

MSC/M/52/2017
(Adopted at MSC-53)

Minutes
of the 52nd Meeting of the Member State Committee (MSC-52)
7-9 February 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 52nd 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 modified by the MSC Secretariat based on a request from a member with addition of an item to any other business on potential establishment of expert group on UVCBs and with addition of the information document on substance evaluation status report for discussion following a request from a member (final Agenda is attached to these minutes).

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-52.

Item 4 - Administrative issues

- **2016 Satisfaction survey**

SECR gave a brief report on the status of MSC-related actions arising from the 2015 Satisfaction Survey and provided feedback from the 2016 Stakeholder survey outcome, relevant for MSC and the actions planned in this regard. The Committee was informed of a new initiative by the MSC Chairman to organise briefings for MSC ASO observers on substance- (SEv) and dossier evaluation (DEv) cases agreed in written procedure. The objective of these briefings is to further increase the transparency of MSC SEv and DEv agreement seeking.

- **Outlook for MSC-53**

The Chairman presented an outlook on the potential length of the next meeting which is expected to require approximately three plenary days. The Chairman also presented an early stage estimation for the length of the MSC-54 meeting in June.

Item 5 – Adoption of the minutes of the MSC-51 meeting

The minutes of MSC-51 were adopted as modified at the meeting.

Item 6 – Substance evaluation

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

a) Discussion on the MSC opinion on the draft Community Rolling Action Plan (CoRAP) update

The Rapporteur presented the draft opinion and its annex and explained that since the December MSC-51 meeting 14 justification documents were updated on the request of the Working Group members. Overall, the changes made since the referral of the draft CoRAP update 2017-2019 included 1) withdrawal of six substances already in CoRAP and withdrawal of one substance newly introduced in the draft CoRAP; 2) changes in years of evaluation; 3) changes in initial grounds of concern and 4) notification and inclusion of a new substance.

Concerning the titanium dioxide entry (EC 236-675-5), which was included in the CoRAP already in 2012 for evaluation in 2014, it was proposed to maintain the evaluation year 2018 for that substance as indicated in the draft CoRAP update. Some relevant information on the substance following the outcome of a compliance check appeal, and the opinion of RAC on the proposal for harmonised classification would, will most likely only become available later on in 2017. MSC updated the text of the opinion to reflect this information

on titanium dioxide and to indicate the intention of the evaluating MSCA to start the evaluation preparations in 2017 once the expected information becomes available.

An industry stakeholder observer expressed that the titanium dioxide evaluation should be initiated as soon as possible and appreciated the additional text in the MSC opinion with a clear way forward.

Another stakeholder observer expressed regret that evaluation of some substances was postponed. SECR explained that postponement of the substance evaluation (SEv) does not necessarily mean delay. SEv is postponed to await the outcome of compliance check results since in many cases this will provide sufficient information for clarification of the identified concern and in consequence the substance evaluation will be redundant. SECR will consider how to communicate the reasons for withdrawal of substances.

b) Adoption of the MSC opinion

MSC adopted by consensus the opinion on the draft annual CoRAP update 2017-2019 and its annex as amended during the meeting. MSC also gave the mandate requested by the Rapporteur for any necessary editorial changes before publication. It was concluded that the MSC opinion together with the final update to CoRAP will be published on the ECHA website on 21 March 2017.

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 six substance evaluation cases (see Section V for more detailed identification of the cases). WP was launched on 12 January 2017 and closed on 23 January 2017. By the closing date, unanimous agreement was reached on all the six draft decisions (DD) with one abstention received for three cases.

b. Introduction to and preliminary discussion on a draft decision 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)

SEV-DE-008/2015 - 2,2'-dimethyl-4,4'- methylenebis (cyclohexylamine) (EC No. 229-962-1)

Session 1 (open)

Two representatives of the Registrants participated in the initial discussion. The Registrants had not submitted comments on the Proposals for Amendments (PfAs). Hence, they could not present their views on the PfAs but could provide answers to any scientific and dossier-content related questions posed to them during the meeting. In absence of specific confidentiality concerns in draft decision (DD), an open session was held.

The evaluating Member State Competent Authority (eMSCA) from Germany (DE-CA) presented the outcome of substance evaluation (SEv) of the above-mentioned substance performed on the basis of the initial grounds for concern relating to potential endocrine disruption. In the course of the evaluation an additional concern for reproductive toxicity was identified.

The draft decision (DD) consulted with the Member State Competent Authorities (MSCAs) and ECHA had one request for information. It requested for an extended one-generation reproductive toxicity study (EOGRTS) in rats by the oral route: EU B.56/OECD TG 443 with the expansion to include cohorts 2A and 2B to address developmental neurotoxicity and extension of Cohort 1B to produce the F2 generation. Furthermore, it requested a pre-mating period of 10 weeks with the neuro-histopathological investigations of Cohort 2A and 2B animals, including sections of choroid plexus.

MSC was guided by the expert from the eMSCA through the information on the substance (including PfAs, and the eMSCAs responses to them). The expert further explained that ECHA conducted a compliance check (CCH) on the dossier of the lead Registrant in 2013 and concluded that there is a standard information gap for reproductive toxicity. However, due to the expected legislative change for the appropriate study test method (EOGRTS) to be applied for this endpoint, codified later by Commission Regulation (EU) 2015/282 of 20 February 2015, the reproductive toxicity endpoints was at that time not included in the CCH-decision.

PfAs were received both on study design as well as on the scope of the decision.

PfAs on the study design proposed to: 1) add a request for cohort 3 (developmental immunotoxicity, DIT), due to the increases of immune-relevant blood cell values, and absolute and relative adrenal weights; 2) provide more detailed arguments on the available screening study (OECD TG 422) not covering the functional fertility of F1; 3) specify and add reasoning for the administration route (by gavage or feeding study); 4) consider the proposal of the Registrant to conduct a DNT study according to OECD TG 426; 5) reflect why the modified one generation reproduction test is not regarded as a validated alternative to the DNT study proposed as alternative by the Registrant; 6) remove the extension of the cohort 1B to include the F2 generation since the concerns for fertility and related ED mode of action are not adequately substantiated by the observed effects on the testis and *in vitro* data; 7) use results from the mutagenicity request in the 2013 CCH decision to justify the request for the 2nd generation since the ED concern is not supported by the available data; 8) include the reasons for the rejection of the Registrants' adaptation argument for the standard information requirement of Annex X, 8.7.3. since the sources of information the Registrants provided, together with their justification for the adaptation, do not allow conclusion on the dangerous (hazardous) property of the registered substance with respect to the reproductive toxicity and developmental neurotoxicity and 9) show the difference in toxicological profiles between DMDC (the substance under evaluation) and PACM - 4,4'-methylenebis (cyclohexylamine) (the read across substance) and 10) to delete from the DD text the specific reference to BoA decision A-005-2014.

PfAs on the scope of the DD proposed to: 1) move the request under compliance check (CCH) since information requested is based on a data gap rather than a concern; 2) introduce more clear case-specific concerns; and 3) address the substance evaluation DD to all the Registrants irrespective of specific tonnage band requirements of operators pursuant to Articles 10 and 12 of REACH.

An additional PFA argued that since the Registrants had not provided any substance specific justification, their request to extend the deadline from 27 to 36 months should not be granted.

During the discussion at the meeting, the Registrants' representatives were asked some clarifying questions to assist in the determination of the study design. Regarding the oral 90d repeated dose toxicity study whose results triggered an endocrine disruption concern, they confirmed that in this study, the general state of health of the animals was poor and there was a decrease in body weight of 42% compared to the control at the highest dose used. The PFA submitter hence reiterated that at such conditions one cannot find it scientifically credible to associate the effects seen, with endocrine disruption effects. This reasoning received support from several MSC members.

Regarding the developmental neurotoxicity, the Registrants' representatives were asked whether the DNT cohort in EOGRTS was enough to address the concern or whether they were more supportive of performing a full developmental neurotoxicity study based on OECD TG 426. They expressed the preference to first perform the EOGRTS with the DNT cohort and based on the results decide whether OECD TG 426 is needed. This however, triggered an objection from one MSC member who pointed out that if the endpoints of learning and memory are not investigated, as in the case in a DNT cohort in EOGRTS, then one cannot tell if these endpoints have been effected. The Registrants' representatives explained that if there are concerns with learning and memory, these parameters could be

included in the DNT cohort when performing EOGRTS. The eMSCA expert was considering this option positively.

Regarding the route of administration, when considering oral route by gavage dosing should be high enough, hence the eMSCA expert asked the Registrants' representatives for some detail on the dosing done in the rabbit study.

Regarding the proposal to include the DIT cohort in the EOGRTS, the MSC member from the PfA submitting country explained that due to the inflammatory response seen in the 90-day study at the highest doses, immunotoxic effects cannot be excluded. This however, could not be fully supported from the scientific data due to the high toxicity at the highest dose.

Session 2 (closed)

Regarding the study design, the discussion focused on whether the DNT cohort in EOGRTS could be extended with the additional parameters of learning and memory based on the PfA submitted. It was, however, concluded that such extension of the DNT cohort was not explicitly requested in the PfA. It was also concluded that a separate developmental neurotoxicity study (OECD TG 426) is not requested at this stage, since this study will not tackle several developmental/reproductive toxicity endpoints covered by EOGRTS (OECD TG 443) but not covered by such a DNT study. However, a DNT study might become necessary if the concerns related to developmental neurotoxicity remain after conducting the requested EOGRTS with inclusion of the DNT cohorts according to OECD TG 443. To take into account the concerns expressed in a PfA and the comment by the Registrants to investigate the potential developmental neurotoxicity by the more comprehensive study according to OECD TG 426, MSC agreed to request the Registrants to consider enhancement of the DNT investigation (based on OECD TG 443 paragraph 50) with cognitive tests, e.g. with testing of the cohort 2A for effects on learning and memory at PND 60-75.

Regarding the extension of the cohort 1B to include the F2 generation, MSC used as basis the understanding that generally up to 30% reduction in body weight compared to the controls has no significant effect on the weight of the testis. However, since in this case there was a 42% reduction in body weight compared to the controls and there were signs of poor general condition of the animals in the high dose, as confirmed by the Registrants' representative, the MSC considered that the changes observed in the testis are likely a consequence of high general toxicity and not to a potential ED mode of action. Furthermore, the result from the mutagenicity study requested under CCH were negative. Hence, MSC concluded there were insufficient grounds to trigger the request for extension of the cohort 1B to include the F2 generation.

In conclusion, MSC agreed by consensus on the request for an Extended One Generation Reproduction Toxicity Study (OECD TG 443) (EOGRTS) in rats, by the oral route: EU B.56/OECD TG 443 with the expansion to include cohorts 2A and 2B to address developmental neurotoxicity with an option to consider enhancement of the investigations to include testing on cognitive effects as describe above, a pre-mating period of 10 weeks, and for the neuro-histopathological investigations of Cohort 2A and 2B animals to also include sections of choroid plexus. Neither the cohort 3 (developmental immunotoxicity) nor an extension to mate cohort 1B animals to produce the F2 generation are requested.

Regarding the scope of the decision, whether the request is made to fill a REACH standard information gap or to address a specific concern, the view of the eMSCA was that a standard information gap can constitute a concern which in itself can justify a request for provision of the information under SEv. Additionally considering that a CCH on the substance was carried out already, moving the request under a new CCH would mean further delay in the filling of an already identified standard information gap for the substance. This view received support from MSC, in fact many members agreed that a standard information gap can indeed constitute a concern under SEv.

Furthermore, the eMSCA expressed the view that on grounds of proportionality the decision should only be addressed to those registrants who are obliged to submit this study as standard information and also to bear the appropriate costs. According to the

eMSCA, it would not seem to be proportionate to address this decision to registrants for whom the standard information requirement does not apply.

This approach did however not receive full support of MSC since it deviates from the current line where a SEv decision is addressed to all the registrants irrelevant of the tonnage band. Furthermore, if this approach is to be generally used for other SEv cases, it will lead to additional tasks of checking the tonnage band of each registration for each registration dossier to individually assess exposure based waiving and other dossier specific information. Considering that the eMSCA performs substance evaluation on an IUCLID dossier that aggregates all the registrations into one and does not differentiate amongst registrants, the approach by the eMSCA was seen as a considerable heavy addition to the current process as regards complexity and workload. An additional concern was that it may require the eMSCA to give consideration to, and take into account, data and cost sharing issues amongst registrants.

A minority of MSC members was of the opinion that these arguments require a policy discussion at the REACH Committee. Hence, MSC could not reach unanimous agreement on this decision with eight members voting against. The Norwegian member also voted against (see Annex VI for the MSC Justification for the disagreement for the SEV-DE-008/2015). The MSC Secretariat will refer the decision to the Commission for further decision making without undue delay once minutes of MSC-52 are agreed.

SEV-IE-023/2015 - 3-trimethoxysilylpropyl methacrylate (EC No. 219-785-8)

Session 1 (open)

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

The eMSCA from Ireland (IE-CA) presented the outcome of SEv of the above-mentioned substance which was performed by the IE-CA on the basis of the initial grounds for concern relating to human health/suspected sensitiser, further evaluation of repeated dose toxicity and reproductive toxicity data; exposure/wide dispersive use, consumer use, exposure of workers, high (aggregated) tonnage. In the course of the evaluation, the eMSCA identified additional concerns regarding mutagenicity (clastogenicity).

The draft decision (DD) consulted with the MSCAs and ECHA requested among others a Local Lymph Node Assay (LLNA; EU B.42/OECD TG 429) and an *in vivo* mammalian alkaline comet assay (comet assay; OECD TG 489) in rats, inhalation route.

MSC was guided by the expert from the eMSCA through the information on the substance (including PfAs, the Registrants' comments and the eMSCAs responses to them). PfAs were received on the LLNA and the comet assay. For both endpoints it was proposed to specify that a freshly prepared formulation/solution of the registered substance in an appropriate vehicle should be used as methacrylates are known to polymerise in liquids. This was accepted by the eMSCA before the meeting and supported in the Registrant's comments. The remaining PfAs were all open for discussion at the meeting.

With regards to the LLNA a PfA proposed to give the Registrant the option to either carry out *in vitro* testing (OECD TG 442C, 442D and 442E) or conducting a LLNA. In the view of the PfA submitter, unlike what is written in the DD, there is no reason hindering the use of *in vitro* skin sensitisation tests for substances which react rapidly with water. This approach would also respect the requirement to only conduct animal testing as a last resort. Hence, in their view, LLNA should only be conducted if it can be demonstrated that *in vitro* testing is not technically possible.

Another PfA suggested to add further argumentation for choosing the LLNA in accordance with OECD TG 429 since it not only provide results which can be used to determine whether the substance is a skin sensitiser or not, but also generates information needed for a potency assessment relevant for sub-categorising in category 1A or 1B according to the CLP Regulation. Furthermore, it proposed to mention the advantages LLNA has over a guinea-pig maximisation test (GPMT) or Buehler test (OECD TG 406) in respect to potency evaluation and animal welfare.

With regard to the comet assay a PfA requested to change the inhalation route to oral exposure through gavage and with analysis of stomach, intestines and liver tissue. According to this PfA since neither nasal nor laryngeal tissues are yet validated for the comet assay by inhalation the results might not be reliable, and information obtained with either route would be equally appropriate for hazard classification. Another PfA supporting the inhalation route suggested adding text to ensure that the aerosol exposure for inhalation exposure is similar to real life conditions (i.e. the likely most relevant human exposure route).

Regarding the LLNA the Registrant's representative argued that it is not an appropriate choice of test in this case due to the potential false positives for silicon based substances, and asked for an *in vivo* GPMT or Buehler test be considered as an alternative. The Registrants anticipate that in this particular case, *in vitro* tests will not be appropriate due to instability of the test substance.

Regarding the comet assay, the Registrants' representative expressed preference for the inhalation route, but shared the concern that certain tissues are not validated, and thus preferred to use standard tissues like lung and liver. Furthermore she favoured the use of aerosolised substance versus the hydrolysate, and stressed that the substance to which the organism will be exposed is different if exposed orally versus inhalation, because of the effect of pH on hydrolysis rate. On this basis, the member of the PfA submitting country decided not to pursue further the oral route and agreed with requesting the comet assay using inhalation exposure. However, in order to be able to accept a negative outcome, the need to include an appropriate concurrent positive control, administered by the inhalation route, was raised and discussed.

Session 2 (closed)

On skin sensitisation, MSC considered whether classification on the basis of *in vitro* results was possible. It was recognised that it is neither yet clear according to the CLP regulation nor at an international level if *in vitro* results can be used for sub-categorisation as 1A or 1B. Furthermore, for this case, due to the physico-chemico properties of the registered substance, the applicability of the *in chemico/in vitro* test methods for the registered substance is unclear. The *in chemico/in vitro* test methods require incubation with the test material for at least 24 hours in an aqueous solution buffered to various pHs. Therefore, given the rapid hydrolysis and limited solubility of the registered substance in water and the propensity of the hydrolysis products to polymerise in water there is uncertainty whether the registered substance can be reliably tested in the proposed *in chemico/in vitro* tests. Furthermore, the LLNA allows the use of an oil-based delivery system through which these substance-specific issues may be avoided. Therefore, MSC considered that for this specific case the LLNA according to OECD TG 429 is more appropriate than the *in chemico/in vitro* studies and due to also animal welfare consideration this test method was also preferred over the alternatively proposed OECD TG 406 test method. Hence, the decision was not amended as regards the requested test method for skin sensitisation.

Regarding the choice of tissue to be sampled for the comet assay, MSC agreed on requesting testing by inhalation but acknowledged that there may be technical challenges to testing the laryngeal tissue and therefore MSC unanimously agreed to request sampling of the larynx if technically feasible.

In conclusion, MSC agreed unanimously to keep the request for LLNA (OECD TG 429) and the comet assay (OECD TG 488). The latter exposing the animals via an aerosolised atmosphere of the registered substance, and requesting analyses of the following tissues: nasal epithelium, lungs, liver and if technically feasible the larynx. For both tests, due to the hydrolytic instability of the registered substance MSC agreed that the study shall be conducted with freshly prepared test solutions in an appropriate vehicle. The selection of the vehicle shall be scientifically justified and should be chosen to minimise the rate of hydrolysis.

d. General topics

- **Appeals update**

SECR gave an overview of the status of recent appeals on evaluation submitted to the Board of Appeal of ECHA and pending cases submitted to the European Court of Justice relating to the authorisation process. MSC took note of the information received.

- **SEv report**

The SEv report was submitted to MSC as a document for information without discussion at the meeting unless members request for it to be discussed. One member requested clarification on the informal process proposed by ECHA for collection of information on exposure from the registrants. In the power point document it was indicated that if an eMSCA includes in the SEv DD a request for information on exposure a justification for not using the informal route would need to be given. SECR agreed that the wording in the slide is not optimal. SECR explained that after exploring the possibility to obtain exposure information through an Article 36 decision it was concluded that a more appropriate and effective option would be an informal interaction with the registrant and eMSCA sending a letter with exposure questions/requests to the registrant(s). The slide intended to explain that ECHA would like to get an understanding on how often such letter requests lead to positive results. If this option turns out not to be an effective measure, then other options should be sought.

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 16 dossier evaluation cases (see Section VII for more detailed identification of the cases). WP was launched on 13 January 2017 and closed on 23 January 2017. By the closing date, unanimous agreement was reached on 14 DDs. For 2 DDs, WP was terminated by the MSC Chairman on the basis of Article 20.6 of the MSC Rules of Procedure as at least one MSC member requested discussion of the cases at the MSC-52 meeting.

Two MSC members from Germany and the Netherlands requested the floor to explain why they had abstained from voting on the case CCH-149/2016. In their view ECHA should not change its administrative practices to the follow-up of decisions according to Article 41 (3), although it may feel bound by the Board of Appeal's decision in case A-019-2013, because this can lead to unnecessary delays in the enforcement of Article 41 decisions and contains the risk of misuse. From their point of view, no further decision following REACH Articles 42 (1) and 51 is necessary and thus they intervene in the currently pending Court of Justice proceeding "Esso Raffinage v. ECHA "(T-283/15). Both MSC members also stated that they would abstain from voting on similar cases in the future.

The MSC member from Germany requested the floor to explain that they abstained from voting on the case CCH-152/2016 because of the discussion which recently started on the potential use of the long-term toxicity fish sexual development test (FSDT; OECD TG 234) in the Dossier Evaluation process. In their opinion the FSDT is the most appropriate test to clarify the estrogenic mode of action of the substance and it should be requested even if other endocrine modes of action might occur which might require additional tests. The Chairman informed MSC about an *ad hoc* expert group that will prepare a discussion paper whether and when requesting OECD TG 234 under dossier evaluation process is possible. It is expected that MSC will discuss this paper and its conclusions in one of MSC's future meetings.

The MSC member from the Netherlands also explained why he had abstained from voting on the case TPE-091/2016 in the written procedure. In his opinion, the requested information for this substance could potentially be generated using a read-across from the substance that was discussed in MSC in 2015 (TPE-052/2015).

SECR informed MSC that they will need to further consider what to do with it.

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 proposals when amendments were proposed by MS's (Session 2, closed)

CCH-121/2016 Reaction mass of dimethyl adipate and dimethyl glutarate and dimethyl succinate (EC No. 906-170-0)

Session 1 (open)

No 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 three PfAs to ECHA's DD were submitted in total, two of which were discussed in the meeting and are outlined below.

Two PfAs were on the extended one-generation reproductive toxicity study (EOGRTS) suggesting to include developmental neurotoxicity (DNT) and developmental immunotoxicity (DIT) cohorts due to effects observed after exposure to the main constituent dimethyl glutarate (DMG) of the registered substance. The PfAs argued that the observed decreased testosterone levels in the mid and high dose groups with DMG in a 90-day inhalation study (OECD TG 413) raise concerns sufficient to trigger the inclusion of the DNT and DIT cohorts. It was further argued that it has been shown that serum testosterone levels and androgen signalling during early development are important for (a) for normal sexual differentiation of the brain (DNT) and (b) normal functioning of the immune system (DIT).

The Registrant in his written comments disagreed with these PfAs, arguing: (a) the fluctuations of testosterone levels were due to homeostasis and were not adverse effects; (b) both PfAs were based on the unsubstantiated assumption that triggers exist for the DNT and DIT cohorts; and (c) both PfAs were inconsistent with earlier findings on DMG in the context of substance evaluation.

Both MSC members of the PfA submitting countries repeated the arguments of the PfAs that the main constituent DMG of the registered substance decreased serum testosterone levels by around 50% compared with controls at mid and high exposure levels in repeated dose toxicity (RDT) study via inhalation route. Moreover, it also decreases luteinizing hormone (LH) up to 71% in high exposed group male rats after inhalation. One of the participants from a MSCA making one of the PfAs explained further that sex hormones have a crucial role in brain development, and insufficient levels of testosterone in the developing male offspring could feminize the brain, both in rats and humans, and therefore right levels of these hormone are very important already in a very early stage around birth. It was further explained that during normal male development two testosterone surges both occur just before birth in humans but just before and just after birth in rats and further that the testosterone surge was vital for the normal male programming of the developing brain. It was also emphasised that as whereas the first of the mentioned testosterone surges are not controlled by pituitary hormones the second surge is, similar to the situation in adult rats. This is also why the DNT study in rats includes exposure not only before but is continued in an appropriate period of time after birth. Based on this it was argued that the observed decrease in serum testosterone levels as observed in adult rats due to exposure to the registered substance was relevant in respect to concerns for effects on the developing brain i.e. DNT effects. Similarly, the sex hormones affect the developing immune system. Hence, in the view of the participants from the PfA submitting countries both DIT and DNT cohorts should be included in EOGRTS design, also considering that requesting these cohorts would not trigger the need for additional animals.

SECR responded that the reduction in testosterone serum level was not dose-dependent (59 and 50% at the mid and high exposure level) and reduction in LH was 71% and observed only at the highest exposure level. Those effects were observed in adult animals

and it is unclear if these mechanisms would be applicable to testosterone levels during development and also to humans. It was acknowledged that correct levels of testosterone (in the brain) are indeed critical for brain development and are more relevant before birth for brain sexual organisation. It was noted that there was no change in serum estradiol concentration in female rats.

A participant from another MSCA supported the view of the two PfA-submitting countries. Furthermore, in response to whether the foetal testosterone levels are controlled by LH during programming of brain sexual differentiation, she referred to the scientific articles showing that the peri- and early postnatal testosterone synthesis in the rat is LH dependent.

Some other MSC members expressed their support the views expressed in the PfAs, while other MSC members supported the views of SECR.

A stakeholder representative reminded that even if the triggering of DIT and DNT cohorts would not involve additional animals, it would not mean that there are no animal welfare concerns because the animals would suffer longer during the study.

Another stakeholder representative noted that, when there was evidence for concern, even if it was not clear, one should investigate further to rule out the possibility for a certain property. In this context the representative referred to the precautionary principle mentioned in the preambles of REACH.

SECR agreed that the precautionary principle has been used to draw-up the articles and Annexes of REACH, which include the EOGRTS as a standard information requirement while the criteria for including additional cohorts require that there has to be evidence to justify the concern and inclusion of additional cohorts. Therefore, in case a certain property cannot be ruled out, it does not mean it can be used as a trigger for further testing.

A MSC member questioned when would there be enough evidence to claim that a substance would have a certain effect in the context of triggering the EOGRTS cohorts if the arguments such as those in this particular case from the two PfA proposing countries were rejected.

Session 2 (closed)

The Chairman reminded MSC to consider the Registrants comment on the outcome of the substance evaluation on DMG (main constituent of the registered substance). The MSC member of the eMSCA, which had concluded the substance evaluation on DMG, confirmed that he supported the approach not to include the cohorts, as this country had not identified any concerns for endocrine disruption or reproductive toxicity.

Several MSC members voiced that they could not agree with DD as provided in advance of the meeting and informed MSC that as the majority of MSC members seemed to be in favour for the DD, they jointly prepared a justification document for their foreseeable 'No' vote. The Chairman asked them to ensure that all arguments included in the justification had been presented to MSC prior to its voting, after which one of the members informed MSC of the main elements, that a significant observed reduction in testosterone and LH serum levels in adults indicate a hormonal disturbance relevant for a concern for developmental neurotoxicity and developmental immunotoxicity and therefore in accordance with the triggering of the DNT and DIT cohorts in EOGRTS.

MSC did not reach unanimous agreement on ECHA's DD as provided for the meeting.

Six MSC members voted against the decision. The Norwegian member also voted against. The Chairman invited the disagreeing MSC members to provide written justification for the disagreement (see Section VIII). SECR will refer the DD to the Commission, which will prepare a decision in accordance with the procedure of Article 133(3) of REACH.

CCH-122/2016 (1-methyl-1,2-ethanediyl)bis[oxy(methyl-2,1-ethanediyl)] diacrylate (EC No. 256-032-2)

Session 1 (open)

No representative of the Registrant participated in the initial discussion. In absence of specific confidentiality concerns in DD, an open session was held.

SECR explained that seven PfAs to ECHA's DD were submitted in total, two of which were discussed in the meeting and are outlined below. The PfA on EOGRTS requested for sequential testing to take into account results from mutagenicity study before performing EOGRTS, because (a) the uses were leading to significant exposure of professionals; and (b) there were indications from the *in vitro* studies in the dossier that the substance may be genotoxic. Therefore there should be two separate deadlines for the Registrant to submit the requested information. The information on mutagenicity should be submitted by the shorter deadline in order to allow ECHA to confirm the EOGRTS design before it is started.

The PfA on simulation test on ultimate degradation in surface water requested:

(a) to indicate that the Registrant had not provided evidence that such a test is not needed by appropriate reference to the CSR (PBT/vPvB assessment and/or quantitative risk assessment);

(b) for the Registrant to justify that the extraction procedure or solvent chosen is appropriate to conclude that any loss of substance is not due to irreversible binding (i.e. non-extractable residues; NER) to suspended particulate matter (SPM);

(c) to specify that the request is for the "pelagic test";

(d) the Registrant to consider to perform the simulation degradation testing in surface water using water containing 5 and 30 mg SPM dw/L or approximately 15 mg SPM dw/L.

SECR had modified the DD in advance of the meeting based on the PfA on simulation test on ultimate degradation in surface water parts (a), (c) and (d).

The Registrant had provided written comments on the DD (not reflected here) and a PfA that did not require further discussion at the meeting.

It was questioned why the mutagenicity study request in combination with EOGRTS is handled differently compared to requests for a 90-day study in combination with EOGRTS. SECR responded that for 90-day study the Registrant may not be so well informed as how to evaluate the triggers for further testing. The Registrant is in a better position to decide on the need to include the additional cohorts in case when mutagenicity study is requested in combination with EOGRTS. The MSC member of the PfA submitting country could agree with SECR that the results from mutagenicity study are easier to use for further triggering of cohorts in EOGRTS compared to 90-day study.

Some MSC experts challenged SECR explanation on the DD text concerning non-extractable residues (NER). Even though they accepted that this issue may be even more relevant for simulation tests on sediment and soil due to much higher organic carbon content compared to the pelagic test, they also argued that the organic carbon content in SPM (with an EU default value of 15 mg SPM dw/l) is much higher than the substance concentrations normally used in simulation degradation surface water tests and therefore irreversible binding and appropriate extraction methods are relevant for pelagic tests as well.

SECR responded that a Guidance review is ongoing but that this matter (in relation to OECD TG 309) had not until now been discussed and agreed in that context. Furthermore, they considered that the OECD TG 309 (pelagic test) describes that mass balance should be provided (including NER), and in their view therefore highlighting this specific issue in the DD would not be vital. However, they did not recognize any strong objections to request the registrant to specify NER extraction method and solvent used for the reasons provided also in this case when requesting a surface water degradation test. Furthermore, in line with previous decisions on the SPM content SECR agreed to change the DD text from "*approximately 15 mg/l*" to "*10-20 mg/l*".

A MSC expert noted that extraction of substances has more to do with recovery than the mass balance. Often adsorption is considered dissipation and could therefore,

inadvertently, be included in the calculation of half-life. Hence, a proper extraction method should be used by the Registrant (e.g. specific Soxhlet).

Session 2 (closed)

Based on the discussion in MSC the wording of the DD was strengthened accordingly. The Registrant is requested to take into account the results of the mutagenicity study in the design for EOGRTS. For simulation testing in surface water there is further wording regarding NER, requesting the Registrant to justify scientifically that the extraction procedure and solvent chosen is appropriate in respect to determining the level of NER.

MSC agreed unanimously to the DD as amended at the meeting.

CCH-125/2016 Cyclohexyl methacrylate (EC No. 202-943-5)

Session 2 (closed)

MSC agreement was initially sought in WP, which was terminated by the Chairman of MSC in accordance with Article 20(6) of the MSC Rules of Procedure.

One MSC member had requested stopping the written procedure to allow a discussion in the plenary meeting. The MSC member referred to the PfA on exposure assessment on human health requesting to recalculate the exposure estimates for glove efficiency and dermal protection.

Following this clarification the DD was considered acceptable as provided.

MSC agreed unanimously to the DD as provided for the WP and the meeting.

CCH-129/2016 Dinitrogen tetraoxide (EC No. 234-126-4)

Session 1 (open)

No representative of the Registrant participated in the initial discussion. In absence of specific confidentiality concerns in DD, an open session was held.

SECR explained that four PfAs to ECHA's DD were submitted. A PfA on EOGRTS requested to remove the request indicating that N₂O₄ is in equilibrium with nitrogen dioxide (NO₂), and that NO₂ degrades rapidly in water to nitrous and nitric acids. Systemic exposure would be to nitrite and nitrate anions, which have known properties, and local exposure would be limited by the formation of nitric acid. There is sufficient information on the registered substance for the endpoints of reproductive toxicity and further testing is unnecessary, because of the known rapid formation of acid from the registered substance, the potent corrosion from the acid, and the consequent low systemic exposure to breakdown products.

The second PfA on pre-natal developmental toxicity study (PNDT) requested to remove the request based on the same reasoning as for EOGRTS study above.

Two PfAs were on *in vivo* mammalian alkaline comet assay (OECD TG 489). One of them agreed with a standard information gap and requested to reword the request on the comet assay to reflect that the read-across to NO₂ would be acceptable for this endpoint. Additionally, it stated that the submission of a genotoxicity study on NO₂ (the accepted analogue substance) by Han *et al.* (2013) and self-classification of dinitrogen tetraoxide (the registered substance) as a mutagen 1B (as a precautionary measure) would satisfy the requirement for the *in vivo* mammalian alkaline comet assay. Also, this PfA considered that further testing would be in conflict with the animal welfare considerations, specifically not to test corrosive substances at levels causing corrosivity.

The second PfA on the same endpoint requested to add nasal tissue to address the potential for mutagenicity at tissues of first site of contact. *In vitro* data indicated that the substance may be a direct acting mutagen with concerns for possibility of effects in initial site of contact tissues.

SECR had modified the DD in advance of the meeting based on the first PfA on the *in vivo* mammalian alkaline comet assay, and had deleted the requests for EOGRTS and PNDT.

The Registrant had provided written comments on first three PfAs by agreeing on them.

The MSC member representing the CA submitting PfA agreed with the way SECR had responded to their PfAs and updated the DD accordingly on *in vivo* mammalian alkaline comet assay and on EOGRTS.

Session 2 (closed)

The MSC discussed the first PfA on *in vivo* mammalian alkaline comet assay extensively and concluded that the study provided on analogue substance NO₂ by Han *et al.* (2013). The MSC considered that the study appeared to fulfil the information requirement of the decision request for genetic toxicity. Regarding the Registrant's proposal to self-classify dinitrogen tetroxide (the registered substance) as a mutagen 1B the MSC considered that to request self-classification does not fall within its remit.

SECR explained that it does not take into account dossier updates after the DD is sent to the Registrant for the first time. The study provided in the Registrant's comment to the PfA will be evaluated during the follow-up process when made available in a dossier update.

MSC agreed unanimously to the DD as submitted to the meeting.

CCH-131/2016 – N-butylbenzene-sulphonamide (EC No. 222-823-6)

Session 1 (open)

No 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 three PfAs to ECHA's DD were submitted on extended one-generation reproductive toxicity study. The first PfA suggested aligning the wording with the agreement reached in MSC-50 on the MSC Manual of Decisions and Opinions (MoD) text. The two other PfAs suggested including additional arguments for the already included developmental neurotoxicity (DNT) and immunotoxicity (DIT) cohorts. This was based on specific mechanisms or modes of action (MoA) investigated in two *in vitro* studies. The substance is shown to inhibit growth of human prostate cells *in vitro*, which is initially dependent on androgens. According to the PfA, anti-androgenic substances affect normal sexual differentiation of the brain and functioning of the immune system, thus raising concerns on DNT and DIT.

SECR had modified the DD in advance of the meeting based on the first PfA.

The Registrant had not provided written comments on the PfAs.

A MSC member maintained the view that in an *in vitro* study the registered substance was shown to act as a receptor-specific androgen antagonist, which in his view is sufficient to indicate an endocrine disrupting mode of action. Some MSC members shared the view that there were clear indications on anti-androgenic effects and requested that justification from the *in vitro* study was to be included in the reasoning to further support triggering of DNT and DIT. One MSC member supported the view from SECR arguing that findings potentially related to endocrine modes of action *in vivo* had been observed at generally toxic doses and that in the sequential testing the results from the 90-day study would be used for final EOGRTS design. SECR argued that DNT and DIT were already triggered, but the particular *in vitro* study was not considered relevant for further justification. It should not be considered, in particular due to its unreliability, inconsistencies in the data presented and insufficient statistical analysis. It was deemed doubtful if such a study could be used as only evidence for triggering. A MSC member responded that it had not been possible to prepare for discussing details of the *in vitro* study in the plenary meeting, and concluded that MSCA experts would need to re-check such details.

Session 2 (closed)

Some MSC members noted the need to allocate more time for discussions with SECR in case new considerations of relevant studies would emerge before or at the plenary meeting. One MSC member emphasized that all relevant arguments would need to be present already in the documentation for the meeting. SECR noted that assessing the

quality of studies referenced in advance by PfA submitters and MSC members would be helpful. Both MSC and SECR acknowledged that the availability of literature references and time available for their evaluation was challenging within the MSC timeline. Hence, to facilitate retrieval data sources referred in a PfA should include full bibliographic information. MSC identified the support from an expert group on scientific issues as one possible way forward.

MSC concluded the discussion on the findings of the *in vitro* study, that SECR had raised concerns on some elements of the study with which other experts of some MSC members did not agree. Noting that DNT and DIT cohorts were already triggered in the EOGRTS design, MSC decided to leave out the *in vitro* findings as additional justification for their triggering.

MSC agreed unanimously to the DD as provided for the meeting.

CCH-132/2016 – Oxirane, mono [(C12-14-alkyloxy) methyl] derivs. (EC No. 271-846-8)

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 two PfAs to ECHA's DD had been submitted. The first PfA requested an additional gene mutation assay: either an *in vivo* mammalian alkaline comet study (OECD TG 489), or a transgenic rodent somatic study (TGR; EU B.58/OECD TG 488). For the former, male germ cells shall be collected at the same time as the other tissues and stored for analysis if positive results are obtained in any of the somatic tissues; for the latter, additional examination of gonadal cells should be considered.

The second and third PfA on extended one-generation reproductive toxicity study (EOGRTS) suggested, firstly, including DNT, because the flash evoked potential (FEP) was affected in both male and female rats, based on an available sub-chronic dermal neurotoxicity study (OECD TG 411) with a constituent (AGE) of the registered substance. The PfA considered this finding to raise a specific concern as signs of functional adverse effects on the nervous system in adult studies, not likely to be secondary to general toxicity. Secondly, the PfAs requested changing the exposure route from oral to dermal. Thirdly, they suggested including additional electro-diagnostic tests.

SECR had modified the DD in advance of the meeting based on the first PfA on gene mutation tests.

The representative of the Registrant had provided written comments prior to the meeting disagreeing with the PfAs. Regarding the first PfA on gene mutation, the representative of the Registrant reiterated that all available studies indicated negative results.

Regarding the other two PfAs on EOGRTS, the representative of the Registrant disagreed with the proposed dermal exposure route, even when it could potentially be the most relevant route of exposure based on the registered uses. According to his view there was no adequate evidence to show significant absorption by the dermal route and the physicochemical properties suggested it would be limited. He also confirmed the disagreement on including DNT, arguing that the flash evoked potential (FEP) was affected in both male and female rats, but for dose response the statistically significant difference did not persist during the study. He further noted that, due to the irritating potential of the registered substance, the decrease in retina activity might be a result of contact with the eye during preening or normal activity, because the dermal area treated with substance was not covered. Therefore, he concluded that both male and female FEPs need to be interpreted with caution due to uncertainty of their significance for human risk assessment. The representative of the Registrant also referred to a scientific article indicating that FEP is a difficult endpoint and could be impacted by other factors, and that matters related to corrosion could cause stress and have an impact on the effects on optical nerves.

SECR confirmed that after the 90-day study with the registered substance the EOGRTS design would be confirmed but stated amongst other also that the FEP responses in the OECD TG 411 study of the registration dossier seemed to be inconsistent as the effects was not similar in male and female rats. A MSC member from a PfA proposing MSCA referred to the same OECD TG 411 study performed with a constituent (AGE) of the registered substance noted that the study was considered reliable by the Registrants with Klimisch score 1, seemed of high quality to him and referred to other literature studies supporting that gender differences of FEP in mice and humans seem to occur so that he did not agree in the expressed statement about inconsistency of results. SECR then raised the concern that in the study there were only statistical effects on the FEP measure but no correlating with observed histopathological examinations, historical FEP control data were not available and questioned also the study's internal validity in other ways. The MSC member from the PfA proposing MSCA did not agree in all of these interventions or felt that limitations of the study was not sufficient to invalidate its reliability and suggested to use different wording in the DD, slightly amended from that in the MoD, to indicate in the decision that it had not been decided whether to include or exclude the extension of DNT and DIT in the EOGRTS design.

Session 2 (closed)

An expert to a MSC member queried what type of arguments would justify deviation from oral route of exposure. SECR informed that, to its knowledge, no EOGRTS had been carried out so far with dermal route. A MSC member doubted if dermal would be at all feasible for this study, although for some other studies it would be possible. SECR noted that in cases with high dermal exposure the route specific toxicity would be considered. MSC concluded that in this case the route of exposure should be oral.

Regarding the inclusion of DNT, an expert to MSC member noted that the standard text ("Currently, ...DNT and DIT... are not requested") implied that currently available information would not lead to triggering, which based on the FEP findings was considered problematic. Some MSC members agreed that more data, in particular results from the 90-day study with the registered substance, could impact decision-making and lead to changes in the final EOGRTS study design. SECR reiterated its view that the standard text was phrased earlier to be as consistent towards the Registrants as possible, and also included in MoD, thus covering the concerns raised.

One MSC member noted that ECHA had rejected a read-across to the constituent AGE proposed by the Registrant for the 90-day study. SECR confirmed this, however, such a seemingly inconsistent read-acrosses can in this case be clearly explained. Data gap filling for avoiding testing requires a robust read-across approach with limited uncertainty, since no further experimental information will be generated, whereas when a concern is triggered and requesting targeted data generation will take place, new experimental data will become available and hence more uncertainty in the read-across is acceptable. SECR also noted that, after receipt of results from the 90-day study, any other relevant information will, if relevant and reliable, be taken into account at the confirmation stage of the EOGRTS study design, i.e. before the EOGRTS testing is initiated.

One MSC member reminded that this substance was listed in the Community rolling action plan (CoRAP) for start of substance evaluation in 2018, which most probably would be delayed if MSC agreement could not be obtained due to disagreement about requests in this compliance check.

MSC concluded that it would request neither DNT nor additional electro-diagnostic tests. It took note of the need to carefully review the results of the forthcoming 90-day repeated dose toxicity study together with a holistic appraisal of any other relevant and reliable information available when confirming the final EOGRTS design.

MSC agreed unanimously to the DD as provided for the meeting. Three members abstained from voting.

CCH-137/2016 1,3-dihydro-4(or 5)-methyl-2H-benzimidazole-2-thione, zinc salt (EC No. 262-872-0)

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's Rules of Procedure.

Two MSC members requested stopping the written procedure to allow clarifications of one of the PfAs. This PFA related to the relevance of extraction methods for non-extractable residues (NERs) due to irreversible binding of the substance to the suspended particulate matter (SPM) in the pelagic water simulation studies, and the introduction in the DD of the same general wording regarding scientific justification that the extraction procedure/solvent chosen is appropriate in respect to the irreversibility of the binding of the substance to the soil and sediment matrix.

SECR had not modified the DD in advance of the written procedure. The Registrant had provided comments on this PFA. SECR amended the DD during the meeting to better reflect the clarifications requested for the extraction methods of NERs and aligned the DD text with another compliance check case discussed during this meeting (CCH-122/2016) for which the same PFA for clarification had been submitted.

MSC supported the amendment of the DD.

MSC agreed unanimously the DD as modified during the meeting.

TPE-096/2016 - 1-Propanaminium, N-(3-aminopropyl)-2-hydroxy-N,N-dimethyl-3-sulfo-, N-(C8-18(even numbered) acyl) derivs., hydroxides, inner salts (List No. 939-455-3) and

TPE-097/2016 - 1-Propanaminium, N-(3-aminopropyl)-2-hydroxy-N,N-dimethyl-3-sulfo-, N-(C12-18(even numbered) acyl) derivs., hydroxides, inner salts (List No. 939-457-4)

Session 1 (open)

No representative of the Registrant participated in the initial discussion. In absence of specific confidentiality concerns in DD, an open session was held.

SECR explained that the two cases TPE-096/2016 (or C8-18 Alkyl Amido Propyl Hydroxy Sultaine - AAPHS) and TPE-097/2016 (or C12-18 Alkyl Amido Propyl Hydroxy Sultaine - AAPHS) were processed simultaneously because of the possible read-across (RA) among them and therefore presented them together in the MSC. Also similarities in constituents, physico-chemical properties, environmental fate, eco-toxicological effects and read-across applied from C8-18 AAPHS (RA source substance) to C12-18 AAPHS (RA target substance) with an expected similarity of mode of action and toxicity were considered. SECR presented the PfAs submitted to ECHA's DD by one MSCA: six PfAs for TPE-096/2016 and nine PfAs for TPE-097/2016.

One general PFA submitted for both cases suggested that based on the information available (including analytical data) the two substances, although registered separately, are essentially the same and a single registration could have covered both. Specifically, both are UVCBs with the chemical components with the same functional groups present and they differ only in respect to overlapping chemical ranges and therefore would have the same ADME (absorption, distribution, metabolism, and excretion), and common breakdown products/mode of action (MoA). It was argued that by not considering the RA as suggested by the Registrant as plausible ECHA asks for duplicate testing. Additionally it was suggested to accept the tests as proposed by the registrant on C8-18 AAPHS (TPE-096/2016) (i.e. tests on 90-day repeat dose toxicity, pre-natal developmental toxicity and fish, early-life stage toxicity test), and to delete the tests additionally introduced by ECHA in both DDs (long-term toxicity testing on invertebrates, short-term toxicity testing on fish, growth inhibition study aquatic plants and short-term toxicity testing on invertebrates). The PFA also requested further substance identity information (SID) on the two compositions, particularly the similarities given by the Registrant.

The Registrant provided written comments prior to the meeting and agreed with the proposals for amendment in regards to the tests and test substance, but questioned what additional SID information they should provide.

SECR amended the DDs for the meeting based on the PfAs as follows: for TPE-096/2016 the read-across section was deleted and the additional tests (long-term toxicity testing on invertebrates, short-term toxicity testing on fish, growth inhibition study aquatic plants and short-term toxicity testing on invertebrates) were removed. For TPE-097/2016 read-across was considered plausible and testing with the source substance C8-C18 AAPHS (TPE-096/2016) for the 3 endpoints proposed by the Registrant (90-day, PNNT, and Long-term toxicity testing on fish) was considered acceptable. In this DD also the additional tests were removed. SECR highlighted that it is critical to carefully identify and characterize the constituents of the test material in the new studies as added as a note for consideration to the Registrant in both DDs.

One MSC member supported the changes in the DD based on the PfAs and shared their view that because of potential differences between the two substances from an (eco)toxicological point of view it is more suitable to test TPE-096/2016 (C8-18 AAPHS) since this covers the whole range of possible alkyl chains and thus could be more toxic than C12-18 AAPHS. Some MSC members emphasised that UVCBs, as natural compounds, vary in composition from one batch to another, suggesting the need for a better justification of the RA in the DD.

Session 2 (closed)

Several MSC members elaborated that based on the constituents of these UVCB substance(s), which all have a similar functional group (Amido Propyl Hydroxy Sultaine) but differ only in alkyl-chain length, the nature of the toxicological effects can be expected to be similar with at most some quantitative (potency) variation. It was clarified that the Registrant had argued that testing the source substance in this context should be considered the worst-case approach, which MSC considered plausible. One MSC member emphasized that in OECD Guidance on UVCBs it is specified that the value of different compounds in two UVCBs have to be more than 10% in order to be considered different. Following that rule for TPE-096/2016 and TPE-097/2016 they could be considered as similar substances.

Both MSC and SECR acknowledged that the variability in composition of different batches of each registered substance could be bigger than differences in composition based on the registered typical concentrations. The text of the DD was further amended during the meeting to clarify some of the uncertainties in the RA, and to take into account the possibility of a need for further testing in case that the information generated shows that the RA is not reliable.

The MSC members supported the amendments of the DD and the clarifications suggested.

MSC agreed unanimously the DD as modified during the meeting.

d. General topics

• Appeals update

See under 6.2.d.

Item 8 – ECHA’s draft recommendation of priority substances to be included in Annex XIV

• Substances for the 8th recommendation: Discussion on the substances suggested for inclusion in the draft recommendation and the respective draft Annex XIV entries prior to public consultation

SECR presented its preparations in advance of the public consultation on ECHA’s 8th draft recommendation for inclusion of substances in Annex XIV. Based on the prioritisation results (which were presented during MSC-51), seven substances were proposed to be included in the draft recommendation and allocation of these substances into three slots of

different latest application dates (LADs) was explained. Those seven substances comprised of NMP (1-methyl-2-pyrrolidone), one phthalate, four phenolic benzotriazoles and the so called Karanal group (a group entry), all of which were among substances with the highest scores in the prioritisation assessment (apart from two benzotriazoles that were included based on grouping considerations). One substance (decaBDE) with a high score was not proposed to be included as the expected restriction will significantly reduce its score. As regards the LAD setting, a same slot was proposed for the group of structurally similar substances, and different slots were proposed to substances/groups of substances expected to cause relatively high workload. Furthermore, substances with expected highest complexity of the supply chain (justifying potentially longer time for industry to prepare Afa) were assigned to comparatively longer LAD slots. SECR was not proposing review periods nor exemptions for uses or for PPORD in the Annex entries.

In the following discussion, several members raised a question of clarification as regards NMP and in particular Commission's plans regarding it and possible other aprotic solvents (DMF, DMAC and NMP). One of the observers from NGOs voiced disappointment for seeing only so few substances to be included in this round. She mentioned that only once before so few substances have been included and that ECHA is not expected to take account of Commission's workload when considering its recommendations. She also noted that in previous rounds substances with lower scores had been included. In responding SECR clarified that the proposal aims to provide some regulatory certainty rather than to take into account Commission's workload. SECR also responded that scores are relative and are used in comparative manner (i.e. there is no cut-off score). Another NGO was pleased to see that finally a number of substances were included because of their PBT and vPvB concern, noting that until now only one PBT and one vPvB was included in Annex XIV. She welcomed the grouping approach for the UV substances because the grouping approach may prevent substitution of one hazardous substance by a substance with similar hazardous properties. She concurred with the view that the list could have been even more ambitious. An observer from industry indicated appreciation to the increased transparency from application of the LAD setting approach. He also pointed out that the parallel consultation of the Commission on SEA has reduced the workload of MSC by taking away comments not belonging to MSC. According to him industry and other stakeholders appreciate this division of commenting.

An observer from the Commission responded on the situation regarding NMP explaining that they wait for the outcome from RAC and SCOEL work on the DNEL/OEL-setting, which has taken some time. However, she confirmed that the NMP restriction would not affect prioritisation as it would not have a significant impact on the volumes of NMP, and therefore there also should not be any contradiction from moving forward with the draft recommendation at this stage. The Dutch alternate member voiced their current preference for Annex XVII inclusion for this substance although a priori they had considered that NMP's prioritisation would not be impacted by the restriction.

The Chairman concluded the discussion by saying that this is now only the first step in the process, and public consultation, with review of comments receive by MSC and its opinion on the draft are still to come, before anything will be submitted from ECHA to the Commission.

Item 9 – Opinion of MSC on ECHA's draft 8th recommendation of priority substances to be included in Annex XIV: Tasks and appointment of Rapporteur and possible working group

a. Task of the (Co-)Rapporteur in drafting the opinion of MSC

b. Appointment of (Co-)Rapporteur

c. Establishment of a MSC Working Group to support the Rapporteur

MSC agreed on the tasks of the rapporteur and the co-rapporteur in drafting the MSC opinion on ECHA's 8th draft recommendation on priority substances for inclusion in Annex XIV. The Committee also appointed two of its members as a rapporteur and a co-rapporteur for this opinion preparation. SECR noted that the timeline for opinion development indicates that the opinion of MSC is expected to be presented for adoption in December this year (MSC-57).

MSC agreed on the mandate of a working group to support the MSC rapporteur in drafting the MSC opinion on ECHA's 8th draft recommendation on priority substances to be included in Annex XIV. Further, MSC appointed six volunteering MSC members as working group members.

Item 10 – Any other business

- **Update on OECD activities**

The MSC observer from OECD made a status update for MSC of the ongoing OECD activities and projects that are of relevance to the MSC work. In the following short discussion, the OECD observer was requested to 'share the MSC regulatory experience' gained in the common areas of interest with the relevant OECD working groups. In this context, another stakeholder observer specifically drew the MSC's attention to the importance of Mutual Acceptance of Data (MAD) and the consequences that non-standard testing requests could have on MAD status inviting MSC to consider this when deciding on deviations of OECD Test Guidelines.

- **MSC Work plan for 2017 and 2018**

SECR introduced MSC with the work plans for 2017 for which six plenary meetings are scheduled, the length of each still tentative, similarly to the Committee's plenary plans so far.

Furthermore, the MSC Chairman presented the initial thoughts regarding the MSC work plan for 2018 for which five plenary meetings are currently considered. The tentative plenary dates and timelines will be presented to MSC at MSC-53.

- **Suggestions from members: Potential establishment of EG on UVCBs**

Following a member's suggestion, MSC also discussed the potential establishment of an expert group or MSC working group on issues related to substances with unknown or variable composition (UVCBs). Several members expressed preliminary interest in participation (either of themselves or their MSCAs' experts) in an *ad hoc* scoping group to develop further the proposal.

Item 11 – Adoption of main conclusions and action points

The conclusions and action points of the meeting were adopted in the meeting (see Annex IV).

II. List of attendees

Members/Alternate members	ECHA staff
ALMEIDA, Inês (PT)	AJAO, Charmaine
ANDRIJEWSKI, Michal (PL)	BELL, David
COSGRAVE, Majella (IE)	BERCARU, Ofelia
DANIHELOVA, Martina (SK)	BROERE, William
DEIM, Szilvia (HU)	BUCHANAN, Steven
DIMCHEVA, Tsvetanka (BG)	CARLON, Claudio
DUNAUSKIENE, Lina (LT)	CESNAITIS, Romanas
FINDENEGG, Helene (DE)	DE BACKER, Liisi
FRANZ, Michel (FR)	DE WOLF, Watze
HERMES, Joe (LU)	DELOFF-BIALEK, Anna
HUMAR-JURIC, Tatjana (SI)	DEYDIER, Laurence
JANTONE, Anta (LV)	DREVE, Simina
KOUTSODIMOU, Aglaia (EL)	FABJAN, Evelin
KREKOVIĆ, Dubravka (HR)	FALCK, Ghita
KULHANKOVA, Pavlína (CZ)	HALLING, Katrin
LONDESBOROUGH, Susan (FI)	HELMINEN, Ulla
LUNDBERGH, Ivar (SE)	HOFFSTADT, Laurence
MC GARRY, Helen (UK)	HUUSKONEN, Hannele
MIHALCEA UDREA, Mariana (RO)	JAAGUS, Triin
PISTOLESE, Pietro (IT)	JOHANSSON, Matti
REIERSON, Linda (NO)	KAPANEN, Anu
STESSEL, Helmut (AT)	KARJALAINEN, Anne-Mari
TYLE, Henrik (DK)	KOJO, Anneli
VANDERSTEEN, Kelly (BE)	KORJUS, Pia
VESKIMÄE, Enda (EE)	KREUZER, Paul
WIJMENGA, Jan (NL)	KUITTINEN, Marko
Representatives of the Commission	LE CURIEUX, Frank
KOBE, Andrej (DG ENV)	MÜLLER, Birgit
Observers	NAUR, Liina
ANNYS, Erwin (Cefic)	REUTER, Ulrike
DE KORT, Patrick (EuPC)	ROSSI, Laura
HÖK, Frida (ChemSec)	RYAN, Paul
KERÄNEN, Hannu (CONCAWE)	ROBERTS, Julian
LEINALA, Eeva (OECD)	RÖCKE, Timo
LEROY, Didier (CEPE)	RÖNTY, Kaisu
LOONEN, Helene (EEB)	STILGENBAUER, Eric
TAYLOR, Katy (ECEAE)	VAHTERISTO, Liisa
VAN VLIET, Lisette (ECEAE)	VASILEVA, Katya
WAETERSCHOOT, Hugo (Eurometaux)	VERSONNEN, Bram
	VOM BROCKE, Jochen

Proxies

- ALMEIDA, Inês (PT) also acting as proxy of MARTÍN, Esther (ES)
- PISTOLESE, Pietro (IT) also acting as proxy of BORG, Ingrid (MT)
- KOUTSODIMOU, Aglaia (EL) also acting as proxy of PALEOMILITOU, Maria (CY)
- COSGRAVE, Majella (IE) also acting as proxy of DEIM, Szilvia (HU) on 7 February
- HUMAR JURIC, Tatjana (SI) also acting as proxy of KOUTSODIMOU, Aglaia (EL) on 9 February from 11 am onwards
- HUMAR JURIC, Tatjana (SI) also acting as proxy of MIHALCEA UDREA, Mariana (RO) on the afternoon of 9 February
- TYLE, Henrik (DK) also acting as proxy of DUNAUSKIENE, Lina (LT) during short periods on 7-9 February

Experts and advisers to MSC members

ATTIAS, Leonello (IT) (expert to PISTOLESE, Pietro)
BARTHELEMY BERNERON, Johanna (FR) (expert to FRANZ, Michel)
BUDASOVA, Jana (EE) (expert to VESKIMÄE, Enda)
COLLINS, Karen (IE) (expert to COSGRAVE, Majella)
COPOIU, Oana (RO) (expert to MIHALCEA UDREA, Mariana)
DE KNECHT, Joop (NL) (expert to WIJMENGA, Jan)
DOBRAK-VAN BERLO, Agnieszka (BE) (expert to VANDERSTEEN, Kelly)
GARCÍA, Patricia (ES), (expert to MARTÍN, Esther)
GRINCEVICIUTE, Otilija (LT) (expert to DUNAUSKIENE, Lina)
HEESCHE-WAGNER, Kerstin (DE) (expert to FINDENEGG, Helene)
HORSKA, Alexandra (SK) (expert to DANIHELOVA, Martina)
KOZMIKOVA, Jana (CZ) (expert to KULHANKOVA, Pavlina)
LITTLE, Joanne (UK) (expert to MCGARRY, Helen)
MALKIEWICZ, Katarzyna (SE) (expert to LUNDBERGH, Ivar)
NYGREEN, Beryl. C. (NO) (expert to REIERSON, Linda)
REILER, Emilie Marie (DK) (expert to TYLE, Henrik)
RISSANEN, Eeva (FI) (adviser to LONDESBOROUGH, Susan)
TARNÓCZAI, Timea (HU) (expert to DEIM, Szilvia)
ZELJEZIC, Davor (HR) (expert to KREKOVIĆ, Dubravka)

MSCA experts for SEV cases

CONWAY, Louise (IE)
ROSENTHAL, Esther (DE)

By WEBEX/phone connection:

During the whole meeting: Esther MARTÍN (ES)
During the agenda item 6: Mandy LOKAJ (DE), Christian UNKELBACH (DE) and Ulrike BERNAUER (DE)
During Wednesday and Thursday: Enrique GARCÍA-JOHN (DG GROW)
During the agenda items 8 and 9: Valentina BERTATO (DG GROW)

Case owners:

Representatives of the Registrants were attending under the agenda item 6b for SEV-DE-008/2015, SEV-IE-023/2015; under the agenda item 7b for CCH-132/2016.

Apologies:

BORG, Ingrid (MT)
COCKSHOTT, Amanda (UK)
MARTÍN, Esther (ES)
PALEOMILITOU, Maria (CY)
RUSNAK, Peter (SK)
WAGENER, Alex (LU)

III. Final Agenda



MSC/A/052/2017

Agenda

52nd meeting of the Member State Committee

7 -9 February 2017
ECHA Conference Centre
Annankatu 18, in Helsinki, Finland

7 February: starts at 9 am
9 February: ends at 5 pm

Item 1 – Welcome and Apologies

Item 2 – Adoption of the Agenda

MSC/A/052/2017
For adoption

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

Item 4 – Administrative issues

For information

Item 5 – Minutes of the MSC-51

- Draft minutes of MSC-51

MSC/M/51/2016
For adoption

Item 6 – Substance evaluation

Item 6.2b on Day 1
Closed session for 6.2c

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

MSC opinion on ECHA's draft update of the Community Rolling Action Plan (CoRAP 2017-2019)

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

ECHA/MSC-52/2017/001
For discussion and adoption

2. Decision making process

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

ECHA/MSC-52/2017/002
For information

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

ECHA/MSC-52/2017/003

For discussion followed by agreement seeking under 6.2c:

MSC code	Substance name	EC No./ Documents
SEV-DE-008/2015	2,2'-dimethyl-4,4'-methylenebis (cyclohexylamine)	229-962-1 ECHA/MSC-52/2017/008-009
SEV-IE-023/2015	3-trimethoxysilylpropyl methacrylate	219-785-8 ECHA/MSC-52/2017/010-011

For discussion

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

Cases as listed above under **6.2b**

For agreement

- d. **General topics**

- Appeals update¹
- SEV status report

For information

Item 7 – Dossier evaluation

**Item 7b on Day 1&2
Closed session for 7c**

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

ECHA/MSC-52/2017/004
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-52/2017/005

For discussion followed by agreement seeking under 7c:

Compliance checks

MSC code	Substance name	EC No./Documents
CCH-121/2016	Reaction mass of dimethyl adipate and dimethyl glutarate and dimethyl succinate	906-170-0 ECHA/MSC-52/2017/012-013
CCH-122/2016	(1-methyl-1,2-ethanediyl)bis[oxymethyl-2,1-ethanediyl] diacrylate	256-032-2

¹ A combination of Appeal updates for Substance and Dossier Evaluation may be introduced, if appropriate.

CCH-129/2016	Dinitrogen tetraoxide	ECHA/MSC-52/2017/014-015 234-126-4 ECHA/MSC-52/2017/020-021
CCH-131/2016	N-butylbenzenesulphonamide	222-823-6 ECHA/MSC-52/2017/018-019
CCH-132/2016	Oxirane, mono[(C12-14-alkyloxy) methyl] derivs.	271-846-8 ECHA/MSC-52/2017/016-017

Testing proposal examinations

MSC code	Substance name	List No./Documents
TPE-096/2016	1-Propanaminium, N-(3-aminopropyl)-2-hydroxy-N,N-dimethyl-3-sulfo-, N-(C8-18 (even numbered) acyl) derivs., hydroxides, inner salts	939-455-3 ECHA/MSC-52/2017/022-023
TPE-097/2016	1-Propanaminium, N-(3-aminopropyl)-2-hydroxy-N,N-dimethyl-3-sulfo-, N-(C12-18 (even numbered) acyl) derivs., hydroxides, inner salts	939-457-4 ECHA/MSC-52/2017/024-025

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 cases returned from written procedure for agreement seeking in the meeting²:

CCH-125/2016	Cyclohexyl methacrylate	202-943-5
CCH-137/2016	1,3-dihydro-4(or 5)-methyl-2H-benzimidazole-2-thione, zinc salt	262-872-0

For agreement

d. Decision making process - General topics

- Appeals update²

For information

Item 8 – ECHA's draft recommendation of priority substances to be included in Annex XIV

Tentative timing: Day 2 pm

- Substances for the 8th recommendation: Discussion on the substances suggested for inclusion in the draft recommendation and the respective draft Annex XIV entries prior to public consultation

ECHA/MSC-52/2017/027-036

For discussion

Item 9 – Opinion of MSC on ECHA's draft 8th recommendation of priority substances to be included in Annex XIV: Tasks and appointment of Rapporteur and possible working group

² Documents are available in CIRCABC in substance specific folders under Dossier evaluation folders.

Invitation for volunteers for the Rapporteurship in drafting the opinion of the MSC on ECHA's 8th draft recommendation for Annex XIV and for Working Group membership

- a. Task of the (Co-)Rapporteur in drafting the opinion of MSC

ECHA/MSC-52/2017/006
For discussion & decision

- b. Appointment of (Co-)Rapporteur

For discussion & decision

- c. Establishment of a MSC Working Group to support the Rapporteur

ECHA/MSC-52/2017/007
For discussion & decision

Item 10 – Any other business

- Update on OECD activities
- MSC Work plan for 2017 and 2018

ECHA/MSC-52/2017/026
For information

- Suggestions from members: Potential establishment of EG on UVCBs

For discussion

Item 11 – Adoption of main conclusions and action points

- Table with conclusions and action points from MSC-52

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 on-going substance evaluation work (presentation slides)
- Status report on on-going dossier evaluation work (presentation slides)
- Brief report of MSC work in 2016 (presentation slides)

IV. Main Conclusions and Action Points



Main conclusions and action points MSC-52, 7-9 February 2017 (adopted at MSC-52)

CONCLUSIONS / DECISIONS / MINORITY OPINIONS	ACTIONS REQUESTED
Item 4 – Administrative issues	
MSC took note of the 2016 Stakeholder survey report and the actions undertaken in this regard.	MSC Chair to organise, in the course of each MSC meeting, briefings for MSC ASO observers on SEV and DEV cases agreed in written procedure.
Item 5 – Minutes of the MSC-51	
MSC adopted the draft minutes as modified at the meeting.	MSC-S to upload final version of the minutes on MSC S-CIRCABC by 10 February 2017 and on ECHA website without undue delay.
Item 6 – Substance evaluation	
6.1. Community Rolling Action Plan (CoRAP) & MSC opinion development	
MSC opinion on ECHA's draft update of the Community Rolling Action Plan (CoRAP 2017-2019) <ul style="list-style-type: none"> • Discussion on the draft MSC opinion • Adoption of the opinion 	
MSC adopted by consensus the draft opinion and its Annex on the draft CoRAP update 2017-2019. MSC mandated MSC-S and the rapporteur to include further editorial changes in the opinion and its Annex as necessary and as already indicated during the presentation.	MSC-S and Rapporteur to review the agreed opinion and include further editorial changes by 16 February 2017. MSC-S to upload the MSC CoRAP Opinion including its Annex on MSC S-CIRCABC by 17 February 2017. SECR to publish the opinion on the ECHA website together with the annual CoRAP update on 21 March 2017.
Item 6.2. - Substance evaluation - Decision making process	
a) Written procedure report on seeking agreement on draft decisions on substance evaluation	
MSC took note of the written procedure report.	MSC-S to upload on MSC S-CIRCABC the final ECHA decisions agreed in written procedure.
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)	
MSC reached unanimous agreement on the following ECHA draft decision as modified in the meeting: SEV-IE-023/2015 3-trimethoxysilylpropyl methacrylate (EC No. 219-785-8)	MSC-S to upload on MSC S-CIRCABC the final ECHA decision of the agreed case.

CONCLUSIONS / DECISIONS / MINORITY OPINIONS	ACTIONS REQUESTED
<p>MSC could not reach unanimous agreement on the following ECHA draft decision:</p> <p>SEV-DE-008/2015 2,2'-dimethyl-4,4'-methylenebis (cyclohexylamine) (EC No. 229-962-1)</p>	<p>MSC-S to refer the decision to the Commission for further decision making, without undue delay once minutes of MSC-52 are agreed.</p>
<p>Item 7 – Dossier evaluation a. Written procedure report on seeking agreement on draft decisions on dossier evaluation</p>	
<p>MSC took note of the report.</p>	<p>MSC-S to upload on MSC S-CIRCABC the final ECHA decisions agreed in written procedure.</p>
<p>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 a testing proposal examination and a compliance check when amendments were proposed by MS-CA's (Session 2, closed)</p>	
<p>MSC reached unanimous agreement on the following ECHA draft decisions (as modified in the meeting):</p> <p>Compliance checks</p> <p>CCH-122/2016 (1-methyl-1,2-ethanediyl)bis[oxy(methyl-2,1-ethanediyl)] diacrylate (EC No. 256-032-2) CCH-125/2016 Cyclohexyl methacrylate (EC No. 202-943-5) CCH-129/2016 Dinitrogen tetraoxide (EC No. 234-126-4) CCH-131/2016 N-butylbenzenesulphonamide (EC No. 222-823-6) CCH-132/2016 Oxirane, mono[(C12-14-alkyloxy)methyl] derivs. (EC No. 271-846-8) CCH-137/2016 1,3-dihydro-4(or 5)-methyl-2H-benzimidazole-2-thione, zinc salt (EC No. 262-872-0)</p> <p>Testing proposal examinations</p> <p>TPE-096/2016 1-Propanaminium, N-(3-aminopropyl)-2-hydroxy-N,N-dimethyl-3-sulfo-, N-(C8-18 (even numbered) acyl) derivs., hydroxides, inner salts (List No. 939-455-3) TPE-097/2016 1-Propanaminium, N-(3-aminopropyl)-2-hydroxy-N,N-dimethyl-3-sulfo-, N-(C12-18 (even numbered) acyl) derivs., hydroxides, inner salts (List No. 939-457-4)</p>	<p>MSC-S to upload on MSC S-CIRCABC the final ECHA decisions of the agreed cases.</p>
<p>MSC could not reach unanimous agreement on the following draft decision, as submitted to the meeting:</p> <p>CCH-121/2016 Reaction mass of dimethyl adipate and dimethyl glutarate and dimethyl succinate (EC No. 906-170-0)</p>	<p>MSC-S to refer the decision to the Commission for further decision making, without undue delay once minutes of MSC-52 are agreed.</p>
<p>Item 9 – Opinion of MSC on ECHA's draft 8th recommendation of priority substances to be included in Annex XIV: Tasks and appointment of Rapporteur and possible working group</p> <p>Invitation for volunteers for the Rapporteurship in drafting the opinion of the MSC on ECHA's 8th draft recommendation for Annex XIV and for Working Group membership</p> <p>d. Task of the (Co-)Rapporteur in drafting the opinion of MSC e. Appointment of (Co-)Rapporteur f. Establishment of a MSC Working Group to support the Rapporteur</p>	
<p>MSC adopted the mandate and the tasks of the rapporteur, and appointed one member as a Rapporteur and another member as a Co-Rapporteur for drafting the MSC opinion on ECHA's 8th draft recommendation for Annex XIV.</p> <p>MSC established a working group to support the Rapporteur and</p>	<p>MSC-S to send the appointment letters to the Rapporteur and the Co-Rapporteur after the meeting.</p>

CONCLUSIONS / DECISIONS / MINORITY OPINIONS	ACTIONS REQUESTED
appointed volunteering members to it.	
Item 10 – Any other business	
<ul style="list-style-type: none"> • Suggestions from members: Potential establishment of an expert group on UVCBs 	
<p>MSC discussed the potential establishment of an expert group on issues related to UVCBs. Several members expressed preliminary interest in participation (either of themselves or their MSCAs' experts) in an <i>ad hoc</i> scoping group.</p>	<p>MSC Chairman to discuss the proposal with the concerned ECHA colleagues.</p> <p>Alternate member from the Netherlands to organise an <i>ad hoc</i> scoping group meeting and report back to MSC at MSC-53 on the potential way forward.</p>
Item 11– Adoption of main conclusions and action points	
<p>MSC adopted the main conclusions and action points of MSC-52 at the meeting.</p>	<p>MSC-S to upload the main conclusions and action points on MSC S-CIRCABC by 10 February 2017.</p>

V. Substance evaluation cases addressed for MSC agreement seeking in written procedure (WP):

Draft decisions unanimously agreed by MSC in WP

MSC code	Substance name used in draft decision	EC number
SEV-DE-005/2015	o-xylene	202-422-2
SEV-DE-006/2015	p-xylene	203-396-5
SEV-DE-007/2015	m-xylene	203-576-3
SEV-UK-031/2015	octamethyltrisiloxane	203-497-4
SEV-UK-032/2015	decamethyltetrasiloxane	205-491-7
SEV-UK-033/2015	dodecamethylpentasiloxane	205-492-2

VI. Justification for the disagreement on SEV-DE-008/2015 (2,2-dimethyl-4,4'-methylenebis(cyclohexylamine))

Eight MSC members (BE, CY, EE, EL, FR, IE, IT, MT), supported by the Norwegian member, voted against SEV-DE-008/2015 as presented and discussed during MSC-52.

In the decision (last paragraphs under 'the concerns identified', it is stated that:
'Furthermore, ECHA is of the opinion that studies to fill standard information gaps can be requested within the SEV procedure to speed up filling the obvious information needs according to the REACH Annexes and to take their results into account within the SEV procedure.

As it is no standard information requirement for registrants of lower production ranges, the information request will only be addressed to the registrants which have to fulfil the requirements pursuant to REACH Annex X due to production range.'

While we agree that studies to fill standard information gaps could be requested under substance evaluation, we are of the opinion that the SEV decision should be addressed to the Registrant(s) that had an active registration on the date on which the draft decision is first sent for comments to the Registrant(s) and who did not cease manufacture upon receipt of the draft decision pursuant to article 50(3) of REACH. Notwithstanding this, we acknowledge that pursuant to article 49 of REACH, Registrant(s) who have registered the substance exclusively as an on-site intermediate under strictly controlled conditions are not addressees of the decision.

For all substance evaluation cases to date, the decisions requesting further testing have been addressed to all registrants (noting the exception outlined above) irrespective of whether their particular use(s) impose a risk concerned basis and irrespective of whether the required test should already have been provided by one or more of the addressees to fulfill registration obligations. We are concerned that this particular decision may change the applied procedure under substance evaluation for future cases. We are of the opinion that it may further complicate the process, as well as perhaps leading to inconsistencies as to how substance evaluation is carried out across different Member States. In addition, it may involve the evaluating Member State needing to give consideration to, and take into account, data and cost sharing issues amongst registrants, something that has not been anticipated.

We are of the opinion that this is a policy issue that requires further consideration. The REACH Committee is hence the most appropriate platform to discuss, clarify and decide on this interplay between the substance evaluation process and the compliance check process.

VII. Dossier evaluation cases addressed for MSC agreement seeking in WP

MSC unanimously agreed on dossier evaluation draft decisions in the written procedure:

Compliance checks (CCH)

MSC ID number	Substance name used in draft decision	EC or List number
CCH-123/2016	N-1,3-dimethylbutyl-N'-phenyl-P-phenylenediamine	212-344-0
CCH-126/2016	Ionone, methyl-	215-635-0
CCH-130/2016	2,4,6-trichloro-1,3,5-triazine	203-614-9
CCH-136/2016	1,1,1,3,5,5,5-heptamethyl-3-[(trimethylsilyl)oxy]trisiloxane	241-867-7
CCH-149/2016	Rape oil, oxidized	305-871-3
CCH-152/2016	Tetraphenyl m-phenylene bis(phosphate)	260-830-6

Testing proposal examinations (TPE)

MSC ID number	Substance name used in draft decision	EC or List number
TPE-064/2016	1,10-decanediyl diacrylate	235-922-4
TPE-087/2016	1,3-dihydro-4(or 5)-methyl-2H-benzimidazole-2-thione	258-904-8
TPE-089/2016	2,2'-ethylenedioxydiethyl bis(2-ethylhexanoate)	202-319-2
TPE-091/2016	Ethanol, 2,2'-iminobis-, N-C12-18-alkyl derivs.	276-014-8
TPE-093/2016	2,2-dimethylpropane-1,3-diyl cyclohex-4-ene-1,2-dicarboxylate	255-180-5
TPE-098/2016	Barium titanium trioxide	234-975-0
TPE-100/2016	N,N''-propane-1,3-diylbis[N'-octadecylurea]	252-667-4
TPE-103/2016	Methylene-bis-4,1-(N-phenylene-N'-butylurea)	416-600-4

Annex VIII Statements as regards agenda item 7

Justification for voting against ECHA draft decision on CCH-121/2016 for Reaction mass of dimethyl adipate and dimethyl glutarate and dimethyl succinate, EC nr. 906-170-0.

from MSC members from Austria, Denmark, France, Lithuania, Netherlands, Norway and Sweden

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 dimethyl adipate and dimethyl glutarate and dimethyl succinate, EC nr. 906-170-0 (CCH-121/2016), for the reasons set out below.

Reaction mass of dimethyl adipate and dimethyl glutarate and dimethyl succinate is an UVCB registered under REACH in the tonnage band more than 1000 tonnes per year. In ECHA's compliance check draft decision, a prenatal developmental toxicity study (Annex X, Section 8.7.2; test method: EU B.31/OECD TG414) and an extended one-generation reproductive toxicity study (EOGRTS, Annex X, Section 8.7.3; test method: OECD TG 443) in rats, oral route are proposed to be requested. In the EOGRTS, the basic configuration and extension of cohort 1A to produce the F2 generation are proposed to be requested.

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

Justification for particular concern for DNT and DIT:

Substance specific information:

Data show that a main constituent of the registered substance disrupts the sex hormone balance (main evidence on androgen balance: decreased luteinizing hormone (LH) and testosterone levels in male rats). In general, it is known that during the perinatal stage LH is released in the pituitary and stimulate testicular androgen production. For this substance, the reported decrease in LH could cause the reported decrease in testosterone levels, in adult animals. The sex hormone balance, including that of androgens such as testosterone, is especially important for the sexual differentiation of the perinatal brain development. The decrease in testosterone levels constitutes an anti-androgenic effect with a known link to developmental neurotoxicity and developmental immunotoxicity (see section below).

Specifically, data from a report available in the registration dossier show that a main constituent of the UVCB substance, dimethyl glutarate (DMG) significantly decreased serum testosterone levels (50-59% of the controls) and luteinizing hormone (LH) levels (up to 71% of the controls) in male rats after inhalation exposure (OECD TG 413, ECHA registration dossier). A prolonged decrease in testosterone levels could be expected to lead to a decrease in androgen dependent organ weights and a decrease in sperm counts. Such effects were not shown in the report. The increase in relative, but not absolute, epididymides weight observed in the mid dose group was considered by the authors to be spurious or related to slight not significant decreases in mean body weights in the respective groups. To us this seems to be plausible. A significant increase in epididymal sperm counts was observed in the mid and high dose groups. A possible explanation could be that the decrease of testosterone happened gradually and the study was terminated before the relevant organ weights and sperm parameters were influenced by this decrease. In addition, the validation studies of OECD 407 and OECD 408 tests indicated that weights of androgen dependent organs in adult animals are normally insensitive to effects of endocrine disruptors. Most importantly, the lack of adverse effects on androgen dependent organ weights and a decrease in sperm counts do not remove the concern that

the observed changes in testosterone and LH levels may cause developmental neurotoxicity and developmental immunotoxicity.

Another main constituent of the UVCB substance, dimethyl succinate (DMS), significantly decreased estradiol levels (to 43% of the controls) in female rats (OECD TG 413, ECHA, registration dossier). This decrease in estradiol levels could theoretically be initiated by a decrease in LH, but LH was not measured in these female animals. The authors indicated that interpretation of the data was confounded by possible differences in estrous cycle and therefore this finding was considered uncertain.

In our view, sufficient information on (key events for) specific sex hormonal mode(s) of action(s) has been provided, i.e., altered sex hormone levels (especially for testosterone and LH levels in young adult male laboratory rats). Also, the associations of these modes of action with developmental neurotoxicity (sexual differentiation of the brain) and immunotoxicity (effects on the development of the normal functioning of the immune system) have been established (see brief description below). Therefore, the triggers to include the DNT and DIT cohorts are met, according to the REACH standard information requirements (column 2 of Annex X) and the corresponding ECHA guidance (see below). We consider the request for DNT and DIT proportional to the concern and respecting animal welfare considerations. It is in this regard noted that inclusion of the investigations of the DNT and DIT cohorts do not increase the number of animals included in the requested EOGRTS.

Association between the sex steroid hormones and developmental neurotoxicity and immunotoxicity:

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. The masculinisation of the default female(-like) brain during fetal and neonatal development is triggered by testosterone and estradiol, both normally occurring in higher concentrations in male than in female fetuses, due to testicular steroidogenesis. Initial testicular hormone production is not dependent on pituitary gonadotropins, but it is established that at the late gestational stage, testosterone synthesis is LH dependent. For instance it has been shown that knock-out of pituitary gonadotropins affects steroidogenesis drastically at the late gestational stage (androgen level 5-10% of controls). The brain is delicately sensitive to androgens and estrogens during late gestation and early postnatal development. For instance, male rats castrated during the critical period are unable to display typical male sexual behaviours in adulthood, but will show female like behaviour. The female rats treated with testosterone during this period permanently lose the capacity to secrete LH and do not show typical female reproductive behaviours, but can exhibit masculine sexual behaviours. Similarly, gender identity and/or behaviour characteristic to the opposite gender were reported from clinical observations of humans with genetic factors affecting either fetal testosterone level or androgen receptor signalling. Importantly, a number of studies support the view that exposure to substances interfering with these hormonal systems via different mechanisms 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 also well established that the gonadal steroid hormones as androgens and estrogens modulate the immune system (Cutolo et al. 2002; Arredouani et al. 2014; Trigunaitte et al. 2015, Adori et al., 2010). Androgens have been shown to affect both the innate and the adaptive immune system, both at the developmental and the functional levels. Androgens target many parts of the immune system, and are generally immunosuppressive; they dampen the immune response (Trigunaitte et al., 2015, Cutolo et al., 2002). Estrogens are reported to exert immunoenhancing activities (Cutolo et al., 2002).

It is therefore reasonable to expect that substances interfering with the sex steroid hormone system via any MoAs impacting the levels of androgens (e.g. testosterone) or

estrogens (e.g. estradiol) in males or females could adversely affect the development of the nervous and/or immune system under fetal and neonatal development. In addition to the examples of mechanisms listed in the ECHA guidance, other data on events showing interference with these sex hormonal systems, (such as those observed with DMG) should be regarded as equally relevant.

We are of the view that clarification of the specific mechanisms causing hormone level changes is not necessary before requesting DNT and/or DIT, as the hormone level changes substantiate the anti-androgenic mode of action and thus the concern.

Furthermore, data indicating more than one MoA related to sex hormone shall not be regarded as "contradictory" or "inconsistent". For example it has been shown that substances showing agonistic (or antagonistic) properties with one type of receptor often are antagonist (or agonist) of another type of receptor, or can be both agonist and antagonist on the same type of receptor.

REACH standard information requirements:

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

"An Extended One-Generation Reproductive Toxicity Study including cohorts 2A/2B (developmental neurotoxicity) and/or Cohort 3 (developmental immunotoxicity) (...) may be required by the Agency in accordance with Article 40 or 41, in case of particular concerns on (developmental) neurotoxicity or (developmental) immunotoxicity justified by (...) specific mechanisms/modes of action of the substance with an association to (developmental) neurotoxicity and/or (developmental) immunotoxicity (...).

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 and/or with the immune system are valid triggers for DNT and/or DIT, respectively. 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)" and for DIT: "...such as oestrogenicity (Adori et al., 2010) and androgenicity (Trigunaite et al., 2015)".

Animal welfare considerations:

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

References:

Adori et al., 2010, Estrogen augments the T cell-dependent but not the T-independent immune response. *Cell Mol Life Sci* 67:1661-74.

Arredouani et al., 2014, New insights into androgenic immune regulation, *Oncoimmunology*. 2014 Dec 13;3(9)

Cutolo et al., 2002, Androgens and estrogens modulate the immune and inflammatory responses in rheumatoid arthritis, *Ann N Y Acad Sci*. 2002 Jun;966:131-42.

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 perturbations 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.

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

Trigunaite et al., 2015, Suppressive effects of androgens on the immune system, *Cell Immunol.* 2015 Apr;294(2):87-94.