progress with the planned actions during 2018.
Item 12 – Adoption of main conclusions and action points	

CONCLUSIONS / DECISIONS / MINORITY OPINIONS	ACTIONS REQUESTED
MSC adopted the main conclusions and action points of MSC-57 at the meeting.	**MSC-S** to upload the main conclusions and action points on MSC S-CIRCABC by 15 December 2017.

V. Statement of the MSC members from Austria, Croatia, Denmark, France, Italy, Lithuania, the Netherlands, Norway, Slovakia, Spain and Sweden on DEv case CCH-113/2017

Justification for voting against ECHA draft decision on CCH-113/2017 for reaction mass of 4-tert-butylphenol and 1,3-phenylenediaminethanamine and -({[3-(aminoethyl) benzyl]amino}methyl)-4-tert-butylphenol, EC nr. 939-071-6.

From: Denmark, Sweden, The Netherlands, Austria, Norway, France, Spain, Lithuania, Croatia, Italy and Slovakia

The members on the Member State Committee (MSC) for the countries named above did not agree with the draft decision from ECHA on Reaction mass of 4-tert-butylphenol and 1,3-phenylenediaminethanamine and -({[3-(aminoethyl) benzyl]amino}methyl)-4-tert-butylphenol, EC nr. 939-071-6 (CCH-113/2017), for the reasons set out below.

The registered substance is an UVCB registered under REACH in the tonnage band 100-1000 tonnes per year. In ECHA's compliance check draft decision, an extended one-generation reproductive toxicity study (EOGRTS, Annex IX, Section 8.7.3; test method: OECD TG 443) in rats, oral route is proposed to be requested. In the EOGRTS, the basic configuration, extension of cohort 1A to produce the F2 generation and cohort 3 (Developmental immunotoxicity) is proposed to be requested.

The MSC members representing countries named above voted against this decision as they are of the opinion that the investigations of developmental neurotoxicity, i.e. DNT cohorts in the EOGRTS study should also be requested for this substance because there is a particular concern for developmental neurotoxicity, based on the justification outlined below.

<u>Justification for particular concern for DNT:</u>

Substance specific information:

Available data provide information that the substance can interfere with signalling through estrogen receptors.

Whether binding and modulation of estrogen receptor activity will lead to an agonistic or antagonistic response will depend on the availability of endogenous estrogens at the site of action. The level of endogenous estrogen varies widely between different life stages and tissues of an organism (*in vivo*) and depends on the assay used (*in vitro*).

In a 90 days repeated dose toxicity study in rats (OECD TG 408) with the registered substance, statistically significant lower mean absolute and relative uterus weights accompanied by histopathological observations (treatment-related atrophy of the cervix, uterus, and vagina) in 9/10 females in the high-dose group (100mg/kg/d) have been reported.

These effects on the adult female reproductive organs suggest an anti-estrogenic activity of the substance *in vivo*, since decreased uterus weight and atrophy of the above mentioned female organs is a sign of lack of estrogenic signalling. In the draft decision, ECHA argues that these effects indicate endocrine-disrupting mode of action, and this information is used to trigger the extension of Cohort 1B to produce the second generation (F2) in the requested EOGRTS.

Further, a main constituent of the registered substance, 4-tert-butylphenol, has been proposed for SVHC identification according to article 57(f) of REACH as an endocrine disruptor in the environment, based on endocrine disrupting properties *in vitro* and *in vivo* in fish. In vitro information is available from assays using both human and fish cell lines, showing weak estrogenic and anti-estrogenic activity. In rodents, there is also some information about effects on the female reproductive tract of this main constituent, which is in line with the observations on the registered substance:

In a 2-generation reproductive toxicity study in rats (OECD TG 416), there is some systemic toxicity in the high dose animals in form of reduced food intake and reduced

weight gain in parental (P) and F1 animals. Some of the effects observed could be secondary to this reduction in weight gain and delayed development of the offspring. However, some effects remain significant also after covariance analysis taking the lower body weight in to account. Examples of effects which remains significant are increase in atrophy of vaginal epithelium in P and F1 females in the high dose group (7500ppm) and in P females in the mid dose group (2500ppm), decreased ovary weight in P and F1 high dose females, decreased uterus weight in high dose F1 females and changes in estrus cyclicity in high dose P females. These observations indicate *in vivo* anti-estrogenic activity.

In our view, for the registered substance, sufficient information on a specific mechanism/mode of action with association to developmental neurotoxicity has been provided, i.e., modulation of estrogen receptor activity *in vitro* and anti-estrogenic activity *in vivo*. Association of this mechanism/mode of action with developmental neurotoxicity (sexual differentiation of the brain) is well-established (see brief description below).

Therefore, the trigger to include the DNT cohort is met, according to the REACH standard information requirements (column 2 of Annex IX) and the corresponding ECHA guidance (see below). We consider the request for DNT proportional to the concern and respecting animal welfare considerations. It is in this regard noted that inclusion of the investigations of the DNT cohorts do not increase the number of animals included in the requested EOGRTS.

Association between the sex steroid hormone signalling and developmental neurotoxicity:

It is well established that the gonadal steroid hormones as androgens and estrogens, and their corresponding receptor signalling pathways, are critical for neurodevelopment. These hormones govern normal sexual differentiation of the brain during the late gestational and early neonatal periods. Sexual differentiation of the brain happens due to actions of the fetal and maternal hormones on the steroid hormone receptors in the brain.

This process, like the differentiation of the reproductive tract, is to a large extent determined by the levels of circulating sex hormones in the blood. In males, the testosterone secreted from the Leydig cells of the testes is secreted into the blood and reaches the brain. Testosterone is converted to estradiol by aromatase in the brain and thereby estradiol masculinises the male brain through estrogen receptor signalling. Female brains are protected from being masculinised by estradiol, because alpha-fetoprotein binds to estradiol and prevents consequently estradiol from entering the brain (Puts et al. 2006).

There is therefore in general a biologically plausible association between the observed specific mechanisms/modes of action of the substance (modulation of estrogen receptor activity *in vitro* and anti-estrogenic activity *in* vivo) and (developmental) neurotoxicity. Further, it has in the literature been shown that substances acting anti-estrogenic *in vivo* can interfere with male sexual behaviour (Luttge et al., 1975),

Importantly, a number of studies support the view that exposure to substances interfering with the sexsystems via different mechanisms/modes of action adversely affects normal sexual brain differentiation and neurodevelopment (Isgor et al., 1998; Hotchkiss et al., 2002; Frye et al., 2012; Pallares et al., 2014;). It is therefore reasonable to expect that substances interfering with the sex steroid hormone system via any mechanism/mode of action impacting the level and/or signalling of androgens (e.g. testosterone) or estrogens (e.g. estradiol) in males or females could adversely affect the development of the nervous system under fetal and neonatal development.

In this case, modulation of estrogen receptor activity *in vitro* and anti-estrogenic activity *in vivo* is observed, and this raises a particular concern for developmental neurotoxicity.

REACH standard information requirements:

The triggers relevant for the inclusion of DNT in this case are given in REACH, annex IX, 8.7.3, column 2, as follows:

"An Extended One-Generation Reproductive Toxicity Study including cohorts 2A/2B (developmental neurotoxicity) (…) may be required by the Agency in accordance with Article 40 or 41, in case of particular concerns on (developmental) neurotoxicity (…)

justified by (…) specific mechanisms/modes of action of the substance with an association to (developmental) neurotoxicity (…).

ECHA guidance:

According to the ECHA guidance (R.7.a, 2016), the information on specific hormonal mechanisms/modes of action with clear association with the developing nervous system are valid triggers for inclusion of the DNT cohorts. In this respect the guidance does not elaborate on all possible relevant types of ED mechanisms/MoAs, but brings a couple of examples i.e., for DNT: "…such as oestrogenicity (Fryer et al., 2012) and anti-androgenicity (Pallarés et al, 2014)".

Animal welfare considerations:

Animals (offspring animals) already included in the study are either discarded (if no DNT concerns) or used to clarify the concern for DNT. Hence the inclusion of DNT cohorts will not increase the number of animals included in the requested EOGRTS.

References:

Frye et al., 2012, Endocrine disrupters: A review of some sources, effects and mechanisms of actions on behavior and neuroendocrine systems, J Neuroendocrinol., 2012 January; 24(1): 144-159.

Gore et al., 2014, Implications of prenatal steroid pertubations for neurodevelopment, behavior and autism, Endocrine reviews, December 2014, 35(6):961-991.

Hotchkiss et al., 2002, Androgens and environmental antiandrogens affect reproductive development and play behavior in the Sprague-dawley rat, Environmental Health Perspectives, volume 110, supplement 3, june 2002.

Isgor et al., 1998, Prenatal gonadal steroids affect adult spatial behavior, CA1 and CA3 pyramidal cell morphology in rats, Hormones and Behavior, 1998, 34, 183-198.

Luttge et al., 1975, Effects of Anti-Estrogens on Testosterone Stimulated Male Sexual Behavior and Peripheral Target Tissues in the Castrate Male Rat, Physiology and Behavior, Vol. 14, pp. 839-846. Brain Research Publications Inc., 1975.

Pallares et al., 2014, Long term consequences of in utero endocrine disruptors exposure on male offspring development, Rec. Farmacol. 2014 7 (2) 39-44.

Puts et al., 2006, Defending the brain from estrogen, Nature neuroscience, volume 9, number 2, February 2006

VI. Statement of the MSC member from UK regarding the SVHC identification of 4,4'-isopropylidenediphenol (bisphenol A) under Article 57 (f) of REACH Regulation as an SVHC substance with endocrine disrupting properties to the environment

We have several concerns for aspects of the fish and amphibian database in the dossier.

A number of "key" studies either have scientific flaws, their results are not consistent with other studies for the same species carried out in other laboratories, or their population-level relevance is unclear.

We remain to be convinced that sufficient information is available to validate the results of one of the key studies (Chen et al, 2015). Interpretation of this and other academic studies and test methods that have not been ring-tested requires additional caution compared to standard methods performed to GLP.

These issues then affect the strength of the conclusions for particular species, and then the weight of evidence for different taxa, when considering where clear adverse apical effects occur where it is diagnostic that these are ED mediated.

We have pointed out issues for a number of studies that were originally rated "reliable with restriction" by the dossier submitter, but were heavily critiqued in previous EU reports. Further critical comments have been submitted by other stakeholders during public consultation. Generally therefore, we think the dossier would have benefitted from a more transparent assessment of study reliability.

While we agree that the effects concentrations of some of the invertebrate data are of high concern, we do not think that the invertebrate data should be mentioned in the conclusions on ED. The state of science is not mature enough to justify this, and we should be making decisions on data that is clearly endocrine related (not just "possibly").

Environmental fate and potency are not considered in the discussion of the population-relevance of the mammalian end points in the conclusions.

In comparison with other substances that have been agreed to be environmental EDCs (e.g. nonylphenol), bisphenol-A is much less persistent, an order of magnitude less bioaccumulative and in general causes comparable effects in the same species at much higher concentrations. We believe that potency is a highly relevant factor in deciding whether a substance is an equivalent level of concern, and there are no fully reliable studies indicating repeatable ED-related adverse apical effects below 10 µg/L. In our scientific view, the fate and potency characteristics based on fully reliable data are not sufficient to identify bisphenol-A as a substance of very high concern in terms of probable serious effects to the environment.

Therefore we have abstained.