MSC/M/56/2017
Adopted at MSC-57

Minutes
of the 56th Meeting of the Member State Committee (MSC-56)
24-26 October 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 56th meeting of the Member State Committee (MSC) (for the full list of attendees and further details see Part II of the minutes).

Item 2 - Adoption of the Agenda

The Agenda was adopted as provided for the meeting by the MSC Secretariat (MSC-S) without further changes (final Agenda is attached to these minutes as Section III).

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

The German member indicated she will not participate in the case-discussion for the substance CCH-092/2017 and the vote will be cast by the alternate member. No potential conflicts of interest were declared by any members, experts or advisers with any item on the agenda of MSC-56.

Item 4 - Administrative issues

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

- **Update on ECHA premises**

The Chairman informed MSC that this agenda item is postponed to the next plenary meeting due to time constraints.

- **Outlook for MSC-57**

The Chairman informed MSC that the next meeting in December is expected to require approximately five plenary days.

Item 5 – Minutes of the MSC-55 meeting

The minutes of MSC-55 were adopted as provided for the meeting.

Item 6.1 – Community Rolling Action Plan (CoRAP) draft update for 2018-2020 & MSC opinion development

SECR presented the draft CoRAP update for 2018-2020. As per previous years, each substance has an accompanying justification document. The draft CoRAP including the initial grounds for concern and contact details of the evaluating Member State Competent Authorities (eMSCA) was published on the ECHA's website during the MSC meeting week i.e. on 26 October. Substances on the CoRAP list were identified through the ECHA's common screening activities ACROSS, which starts with IT pre-selection followed by manual screening performed by Member State Competent Authorities (MSCAs). The draft CoRAP update for years 2018-2020 has a total of 107 substance, 16 new and 91 already included in the 2017-2019 CoRAP update – 26 substances for 2018, 37 substances for 2019 and 44 substances for 2020.

One Stakeholder observer (StO) expressed concern for the low number of new substances in this CoRAP update, which, she suggested, is linked to the need of having a compliance check (CCH) performed on the lead dossier per substance before the substance is evaluated. SECR explained that these CCHs are showing that basic data is missing, and it is the generation of basic data that is making the process seem lengthy when viewing it from the outside. It was also explained that there may be instances where the concern could already be clarified through these CCHs. In such cases substance evaluation (SEV) would no longer be needed.

Another StO wondered if the introduction of a mixture in the new substances was done on purpose. SECR explained that this was registered and disseminated as a substance, so it

was included on the CoRAP as such. Further details on the substance identity of this entry will be known once the substance identification CCH is started for all the new entries in the CoRAP update 2018 – 2020.

The Rapporteur and working group have started reviewing the draft CoRAP update aiming to submit a first draft opinion to MSC for MSC-57 meeting in December.

Item 6.2 – Substance evaluation - Decision making process

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

No SEV cases were submitted for written procedure agreement seeking in this MSC-56 round**.**

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

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

SEV-FR-020/2015 Aluminium chloride basic (EC No. 215-477-2)

SEV-FR-021/2015 Aluminium chloride (EC No. 231-208-1)

SEV-FR-022/2015 Aluminium sulphate (EC No. 233-135-0)

Session 1 (open)

Six representatives of the Registrants participated in the initial discussion. In advance of the meeting, MSC-S had made an effort to discuss with the registrants the possibility to hold one presentation for MSC on a combination of the three cases. This was accepted making the meeting discussion on this group of substances more efficient in this regard. In absence of specific confidentiality concerns in draft decisions (DDs), an open session was held.

The eMSCA from France (FR-CA) presented the SEv outcome of the above-mentioned substances performed on the basis of the initial grounds for concern relating to Human health/Suspected C, M and R; High (aggregated) tonnage. The eMSCA evaluated these three substances as a group, and considered that further information was required to clarify the concern for mutagenicity for all.

The read-across between the three soluble salts under evaluation was considered relevant and acceptable for the endpoint genotoxicity. The eMSCA supported the read-across by bioavailability data, toxicological data and analysis of physico-chemical properties. Therefore, the approach taken by the eMSCA was that mutagenicity testing with the test material of aluminium sulphate with the highest impurity profile (less pure grade) of the standard for water treatment should allow to clarify the mutagenicity concern for all three soluble salts under SEv: aluminium sulphate, aluminium chloride and aluminium chloride basic.

The DDs for all the three soluble salts consulted with the MSCAs and ECHA contained more than one request, including among others a request for mutagenicity testing to be performed with the aluminium sulphate as a test material. The DD for aluminium chloride requested also further information on a sub-chronic toxicity study (90-day) by inhalation in rat. Proposals for amendments (PfAs) were received on the aforementioned requests.

The genotoxicity test requested was a combined *in vivo* mammalian erythrocyte micronucleus test (MN) in bone marrow (EU TM B.12./OECD TG 474) and modified *in vivo* mammalian comet assay on the following tissues: liver, kidney, glandular stomach and duodenum (OECD TG 489) in rats, oral route, including a full study report, using the analogue/registered substance aluminium sulphate. The *in vivo* MN with FISH technique was requested to investigate clastogenic or aneugenic potential of the substance, whilst the *in vivo* mammalian comet assay including additional set of slides with specific enzymes was requested to assess damage to DNA and potential oxidative genotoxic mode of action (MoA).

MSC was guided by the experts from the eMSCA through the information on the substances (including PfAs, the Registrants' comments and the eMSCA's responses to them). The same four PfAs on the genotoxicity endpoint from two MSCAs were submitted for all three DDs. The DDs on aluminium chloride and aluminium chloride basic received an additional PfA on that same endpoint, whereas the DD on aluminium chloride also received a sixth PfA on the 90-day sub-chronic toxicity study.

One PfA proposed to remove the requested genotoxicity study given the clearly negative findings in the standard *in vitro* studies. Limited positive evidence for a clastogenic effect comes from non-standard studies (*in vitro* and *in vivo* using analogue substances) which have a number of deficiencies when compared to modern Test Guidelines. In the event that the genotoxicity study was still requested, an alternative proposal was submitted in a second PfA to combine the mutagenicity testing with the 90-day study by inhalation using aluminium chloride as the test substance.

A third PfA supported the need for further testing on genotoxicity and proposed a change of text under the title 'alternative approaches and proportionality of the request'. Fourthly, it was proposed to consider obtaining information on cross-linking of DNA with chromosomal proteins elicited by aluminium salts e.g. by requesting the comet assay to be modified for such investigation through requesting preparation and analysis of an additional set of slides.

The additional PfA submitted for aluminium chloride and aluminium chloride basic proposed to reflect the results of Cunat et al. (2000)[1] which show no significant bioavailability difference between aluminium sulphate and aluminium chloride. However due to the corrosivity of aluminium chloride the PfA preferred to perform the test on aluminium sulphate.

The sixth PfA submitted for only aluminium chloride on the 90-day sub-chronic toxicity study is the same as the second PfA mentioned above submitted on the genotoxicity study to combine the mutagenicity testing with the 90-day study by inhalation requested for the aluminium chloride, so as to test only on one substance.

The eMSCA accepted to include the proposed text submitted in the third PfA and to reflect the results on Cunat et al. (2000) in the amended DD.

Present at the meeting were the representatives of the Registrants for aluminium sulphate and aluminium chloride basic (the same representatives for both compounds), and aluminium chloride. There were also representatives on behalf of the registrant that opted out from the genotoxicity endpoint for aluminium sulphate since they disagreed with the information provided by the lead on this endpoint. In their opt-out they claimed to have provided more studies than those found in the lead registration dossier.

The Registrants' representatives received before the meeting a copy of the power point presentation prepared by the eMSCA reflecting the updated testing strategy following receipt of the PfAs and the Registrants comments on the PfAs. The updated testing strategy requested for a 90-day toxicity study by inhalation on aluminium chloride and a combined *in vivo* mammalian erythrocyte micronucleus and Pig-a test with modified *in vivo* mammalian comet assay on the following tissues: liver, kidney, glandular stomach and duodenum, oral, rats on aluminium sulphate.

The Registrants' representatives reiterated their disagreement with the genotoxicity concern expressed by the eMSCA. Their interventions at the meeting focused on highlighting that the studies used by the eMSCA in their weight of evidence approach in their view were not relevant, unreliable or inadequate.

The representatives of the Registrants all agreed with the read across approach with insoluble Aluminium hydroxide as presented in their dossiers and comments to the draft

[1] Cunat L, Lanhers, MC, joyeux M, Burnel D. 2000. Bioavailability and Intestinal Absorption of Aluminium in Rats. Effects of aluminium compounds and some dietary constituents. Biological Trace Elements Research. Vol. 76, pp 31-55.

decision. On a separate issue the representatives of the Registrants of aluminium chloride argued that aluminium sulphate is a different substance, with variable purity and not produced directly from the elements. It is registered by different legal entities in a different joint submission, hence they considered that they cannot be asked to test on a substance that is not registered by them.

The representatives of the opt-out Registrants expressed their concern that the assessment they provided over and above the studies found in the lead dossier seemed not to have been evaluated by the eMSCA, and requested the eMSCA to perform such an assessment. They argued this should lead to a conclusion that they should not be addressees in the DD requesting for the further studies.

The Registrants' representatives were unified in the rest of their interventions. They expressed disagreement with the requested combined *in vivo* studies, and also performing the Pig-a assay since there is no OECD guideline yet and the point mutation concern triggering this request was not clear to them, specifically since this was a new element for them seen first on the power point presentation prepared by the eMSCA for the meeting. They reiterated their view that the oxidative mode of action being proposed is based on a wrong theory and unreliable studies. Furthermore, at the meeting they referred for the first time to an unpublished study, which MSC could therefore not consider.

Regarding the Cunat et al. (2000) study they expressed surprise that it is still part of the database since, in their view, it shows that the soluble aluminium salts are not bioavailable because the plasma levels were below those of the control. If therefore there is no absorption there is no mode of action of concern. Hence, the view of Registrants' representative on DNA damage through oxidative stress was that this is a theoretical construct that cannot happen at physiological pH. In this regard, the Registrants' representatives also explained to MSC the dynamic nature of Aluminium. Aluminium mainly occurs as Al^{3+} (aq) under acidic conditions only and as $Al(OH)_4^-$ (aq) at physiological pH which supported the read across used, as poorly soluble aluminium hydroxide complexes will be formed during ingestion..

The Registrants in their comments to the PfAs had introduced a reliable an *in vivo* micronucleus assay (GLP, OECD 474) performed on another read-across substance (1999) which showed negative results, and which they considered is a further support for not having a mutagenicity concern. The eMSCA accepted that the substance may be a potential source substance but could not make a final conclusion as no specific toxicokinetics were available with the read-across substance. Moreover, eMSCA identified some uncertainties with the study itself, with 'no proof of exposure to bone marrow'.In the view of the Registrants clinical signs were observed indicating that systemic exposure was achieved. In a further review of the aluminium-ion toxicity literature to address information on the new source substance, the eMSCA had identified a positive *in vivo* MN assay performed by Paz et al. (2017)[2] on aluminium chloride which, despite some shortcomings associated with its performance, further substantiated the residual mutagenicity concern stemming from the overall database. In contrast, the representatives of the Registrants regarded the study by Paz et al. (2017) as unreliable due to lack of reporting of positive controls, lack of information on the purity of the test substance, absence of increase in micronuclei observed with increasing concentration of the test substance (no dose-response relationship), the observation of histopathological effects that are not associated with exposure to aluminium in other higher dose/longer exposure studies, and high number of micronuclei which were equal to, or greater than, commonly used positive controls such as cyclophosphamide. An MSC member commented on this point that a plateau effect might be explained by the toxicokinetics of aluminium salts.

Overall the Registrants' representatives questioned, supported by one MSC member, why the studies considered by them as unreliable positives were given higher weighting in the

[2] Paz LNF, Moura LM, Feio DCA, Cardoso MSG, Ximenes WLO, Montenegro RC, Alves APN, Burbano RR, Lima PDL. Evaluation of *in vivo* and *in vitro* toxicological and genotoxic potential of aluminium chloride. Chemosphere 175 (2017) 130-137

weight of evidence (WoE) made by the eMSCA than the negative Klimish 1, GLP studies performed according to OECD guidelines, and which meet the REACH annexes requirements for this endpoint.

The expert from the eMSCA reassured the representatives of the opt-out registrant that all the studies that were submitted in their opt-out dossier had been evaluated by the eMSCA. Responding to the challenge regarding the request for Pig-a assay the eMSCA expert explained that Pig-a assay is a complementary test investigating gene mutation The comet assay is an indicator test measuring DNA damage in various tissues relevant for toxicological evaluation and on the other hand the micronucleus measures clastogenicity/ aneugenicity and the pig-a assay measures gene mutation. Moreover, oxidative DNA damages need to be investigated in an additional set of slides in the comet assay as oxidative damage has been observed in numerous *in vivo/ in vitro* studies in several species. The eMSCA expert further explained that the data set used in the WoE, including the studies referred to by the Registrants' representatives, currently does not allow a definitive conclusion on the genotoxicity concern, and that residual uncertainties are addressed by the request for further testing. Responding to the registrant's representative comment that oxidative damage is a theoretical construct, eMSCA clarified that this hypothesis is based on numerous *in vitro* and *in vivo* studies in several species and tissues and is thus not theoretical. With regards to absorption, eMSCA agreed that bioavailability of aluminium compounds by the oral route of exposure is low. Nevertheless, soluble compounds have a higher bioavailability than insoluble compounds. Moreover, the Cunat et al. (2000) study was included in the draft decision because together with other available data, the study supports that aluminium sulphate and aluminium chloride have similar bioavailability.

Regarding the PfA on combining the genotoxicity studies with the 90-day sub-chronic toxicity study with aluminium chloride, one MSC member asked whether it is expected that the inhalation route can ensure a much higher exposure than the oral route considering that bioavailability by inhalation can be ten times higher than by oral route. Registrants' representatives explained that this however depends on the maximum dose that can be administered to the animals based on the dose range finding study, since the animals may only tolerate relatively low doses since aluminium chloride is corrosive. Due to these uncertainties and technical difficulties to combine the studies, the expert from the eMSCA stressed their preference to conduct the genotoxicity studies separately from the 90-day sub-chronic toxicity study.

Session 2 (closed)

Discussions on understanding the bioavailability of Aluminium and how best to weigh the negative results compared to the positive results continued in closed session. Several MSC members expressed similar views as the eMSCA that a residual concern on genotoxicity remains when looking at the overall dataset. In the context of these discussions, an MSC member flagged the need for a more general discussion at a later stage on how to deal with negative results from studies carried out according to previous versions of revised OECD test guidelines, where it was not yet a requirement to show that the substance has reached the bone marrow or other tissues.

Regarding the proposed testing strategy it was already clear from the discussion in the open session that combining the *in vivo* MN and *in vivo* comet assay with specific investigation for DNA damage with the 90-day sub-chronic toxicity study as proposed in one of the PfAs, was not favoured. Hence the discussion focused on the request in the amended draft decision presented by the eMSCA at the open session: 'a combined *in vivo* mammalian erythrocyte MN in bone marrow (EU TM B.12./OECD TG 474) with Pig-a test and modified *in vivo* mammalian comet assay on the following tissues: liver, kidney, glandular stomach and duodenum (OECD TG 489) in rats, oral route, including a full study report, using the analogue/registered substance aluminium sulphate.'

Regarding the Pig-a assay, the eMSCA required this test in the amended DD following a reassessment of the whole database responding to the written comments to the PfAs from the Registrants including the additional study on a different source substance provided at this stage of the process. Its technical feasibility, low cost, fast processing with only few

micro litres blood sample needed, made it an attractive option for the eMSCA to include the assay in the test design. However, during the MSC discussions, MSC identified some drawbacks for such inclusion. They agreed with the Registrants' representatives' argument that there is no OECD guideline in place, and from a procedural point of view considered that introducing a Pig-a assay at this stage as a formal requirement, without a clear link to a PfA requiring such inclusion, impacted the rights of the Registrants to be heard. Hence, MSC unanimously agreed not to include a requirement for a Pig-a assay, but include only a note for consideration for the Registrants to consider integration of a Pig-a assay in the currently requested study.

Regarding the modified comet assay design and its additional set of slides to investigate oxidative MoA, eMSCA expert explained that the oxidative stress MoA is the most plausible MoAbased on the available evidence and is not a theoretical hypothesis. Investigating additional oxidative DNA damages would reduce the possibility of "false" negative. Indeed, a chemical can induce specifically oxidative DNA damage that would be recognized in the comet assay using specific enzymes but not in the standard comet assay. This modification requires additional slides in the standard alkaline comet assay (OECD TG 489) which are treated with enzyme (hOGG1 or Fpg) between the lysis and alkaline treatment. MSC recognized the technical drawback that the OECD test guideline does not specify how to perform this modification, however protocols for such modification are clearly specified in different publications, hence these were included in the decision together with further technical specification to help the Registrants, as unanimously agreed by MSC.

Regarding the concern raised by the Registrants for aluminium chloride who raised the argument of variable purity and relevance of the test carried out with aluminium sulphate for the aluminium chloride, MSC specifically considered the purity of the test substance – aluminium sulphate when performing the genotoxicity tests – to be the one with the highest level of aluminium ion. For all the three decisions, MSC unanimously agreed, following the proposal of ECHA, to change the purity of the test substance from type 3 to type 1 to ensure that the test material remains representative material for all three salts. Type 1 of EN878:2004 corresponds to the highest pure grade of technical aluminium sulphate.

With regards to the route of exposure (oral vs inhalation in combination with the 90-day sub-chronic toxicity study), the oral route was considered to be the most appropriate for the mutagenicity assays. It was the most commonly used route of administration for genotoxicity tests, and a combination of a 90-day sub-chronic toxicity study with both mutagenicity assays would make it a more complex design which increases the risk of complications negatively impacting the reliability of the mutagenicity results. Furthermore, the oral route was the most realistic route with regard to consumer exposure. Hence, for all the three decisions, MSC unanimously agreed not to combine the mutagenicity assays with the 90-day sub-chronic toxicity study, and to keep the oral route as the route of exposure for the assays. With regards the route of exposure for the 90-day sub-chronic toxicity study the inhalation route was maintained, to allow the investigation of site of contact toxicity upon longer-term worker exposure to aluminium chloride.

Regarding the comment from the opt-out Registrant not to be addressees in the DD, MSC unanimously agreed to keep unchanged the addressees of the SEV decision for aluminum sulphate since all the additional studies submitted by the opt-out Registrant had been evaluated by the eMSCA.

The MSC unanimously agreed on the three draft decisions as amended in the meeting. The member from UK abstained from voting. Furthermore, MSC gave an editorial mandate to the eMSCA to finalise the three decisions by not later than 10 November 2017.

SEV-DE-008/2015 Benzotriazole (EC No. 202-394-1)

Session 1 (open)

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

The eMSCA from Germany (DE-CA) presented the SEv outcome of the above-mentioned substance performed on the basis of the initial grounds for concern relating to potential endocrine disruption (Environment) and exposure of the environment. The eMSCA considered that further information was required to clarify these concerns.

DD consulted with the MSCAs and ECHA had requests for an *in vivo* testing: Fish sexual development test (FSDT, OECD TG 234) with measurement of substance and its metabolites 5-hydroxy-1H-benzotriazole (5-OH-BTA) and 4-hydroxy-1H-benzotriazole (4-OH-BTA) and for *in vitro* testing (using the substance and 5-OH-BTA with/without metabolic activation (S9 Mix)): Steroidogenesis assay (OECD TG 456) and E-Screen Assay.

MSC was guided by the expert from the eMSCA through the information on the substance, including 11 PfAs received from three MSCAs, the Registrants' comments on the PfAs and the eMSCAs responses to them.

With regard to the requested *in vivo* FSDT, PfAs proposed: to include histopathological examination of both liver and kidney, as well as gonad histopathology (OECD GD 123) in order to obtain as much information as possible from the study about possible endocrine effects; to better justify the request; not to specify zebrafish as a preferred species, (but depending on the test guideline, an equal choice to be given to zebrafish, medaka or fathead minnow); to test one higher concentration (e.g. 1 mg/l), as the specified test concentration may not induce any apical adverse effects. A PfA suggested instead of FSDT either to request for a combined FSDT with a fish short-term reproduction assay (OECD TG 229) or to perform an extended one-generation reproduction test (EOGRT, OECD TG 240).With respect to the measurements of test substances and metabolites, one PfA further stated that biodegradation products with estrogenic potential might be generated in fish or surface waters and that transformation products formed via biodegradation are not addressed.

As regards the requested *in vitro* steroidogenesis assay (OECD TG 456), a PfA was made to either better explain the need for *in vitro* testing and to consider adding testing of the other metabolite (e.g. 4-OH-BTA) and of the biodegradation product (di-hydroxy-1H-benzotriazole), or to consider at this stage to drop requesting the OECD TG 456. Another PfA proposed a tiered approach where the *in vitro* tests should be performed after the *in vivo* test and only when ED effects are observed. In addition, it noted that the test should be carried out first with the parent substance and the metabolite 5-OH-BTA, (since a test with S9 mix may not be needed if the results would indicate steroidogenesis activity).

With regard to the requested *in vitro* E-screen test, a PfA suggested to replace this test with the internationally accepted OECD TG 455 and to consider adding testing of the other metabolite (e.g. 4-OH-BTA) and of the biodegradation product (di-hydroxy-1H-benzotriazole) (QSAR were provided in supplemental material). The PfA also proposed that it would be appropriate to first request a test for the identification of biodegradation products in surface water and/or sediment. An alternative approach suggested in the PfA was to ask the registrant to perform a suitable *in vitro* test with fish estrogen receptor activation, if available, instead of the OECD TG 455 request with human estrogen receptors. Another PfA suggested also replacing the E-screen with OECD TG 455 testing for the parent substance and the metabolite 5-OH-BTA, and only to, perform *in vitro* testing when the results of the *in vivo* fish test would indicate potential estrogenic activity. (Noting the ongoing validation work for OECD TG 455 with S9, testing with S9 may be needed only if the *in vitro* results with OECD TG 455 are negative and there is *in vivo* evidence indicating potential estrogenic activity).

In addition, a PfA proposed some text changes and a more general refinement of the wording in the DD. Another PfA also suggested that *in vitro* tests focus only on E and S pathways and to consider requesting an OECD TG 458 to assess the potential anti-androgenic effects, when the *in vivo* test gives rise to this concern.

Registrants submitted written comments on the received PfAs and expressed a general concern regarding limitations in laboratory capacity to perform higher tier testing (especially „non-standard" one) within the given legal and procedural timeframe. Further, the Registrants agreed with most of the PfAs, while pointing out some of

analytical/technical limitations. Due to limited lab capacity and/or validation needs, the Registrants agreed with the PfAs to request an internationally recognized guideline study instead of E-screen or a standard test design instead of the experimental testing with fish cells (OECD TG 455). As regards the requested testing with dihydroxylated benzotriazoles, it was noted that these substances are commercially not available and would have to be synthesized first. While agreeing with the PfAs' submitters on the different sensitivity of zebrafish and medaka, the Registrants expressed preference to test zebrafish due to the more robust historical dataset for this test species and greater experience in handling of the selected laboratory. Furthermore, they agreed to perform histopathology of the liver (and kidney) during the histopathology of gonads according to OECD TG 123 and to use at least one higher test concentration. However, the Registrants also expressed concerns regarding analytical challenges to identify and quantify the parent substance and potential metabolites in fish and/or water, while in their view no bioaccumulation in fish should be expected.

Taking into account the PfAs received and the Registrants' comments on them, eMSCA amended the DD in advance of the plenary by: replacing FSDT with MEOGRT (OECD TG 240) to be performed with medaka including histopathology of liver, kidney and gonads, with measurement of substance and its metabolites 5-OH-BTA, 4-OH-BTA and di-OH-BTA in fish and test medium (and well as hormone levels), and further asking for *in vitro* testing with the steroidogenesis assay (OECD TG 456), the estrogen receptor activation instead of E-screen (OECD TG 455), and the androgen receptor transactivation assay (OECD TG 458), all three conditional to the *in vivo* test results revealing endocrine-related effects. The eMSCA also introduced some further modifications to the DD text based on the PfAs received. In case ~~of~~ possible thyroid-related effects were observed in the in vivo test, conditionally a porcine thyroid peroxidase inhibition assay was proposed (as a hint for a possible thyroid receptor binding was indicated by QSAR provided in the supplemental material of a PfA).

The MSC thoroughly discussed the issues raised in the PfAs, Registrants' comments and the way they have been addressed in the revised DD.

As regards the *in vivo* testing, a member noted that request for an OECD TG 240 would allow substance investigation during the whole life cycle and full reproductive cycle that would not be possible with OECD TG 234 solely. The same result could be achieved also with combined testing according to OECD TG 229 followed by OECD TG 234. However, several members expressed their reservations towards such a combined request, as it has not been done. A member asked if there are indications from studies also with mammalian species that the reproductive phase or offspring would be affected which could justify a need to request a test including the reproductive stage. The members also shared the view that currently the available substance-specific information is insufficient to justify triggering of a level 5 test in the OECD ED Framework. Overall, a preference was expressed to keep the FSDT, a level 4 test in the OECD ED Framework, extended to include also histopathological examinations of gonads, liver and kidney.

With regard to the most appropriate test species, several members recommended to leave this choice to the Registrants and asked the eMSCA to clarify in the DD the different species' advantages and disadvantages for generating information on e.g. sexual characteristics when using medaka versus zebrafish (test with medaka has advantage to include secondary sex characteristics and genetic sex determination, plasticity of sex more prevalent in zebrafish) in support of the Registrants' further consideration on the choice of species.

Regarding the proposed test substance concentrations, the committee suggested a reference to the test guideline to be made for Registrants' further consideration and choice, instead of specifying the highest concentration to be tested.

Regarding the proposed *in vitro* testing, a member asked if, apart from the few QSAR predictions indicating ED positive effects of two metabolites, there are indications from other mammalian species for ED effects of benzotriazole or its metabolites to support the ED concern and if not - suggested alternatively to drop all *in vitro* requests at this stage.

eMSCA expert explained that currently no indications in mammalian species are found on the ED effects on fecundity or on off-springs, that could give indications for possible effects on the reproductive period to justify a MEOGRT and agreed on conducting the FSDT. The eMSCA agreed on dropping in vitro testing at this stage, but expressed a preference to include a recommendation for the Registrants to consider some hormone measurements within the *in vivo* testing. Once the FSDT results are available, the eMSCA may re-consider the need for further *in vitro* testing at the follow-up evaluation stage.

Session 2 (closed)

Taking into account all deliberations, MSC agreed to request in this DD solely *in vivo* FSDT test (OECD TG 234) with benzotriazole, with gonads, liver and kidney histopathological examination, including a measurement of the registered substance and as well a full analytical metabolite spectrum including at least the metabolites 5-OH-BTA and 4-OH-BTA, and to strengthen the justification provided for the request. The committee also agreed to remove the *in vitro* test requests at this stage of the evaluation process. Further in vitro testing might be triggered at a future stage by new information which would then be made available, e.g. further studies obtained from the currently ongoing testing proposal evaluation. Furthermore, some notes for consideration by the Registrants were included with regard to the selection of test species and the highest test substance concentrations and recommendations for considering additional hormone level measurements in the plasma samples during the *in vivo* testing, as specified in the DD.

MSC unanimously agreed on the draft decision as amended in the meeting.

Item 7 – Dossier evaluation

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

SECR introduced the report on the outcome of the written procedure (WP) for agreement seeking on ten dossier evaluation cases (see "Appendix to the MSC-56 agenda" in "Section III Final agenda" for more detailed identification of the cases). WP was launched on 28 September 2017. By the closing date 9 October 2017, MSC reached unanimous agreement on nine DDs. Three members abstained from voting on one case. For one DD, MSC Chairman terminated the WP on the basis of Article 20(6) of the MSC Rules of Procedure.

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

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

CCH-088/2017 Benzaldehyde (EC No. 202-860-4)

Session 2 (closed)

SECR explained that agreement was initially sought in written procedure. The written procedure was terminated by the Chairman of MSC in accordance with Article 20(6) of the MSC Rules of Procedure. A MSC member requested stopping the written procedure to allow discussion on the PfA on extended one-generation reproductive toxicity study (EOGRTS) suggesting to include a developmental immunotoxicity (DIT) cohort. In his request the MSC member introduced a published paper reporting findings on benzaldehyde administered in asthmatic animals.

SECR had not modified the DD in advance of the written procedure based on this PfA. The Registrant had provided written comments disagreeing with this PfA and criticising the design, relevance and interpretation of available studies.

The expert to the MSC member who requested a discussion reiterated their consideration that scientific evidence in the available studies were all showing effects or mechanisms/modes of action associated with DIT, in particular observed suppression of an allergic response, and thus raising a concern. He added that the newly provided information, not included in the PfA, further substantiated these arguments and was

brought forward by the MSC member when requesting stopping the written procedure. In his view, the data he presented shows that benzaldehyde has immunosuppressive effects when investigated in juvenile animals in targeted laboratory tests where the effect on the normal response of the immune system is investigated when the immune system is challenged.

In his view these investigations indicate that the normal function of the immune system can be suppressed by benzaldehyde and is thereby fulfilling the triggering criteria for DIT based on "existing information on the substance itself derived from relevant available *in vivo* or non-animal approaches (e.g. evidence of adverse effects on…the immune system in studies on adult animals). He argued that it should further be taken into account that the DIT cohort in the EOGRTS test includes investigation of suppression or enhancement of immune function and that developing immune systems are generally considered to be more vulnerable to effects induced by chemical substances than adult immune systems, and that the effects induced can have a broader spectrum and last longer or be lifelong.

Some MSC members held the view that such type of investigation is a functional test which should be generally accepted and which is generally regarded as an optimal model to study effects on (allergic) asthma, and thus of relevance for triggering the DIT cohort.

SECR disagreed and considered that using an asthma and allergic disease models, performed in adult animals, are not of relevance with regards to developing animals. In addition, SECR noted that there were two studies under discussion during the meeting. It stated that the first study, included in the PfA, showed no immunosuppressive or immune-enhancing effect on healthy test animals (beyond the irritating properties of benzaldehyde). The newly provided study raised by the MSC member indicated that benzaldehyde had seemingly beneficial effects on sensitised test animals (asthma model). Then SECR added that the newly provided study raised by the MSC member during the written procedure did not include non-sensitised (healthy) animals exposed only with benzaldehyde as concurrent controls, thus not allowing evaluation of potential effects of benzaldehyde in normal healthy animals. Consequently, SECR maintained the view that DIT cannot be triggered. Furthermore, SECR argued that the information submitted during the written procedure should not be taken into account in the current decision-making, mainly because the Registrant did not have an opportunity to comment on it.

The Chairman queried whether all MSC members had a chance to review the information submitted late in the process. One MSC member indicated that they did not have time to review the latter study. One MSC expert supported ECHA assessment that there was no accepted reliable model for asthma and questioned whether the decrease in lymphocytes was serious and severe. Another MSC member noted that in some instances a drug suppressing the immune system may be beneficial, while in others it may result in adverse effects. Several MSC members supported the views for the reasoning in the PfA to include the DIT cohort.

Finally, SECR clarified that (i) a compliance check draft decision on the same substance had already agreed by MSC (end of 2016), and that only F2 and the developmental neurotoxicity (DNT) cohorts of the EOGRTS were discussed during that earlier MSC meeting based on the PfAs submitted; (ii) the Registrant appealed the decision, which was revoked for procedural reasons; (iii) therefore, the current, new decision-making process following the procedures of Articles 50 and 51 of the REACH Regulation was thereafter initiated. SECR further noted that the substance is planned for CoRAP in 2019, with France as eMSCA.

In conclusion, MSC decided not to consider the information submitted during the written procedure on the DIT cohort for the current decision and agreed unanimously to the DD as circulated for the written procedure.

Eight MSC members and Norway abstained from voting. The MSC members from Austria, Denmark, France, Lithuania, the Netherlands, Portugal, Slovakia and Sweden abstained from voting because they supported the inclusion of DIT but recognised some of the above-mentioned procedural issues.

CCH-091/2017 2-Pyrrolidone (EC No. 210-483-1)

Session 1 (open)

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

SECR explained that one proposal for amendment (PfA) to ECHA's DD has been submitted on EOGRTS suggesting to remove cohorts 2A and 2B (DNT - cohorts) due to insufficient scientific justification for their inclusion and in the interests of avoiding unnecessary animal testing.

SECR amended the DD in advance of the meeting based on the PfA removing the justification on cholinesterase inhibition, however did not accept the PfA and did not remove cohorts 2A and 2B from the request for EOGRTS.

The Registrant had provided written comments on the PfAs which were reiterated at the meeting. The Registrant agreed that there are reasons to remove cohorts 2A and 2B from the request due to lack of convincing evidence, from either structural analogues or from the registered substance itself, to suggest that 2-pyrrolidone could be a developmental neuro-toxicant. The representatives of the Registrant explained also their concerns regarding use of data from N-alkylated-pyrrolidone compounds (e.g. N-methyl-2-pyrrolidone – NMP, and N-ethyl-2-pyrrolidone – NEP considered by SECR as structurally analogous to the registered substance) to trigger the inclusion of the DNT cohort without a sound scientific justification.

During the discussion one MSC expert stressed that the arguments referring to structural similarity of the substance with NMP and NEP do not trigger the inclusion of the DNT cohorts, since minor and inconsistent neurotoxic changes were observed in the investigations conducted on these substances. The same expert also indicated that there are significant differences in developmental toxicity profiles between the two N-alkylated pyrrolidones and 2-pyrrolidone which reduces confidence that NMP and NEP are suitable structural analogues.

SECR explained that the concern for neurotoxicity remains as each of the observed neurotoxic effects add to the weight of evidence in support of requesting the DNT cohorts. Additionally SECR refrained from reading-across from NMP and NEP to 2-pyrrolidone, but considers these substances only as structural analogues. It seems that 2-pyrrolidone acts in the brain, since regular oral administration produced significant increases of GABA (gamma-aminobutyric acid), which acts as a neurotransmitter in the central nervous system.

Session 2 (closed)

Some MSC members considered that the lack of data from the 90-day study on the registered substance and of bridging studies from the analogue substances used by the Registrant, might prevent from deciding in a definitive manner on the most appropriate design of the EOGRTS. However, although the observed effects from one study alone might be too weak to trigger the DNT cohort, several weak effects in multiple studies considered together constitute enough justification to trigger the request for the DNT cohorts.

Based on all these considerations, MSC concluded that there is sufficient scientific justification to request the EOGRTS with the inclusion of cohorts 2A and 2B (DNT cohorts).

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

CCH-092/2017 Tetramethylene dimethacrylate (EC No 218-218)

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 a PfA to ECHA's DD had been submitted. The first part of the PfA on EOGRTS suggested including DNT cohorts 2A and 2B, while the second part suggested including DIT cohort 3.

SECR had modified the DD with considerations related to the DIT cohort in advance of the meeting. SECR had however not included the DNT and DIT cohorts in the request for EOGRTS.

The Registrant had provided written comments prior to the meeting and disagreed with the PfA.

The representative of the Registrant argued that there had been no indication for developmental neurotoxicity or immunotoxicity in existing studies, thus the suggested inclusion of further cohorts was not warranted; only in one study (OECD TG 422) a slight reduction in grip strength was observed for the highest dose. This effect was deemed not relevant by the study director, however in the light of rapid ester hydrolysis, it could be understood as weak effect triggered by the sedative alcohol metabolite 1,4-butandiol. He outlined that none of the metabolites is classified for developmental neurotoxicity or immunotoxicity and deemed that no concerns were identified from existing data. In addition, in the read across data, updated this year, he had found no indications on such effects for any member of the multifunctional category.

A MSC member disagreed with ECHA's view on available information not being sufficient to trigger DIT and that the final EOGRTS study design can be concluded after results from the 90-day study become available.

A MSC expert emphasized the that the substance (an ester) rapidly metabolises into 1,4-butandiol, which has shown neurotoxic effects, and that adult and developing neurosystems have different sensibilities, and therefore, that a lack of effects the 90-day repeated dose study would not remove the developmental neurotoxicity concern.

Session 2 (closed)

SECR noted that the information provided in the registration dossier did not indicate neurotoxic effects but that the Registrant had commented in the meeting that a slight reduction had been observed in grip strength in the OECD TG 422. However, currently insufficient data was available to consider inclusion of the DNT cohorts.

A MSC member suggested to remove the amended text in the DD related to considerations on the DIT cohort, as the final assessment on DIT cohort inclusion should await the results from the 90-day study. Another MSC member concurred with SECR assessment and did not consider change in study design necessary at this stage.

Based on the discussion, MSC agreed not to include a paragraph on current triggers for DIT in the DD. It also concluded that the standard text on sequential testing would allow to consider the results from the 90-day study before agreeing on the final design of EOGRTS.

MSC agreed unanimously to the DD as amended at the meeting. Three members abstained from voting, including the members from Denmark, the Netherlands and Sweden.

d. Decision making process - General topics

1) Considerations on the regulatory approach regarding comet-assay modifications for cross-linking agents *(closed session)*

SECR gave a presentation addressing a regulatory approach on modifications of the comet assay to detect DNA crosslinks. MSC took note of the presentation and concluded to request, for dossier evaluation cases, the comet assay in standard form (OECD TG 489) without a modified protocol to detect crosslinks. For appropriate cases, MSC agreed to recommend options to apply a protocol to detect crosslinks. SECR would draft such a "Note for the consideration of the Registrant" for possible MSC adoption in written procedure after the meeting. In addition, SECR should take this into account in its next steps regarding cases CCH-108/2017 and CCH-021/2017.

2) Selecting tissues to be collected and analysed in the TGR assays

SECR gave a presentation on selecting tissues to be collected and analysed in the transgenic rodent (TGR; OECD TG 488) assay via oral route. The presentation referred to a case-specific decision in MSC-54 for CCH-021/2017 to collect, for somatic cells, three tissues (liver, glandular stomach and duodenum), to analyse two tissues (liver and glandular stomach) while keeping duodenum stored/frozen. Duodenum would need to be analysed only if both liver and glandular stomach gave negative results. For germ cells, the presentation referred to the case TPE-003/2016, where in MSC-47 a sampling and analysis approach was agreed and to consider this now as a feasible approach for re-application in other TPEs or CCHs where a TGR is requested. This approach comprises collection of germ cells at the same time as the somatic tissues, to freeze and store these germ cells (up to 5 years, at or below −70ºC), and for Registrants to consider analysis of the germ cells if liver or glandular stomach give positive results. MSC took note of the presentation. A MSC member asked to consider the development of an approach for the inhalation route in future. SECR reminded that further tissues could also be selected based on a concern. A MSC member considered that the analysis of germ cells should be required, instead of being considered, in case of positive somatic cells. A MSC expert noted that the intention was for the duodenum to be analysed in the event of a negative outcome, but questioned what should be done where equivocal results were obtained; however, this was not discussed further at the meeting. MSC agreed to application of the approach presented by SECR in dossier evaluation and asked SECR to prepare an inclusion for the MSC Manual of Decisions and Opinions.

3) Reporting back on the feedback received on use of OECD 234 under dossier evaluation

The item was postponed to the next meeting due to lack of time.

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

(Draft) Responses of ECHA to the comments received in the public consultation on ECHA's 8th draft recommendation

SECR presented its (draft) responses to the main comments received during the public consultation of ECHA's 8th draft recommendation (March-June 2017). Responses on NMP, the only substance commented on, were presented according to thematic blocks: A) Priority and general issues, B) Timelines and C) Exemptions. The discussions in previous MSC meetings were reiterated and it was highlighted that the prioritisation is done per substance as use-type specific scoring is not possible in a sufficiently consistent way due to limitations in available data. Based on the comments from the public consultation SECR noted the uncertainty about possible presence of NMP in articles and hence reflected this by giving a score for article service life as 0-2 instead of 2 used in the draft. As regards the interrelation between authorisation and restriction SECR confirmed that priority of NMP is likely to stay high as the restriction may have limited if any impact on volume and wide-dispersive uses, and in any case, grouping considerations would apply. Responding to the comments on RMOA SECR explained that RMOA is not legally required and it is aimed at helping to get a common understanding but it may also be revisited when new information becomes available. Since comments from many different sectors indicated a higher horizontal and vertical complexity of the supply chain as well as many industrial use sites, SECR had carried out re-assessment of the Latest Application Dates (LADs) using the practical implementation method for LAD setting[3]. This assessment indicated that NMP has the most complex supply chain among the substances in this recommendation round, thus leading to a consideration of putting this substance to the 24 months slot. SECR noted that this may then impact other substances in this round. As regards the comments on exemptions SECR referred to the detailed written responses and the general principles applied. On the specific comment asking if the upcoming restriction would be sufficient basis for an Art. 58(2) exemption, SECR reminded that the underlying EU legislation needs

[3]https://echa.europa.eu/documents/10162/13640/recom_general_approach_draft_axiv_entries_implementation_en.pdf/6fd729d4-4263-7d15-c2a2-13add8359b81

to cover all life cycles. So, although Art. 58(2) may potentially be met for industrial and professional uses by workers, the potential service life of articles and waste stage were not covered. As a concluding remark SECR indicated that the 8th recommendation is planned to be finalised and sent to the Commission early next year.

Item 9 – Opinion of MSC on ECHA's draft recommendation of priority substances t to be included in Annex XIV

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

Discussion on the first draft MSC opinion

The MSC Rapporteur presented the first proposal for the draft opinion of MSC on ECHA's 8th draft recommendation of priority substances for inclusion in Annex XIV as prepared by him, Co-Rapporteur and the Working Group (WG). He invited MSC to confirm the view of the WG that the six substances which did not receive any comments in the public consultation all meet the criteria for prioritisation for inclusion in Annex XIV, and that the entries in the table for the draft recommendation did not need to be reconsidered but were supported by MSC. He then presented the main issues raised for NMP as related to the justification for prioritisation and the prioritisation criteria with the received challenges, as well as issues brought up related to the transitional arrangements, review periods and possible exemptions. For all of the above, except the transitional arrangements, the Rapporteur invited MSC to consider that neither the information received from the public consultation, nor any other updates, did support introduction of changes to ECHA's draft recommendation. For the transitional arrangements, based on the analysis by the WG of the information received, the Rapporteur suggested MSC to consider that the opinion could suggest 24 months as the latest application date instead of the 18 months that was used by ECHA in the draft submitted for public consultation in March.

In the discussion two members expressed that they did not disagree with the priority scoring but expressed clear doubts on inclusion of NMP to the 8th recommendation. The arguments brought forward in this context were that the restriction process should in their opinion first be finalized, as well as the Commission's aprotic solvents strategy, before inclusion of NMP in Annex XIV. Additional argument brought forward by one of those members was the perceived inconsistency with IPPC-requirements as in those the use of NMP is actually part of the Best Available Techniques (BAT) for refineries. The MSC member from CZ made a statement to be included in the minutes (see Section V).

One observer from an NGO expressed their support to inclusion of NMP, given that the substance is toxic to reproduction and it is produced in very high volumes. She also referred to the special nature of the restriction which will improve control only on certain conditions but as such will not limit the use of NMP. Hence, in their view NMP remains of very high priority for authorisation route. An observer from industry asked about the scoring used for SMEs. He then raised again the question about possibility to set use specific LADs. He suggested that this could be used if there are some major uses or groups of uses as this could balance the workload at the later stages of the process.

As a response to the interventions the Rapporteur reiterated that the objectives and the task of MSC is to assess that the priority assessment among other substances has been carried out according to agreed approaches. He also reminded that restriction and authorisation do not need to be seen as contradictory processes. He also confirmed that in the view of the WG the limit value from the NMP restriction does not impact the priority of NMP nor the relevance of its inclusion to Annex XIV.

In responding to the intervention from the observer from industry SECR reminded about earlier discussion and invitation for any inputs in order to improve transparency of how the LADs are set. However, the difficulties in finding factors to use and be able to assess for a consistent LAD setting from the data available, including those for any use specific LADs, remain. SECR reminded that industry can always submit their AfAs, including use-specific ones, before the set LAD. As regards the scoring for Wide Dispersive Use (WDU), SECR clarified that industrial, professional and consumer uses are differentiated and used in the approach, without any separate scoring for SMEs. SECR repeated its view that it would be

advantageous to have all the aprotic solvents in the same phase so as to allow their handling in the most appropriate way. On behalf of COM SECR also confirmed that the foreseen strategy on the aprotic solvents is expected to be finalised by the end of the year, as part of a long term plan. In view of its still high priority SECR questioned what the reasoning/justification was for not including NMP to the next recommendation. In responding to the two members' doubts about inclusion of NMP, SECR also reassured that the legislators have thought through interfaces between different pieces of legislation, however noting that such assessment lies in the remit of COM rather than ECHA/SECR. On the specific intervention by the member of CZ, SECR noted that part C of the responses reflects on other EU legislation with regard to possible Art. 58(2) exemptions which also includes a reference to IED (IPPC).

As a concluding remark the rapporteur invited for any further written comments on the draft opinion in order for him to finalise the second draft opinion for discussion and adoption at the next meeting.

b. Update to MSC Working Procedures on providing an opinion on ECHA's draft recommendation of priority substances

SECR presented a proposal for an update to the MSC working procedures concerning the MSC's opinion development on an ECHA's draft recommendation under Article 58 (3) of REACH Regulation. It was noted that the update is based on the experience gained in the past years and aims to align the working procedures with the current working practices, the documentation published, and the IT tools currently used in MSC work. MSC adopted the update to its working procedures without further discussion.

Item 10 – Any other business

a. Feedback from review of MSC processes – possible priority actions

The Chairman presented to MSC possible priority actions based on the feedback received, both from phone calls with members and workshops with ECHA secretariat, as well as from MSC's regular observer stakeholders' annual survey. Further topics for ECHA's internal discussions that MSC-S could initiate or participate in were also listed. MSC members and stakeholders provided their priority rankings for the presented actions and for the suggestions for ECHA's internal discussion. MSC-S will take MSC members' input into consideration for planning next steps for the actions, and will report on their implementation plans at MSC-57.

b. Update on appeals and court cases (*partly closed session*)

SECR gave an overview of the status of pending cases submitted to the European Court of Justice relating to the authorisation process and appeals on evaluation submitted to the Board of Appeal of ECHA. MSC took note of the update. A compilation prepared by SECR with some key conclusions and learnings from the cases concluded by the Board of Appeal was presented in closed session. In addition to the MSC Manual of Decision and Opinions, this compilation may be of help to non-legal experts in SECR, eMSCAs and MSC in preparation of draft decisions and during the agreement seeking process.

Item 11– Adoption of main conclusions and action points

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

II. List of attendees

Members/Alternate members
ANDRIJEWSKI, Michal (PL)
BORG, Ingrid (MT)
COCKSHOTT, Amanda (UK)
CONWAY, Louise (IE)
DE KNECHT, Joop (NL)
DIMCHEVA, Tsvetanka (BG)
DUNAUSKIENE, Lina (LT)
FINDENEGG, Helene (DE)
FRANZ, Michel (FR)
HERMES, Joe (LU)
HORSKA, Alexandra (SK)
HUMAR-JURIC, Tatjana (SI)
JANTONE, Anta (LV)
KREKOVIĆ, Dubravka (HR)
KULHANKOVA, Pavlína(CZ)
LONDESBOROUGH, Susan (FI)
LUNDBERGH, Ivar (SE)
MENDONÇA, Elsa (PT)
NYITRAI, Viktor (HU)
MIHALCEA UDREA, Mariana (RO)
PISTOLESE, Pietro (IT)
REIERSON, Linda (NO)
STESSEL, Helmut (AT)
TYLE, Henrik (DK)
VANDERSTEEN, Kelly (BE)
VESKIMÄE, Enda (EE)
Observers
ANNYS, Erwin (Cefic)
FAßBENDER, Christopher (PETA)
KERÄNEN, Hannu (CONCAWE)
LOONEN, Helene (EEB)
WAETERSCHOOT, Hugo (Eurometaux)

ECHA staff
AHRENS, Birgit
AJAO, Charmaine
BERCARU, Ofelia
BICHLMAIER, Ingo
BORNATOWICZ, Norbert
BROERE, William
CALEY, Jane
CARLON, Claudio
DE WOLF, Watze
DELOFF-BIAŁEK, Anna
DREVE, Simina
HAUTAMÄKI, Anne
HOFFSTADT, Laurence
HUUSKONEN, Hannele
JAAGUS, Triin
JOHANSSON, Matti
KARHU, Elina
KOJO, Anneli
LE CURIEUX, Frank
LEPPÄRANTA, Outi
LOUEKARI, Kimmo
NAUR, Liina
PELLIZZATO, Francesca
RÖNTY, Kaisu
SCHULTHEISS, Christian
SOBANSKA, Marta
TOLLOSA, Meskerem
TRNKA, Jan-Peter
VAHTERISTO, Liisa
VASILEVA, Katya
WOLLENBERGER, Leah

Proxies

- BORG, Ingrid (MT) also acting as proxy of PALEOMILITOU, Maria (CY)
- FRANZ, Michel (FR) also acting as proxy of KOUTSODIMOU, Aglaia (EL)
- PISTOLESE, Pietro (IT) also acting as proxy of MARTÍN, Esther (ES)
- LONDESBOROUGH, Susan (FI) also acting as proxy of COCKSHOTT, Amanda (UK) for Thursday from 14:00 onwards
- TYLE, Henrik (DK) also acting as proxy of DUNAUSKIENE, Lina (LT) for short periods during the meeting.

Experts and advisers to MSC members

ATTIAS, Leonello (IT) (expert to PISTOLESE, Pietro)
CIESLA, Jacek (PL) (expert to ANDRIJEWSKI, Michal)
COPOIU, Oana (RO) (expert to MIHALCEA UDREA, Mariana)
DANIHELOVA, Martina (SK) (expert to HORSKA, Alexandra)
DOBRAK-VAN BERLO, Agnieszka (BE) (expert to VANDERSTEEN, Kelly)
GARCÍA HERÁNDEZ, Patricia (ES) (expert to MARTÍN, Esther)
GRINCEVICIUTE, Otilija (LT) (expert to DUNAUSKIENE, Lina)
INDANS, Ian (UK) (expert to COCKSHOTT, Amanda)
KOZMIKOVA, Jana (CZ) (expert to KULHANKOVA, Pavlina)
LECOQ, Pierre (FR) (adviser to FRANZ, Michel)
MALKIEWICZ, Katarzyna (SE) (expert to LUNDBERGH, Ivar)

NYGREEN, Beryl C. (NO) (expert to REIERSON, Linda)
RISSANEN, Eeva (FI) (adviser to LONDESBOROUGH, Susan)
ROSENTHAL, Esther (DE) (adviser to FINDENEGG, Helene)
ROUSSELLE, Christoph (FR) (expert to FRANZ, Michel)
TARNOCZAI, Tímea (HU) (expert to DEIM, Szilvia)
UNKELBACH, Christian (DE) (expert to FINDENEGG, Helene)
ZELJEZIC, Davor (HR) (expert to KREKOVIC, Dubravka)

MSCA experts for SEv cases:
HASSOLD, Enken (DE)
PRINTEMPS, Nathalie (FR)

By WEBEX/phone connection:
During the Agenda Item 6.1: Johanna BARTHELEMY-BERNERON (FR)
During the Agenda Item 6.2 b+c. on SEV-FR-020/2015, SEV-FR-021/2015 and SEV-FR-022/2015: Minne HERINGA (NL)
During the Agenda Item 6.2 b+c. on SEV-DE-008/2016: Ian DOYLE (UK), Jürgen ARNING (DE) and Sabine GERMER (DE)
During the Agenda Item 7.2 b+c. on CCH-091/2017: Lindsay PEPPIN (UK)
During the Agenda Item 7.2 b+c. on CCH-088/2017: Rob van BRIEL (NL)
During the Agenda item 7d3: Els BOEL (BE)
During the whole meeting: Esther MARTÍN (ES)
During the whole meeting from COM: Katrin SCHUTTE (DG ENV) and Enrique GARCIA-JOHN (DG GROW)

Case owners:
Representatives of the Registrants were attending under the Agenda Item 6.2 b for SEV-FR-020/2015, SEV-FR-021/2015 and SEV-FR-022/2015; under the Agenda Item 7 b for CCH-091/2017 and CCH-092/2017.

Apologies:
ALMEIDA, Inês (PT)
DEIM, Szilvia (HU)
KOUTSODIMOU, Aglaia (EL)
MARTÍN, Esther (ES)
PALEOMILITOU, Maria (CY)
WAGENER, Alex (LU)
WIJMENGA, Jan (NL)

III. Final Agenda

MSC/A/056/2017

Agenda

56th meeting of the Member State Committee

24-26 October 2017
ECHA Conference Centre
Annankatu 18, in Helsinki, Finland

24 October: starts at 9:00 am
26 October: ends at 17:00

Item 1 – Welcome and Apologies

Item 2 – Adoption of the Agenda

MSC/A/056/2017
For adoption

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

Item 4 – Administrative issues

- Update on ECHA premises
- Outlook for MSC-57

For information

Item 5 – Minutes of the MSC-55

- Draft minutes of MSC-55

MSC/M/55/2017
For adoption

Item 6.1 – Community Rolling Action Plan (CoRAP) draft update for 2018-2020 & MSC opinion development

- Introduction of the annual draft CoRAP update by ECHA

ECHA/MSC-56/2017/008
For information and discussion

Item 6.2 – Substance evaluation - Decision making process

Timing for item 6.2b is Day 1
Closed session for item 6.2c

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

- no cases

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

For discussion followed by agreement seeking under 6.2c:

ECHA/MSC-56/2017/009

MSC code	Substance name	EC No./Doc.
SEV-FR-020/2015	Aluminium chloride basic	215-477-2 ECHA/MSC-56/2017/010-011
SEV-FR-021/2015	Aluminium chloride	231-208-1 ECHA/MSC-56/2017/012-013
SEV-FR-022/2015	Aluminium sulphate	233-135-0 ECHA/MSC-56/2017/014-015
SEV-DE-008/2016	Benzotriazole	202-394-1 ECHA/MSC-56/2017/016-017

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 **6.2 b**

For agreement

Item 7 – Dossier evaluation

Timing: Day 2 for item 7b
Closed session for 7c and 7d1

a. Written procedure report on seeking agreement on draft decisions on dossier evaluation[4]

ECHA/MSC-56/2017/001
For information

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

ECHA/MSC-56/2017/002

For discussion followed by agreement seeking under 7c:

Compliance checks

MSC code	Substance name	EC No./Documents
CCH-091/2017	2-Pyrrolidone	210-483-1 ECHA/MSC-56/2017/003-004
CCH-092/2017	Tetramethylene dimethacrylate	218-218-1 ECHA/MSC-56/2017/005-006

For discussion

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

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

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

CCH-088/2017 Benzaldehyde EC No. 202-860-4
ECHA/MSC/D/2017/147-148[5]

For agreement

d. Decision making process - General topics

1) Considerations on the regulatory approach regarding comet-assay modifications for cross-linking agents
   - Reflection on cases CCH-108/2016 (MSC-51), CCH-021/2017 (MSC-54) and TPE-027 (MSC-55) *(Closed session)*

ECHA/MSC-56/2017/019
For discussion and decision

2) Selecting tissues to be collected and analysed in the TGR assays

ECHA/MSC-56/2017/025 (ppt)
For discussion and decision

3) Reporting back on the feedback received on use of OECD 234 under dossier evaluation

For information

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

Timing: Day 2

- (Draft) Responses of ECHA to the comments received in the public consultation on ECHA's 8th draft recommendation

ECHA/MSC-56/2017/020-024
For information and discussion

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

Timing: Day 2

a. MSC opinion on ECHA's Draft 8th recommendation of priority substances to be included in Annex XIV
   - Discussion on the first draft MSC opinion

ECHA/MSC-56/2017/018
For discussion

b. Update to MSC Working Procedures on providing an opinion on ECHA's draft recommendation of priority substances

ECHA/MSC-56/2017/007
For discussion and adoption

Item 10 – Any other business

a. Feedback from review of MSC processes – possible priority actions

For discussion

b. Update on appeals and court cases

For information

Item 11 – Adoption of main conclusions and action points

[5] Available in MSC CIRCABC, in the folder for the case under 05. Dossier evaluation.

- Table with conclusions and action points from MSC-56

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)
- Update from other ECHA bodies (ECHA/MSC/I/2017/024)

Appendix to the MSC-56 agenda:

List of evaluation cases agreed in written procedure in advance of the MSC-56 meeting:

Compliance checks

MSC code	Substance name	EC/List No.
CCH-084/2017	Bis(piperidinothiocarbonyl) hexasulphide	213-537-2
CCH-085/2017	N-[2-(piperazin-1-yl)ethyl]C18-unsatured-alkylamide	629-767-5
CCH-086/2017	Esterification products of 4,4'-isopropylidenediphenol, ethoxylated and 2-methylprop-2-enoic acid	609-946-4
CCH-089/2017	Betaines, C12-14 (even numbered)-alkyldimethyl	931-700-2
CCH-095/2017	2-[2-[2-[2-(1-methyl-2-prop-2-enoyloxy-ethoxy)-ethoxymethyl]-2-[2-(2-prop-2-enoyloxypropoxy)-ethoxymethyl]butoxy]ethoxy]propyl prop-2-enoate	601-566-7
CCH-102/2017	Benzyl salicylate	204-262-9
CCH-103/2017	1-methylimidazole	210-484-7
CCH-104/2017	2-ethyl-4-methylimidazole	213-234-5

Testing proposal examinations

MSC code	Substance name	EC/List No.
TPE-033/2017	2,5-bis-isocyanatomethyl-bicyclo[2.2.1]heptane	411-280-2

IV. Main Conclusions and Action Points

Main conclusions and action points
MSC-56, 24-26 October 2017
(adopted at MSC-56)

CONCLUSIONS / DECISIONS / MINORITY OPINIONS	ACTIONS REQUESTED
Item 5 – Minutes of the MSC-55	
MSC adopted the draft minutes as provided for the meeting.	**MSC-S** to upload final version of the minutes on MSC S-CIRCABC by 26 October 2017 and on ECHA website without undue delay.
Item 6.1 – Community Rolling Action Plan (CoRAP) draft update for 2018-2020 & MSC opinion development • Introduction of the annual draft CoRAP update by ECHA	
MSC took note of the draft CoRAP update.	**MSC-WG** to take into account the changes introduced in the draft CoRAP following the referral.
Item 6.2 – Substance evaluation - Decision making process **d. Introduction to and preliminary discussion on draft decisions on substance evaluation after MS-CA's/ECHA reactions *(Session 1, open session)*** **e. Seeking agreement on a draft decision when amendments were proposed by MS-CA's/ECHA *(Session 2, closed)***	
MSC reached unanimous agreement on the following ECHA draft decisions as modified in the meeting: SEV-FR-020/2015 Aluminium chloride basic (EC No. 215-477-2) SEV-FR-021/2015 Aluminium chloride (EC No. 231-208-1) SEV-FR-022/2015 Aluminium sulphate (EC No. 233-135-0) SEV-DE-008/2016 Benzotriazole (EC No. 202-394-1) MSC gave a mandate to eMSCA from FR detailing the editorial changes that need to be done to the three SEV decisions from FR, after the meeting, not later than 10 November.	**MSC-S** to upload on MSC S-CIRCABC the final ECHA decisions of the agreed cases. **eMSCA from FR** to submit to MSC-S via the Evaluation S-CIRCABC, the agreed decisions updated based on the mandate given by MSC not later than 10 November 2017.
Item 7 – Dossier evaluation **a. Written procedure report on seeking agreement on draft decisions on dossier evaluation**	
MSC took note of the report.	**MSC-S** to upload on MSC S-CIRCABC the final ECHA decisions agreed in written procedure.
Item 7 – Dossier evaluation **b. Introduction to and preliminary discussion on draft decisions on testing proposals and compliance checks after MS-CA reactions *(Session 1, open session)*** **c. Seeking agreement on draft decisions on compliance checks when amendments were proposed by MS-CA's (Session 2, closed)**	
MSC reached unanimous agreement on the following ECHA draft	**MSC-S** to upload on MSC S-CIRCABC the

CONCLUSIONS / DECISIONS / MINORITY OPINIONS	ACTIONS REQUESTED
decisions (as modified in the meeting): **<u>Compliance checks</u>** CCH-091/2017 2-Pyrrolidone (EC No. 210-483-1) CCH-092/2017 Tetramethylene dimethacrylate (EC No.218-218-1) CCH-088/2017 Benzaldehyde (EC No. 202-860-4)	final ECHA decisions of the agreed cases.
Item 7d. Dossier evaluation decision making process -General topics 4) Considerations on the regulatory approach regarding comet-assay modifications for cross-linking agents Reflection on cases CCH-108/2016 (MSC-51), CCH-021/2017 (MSC-54) and TPE-027/2017 (MSC-55)	
MSC took note of the presentation and document on the application of the modified comet assay for cross-linking agents.	**SECR** to request, for dossier evaluation cases, the comet assay in standard form without a modified protocol and, for appropriate cases, to recommend options to apply a protocol to detect cross-linking. **SECR** to draft text for such a "Note for the consideration of the Registrant" and upload it to S-CIRCABC by 10 November 2017 for MSC adoption via a written procedure of 10 days. **SECR** to rectify CCH-108/2016 on this aspect and to inform Board of Appeal and the Registrant. **SECR** to amend the decision on CCH-021/2017 with the approach and text as agreed in written procedure.
Item 7d. Dossier evaluation decision making process -General topics 5) Selecting tissues to be collected and analysed in the TGR assays	
MSC took note of the presentation and suggestions on tissues in TGR assays.	**MSC-S** to prepare an inclusion for Manual of Decisions for MSC-57.
Item 9 – Opinion of MSC on ECHA's draft recommendation of priority substances to be included in Annex XIV **c.** MSC opinion on ECHA's Draft 8th recommendation of priority substances to be included in Annex XIV - Discussion on the first draft MSC opinion	
MSC took note of the first draft opinion prepared by the Rapporteur and the WG, and provided some initial feedback on it.	**MSC** to provide any further written comments to the Rapporteur by 10 November 2017 (using FMB). **Rapporteur** to submit the draft opinion for final discussion and adoption to MSC-S by 28 November 2017.
Item 9 – Opinion of MSC on ECHA's draft recommendation of priority substances to be included in Annex XIV **d.** Update to MSC Working Procedures on providing an opinion on ECHA's draft recommendation of priority substances	
MSC agreed with the Secretariat's proposal for an update of the MSC Working procedure for opinion development on ECHA's draft recommendations.	**MSC-S** to upload the updated MSC working procedure to MSC S-CIRCABC and ECHA website.
Item 10 – Any other business **c.** Feedback from review of MSC processes – possible priority actions	
	MSC to give feedback on the list of

CONCLUSIONS / DECISIONS / MINORITY OPINIONS	ACTIONS REQUESTED
	priorities during MSC-56. **MSC-S** to identify next steps for the priority actions and report back to MSC in MSC-57.
Item 11 – Adoption of main conclusions and action points	
MSC adopted the main conclusions and action points of MSC-56 at the meeting.	**MSC-S** to upload the main conclusions and action points on MSC S-CIRCABC by 27 October 2017.

V. Statement to the minutes of the Czech Republic on the inclusion of 1-Methyl-2-pyrrolidone (NMP) into the 8th ECHA recommendation of priority substances to be included in Annex XIV

The representative on the MSC for the Czech Republic does not support the inclusion of the substance 1-methyl-2-pyrrolidone into Annex XIV.

We doubt about the proportionality and the regulatory consistency of inclusion of the NMP into Annex XIV with regards to the integrated pollution and prevention control legal requirements.

Directive 2010/75/EU on industrial emissions (hereinafter as "**IED**") defines the parameters of integrated pollution prevention and control for defined installation.

Article 11 of IED defines, that Member States shall take the necessary measures to provide that installations are operated in accordance with the following principles:
(a) all the appropriate preventive measures are taken against pollution;
(b) the **best available techniques (BAT)** are applied;
(c) no significant pollution is caused";

Article 14, par. 3 stipulates that the BAT conclusions shall be the reference for setting the permit conditions. IED also defines that decisions on the BAT conclusions are adopted as a delegated act. And finally Article 21 par. 3 presents that within 4 years of publication of decisions on BAT conclusions in accordance with Article 13(5) relating to the main activity of an installation, the competent authority shall ensure that

(a) all the permit conditions for the installation concerned are reconsidered and, if necessary, updated to ensure compliance with this Directive, in particular, with Article 15(3) and (4),where applicable, and
(b) the installation complies with those permit conditions.

Best available techniques are summarised in the BAT Reference Documents (BREFs) and European Commission (EC) ensures that they are publicly available.

The NMP is stated as part of the BAT reference document:
Best Available Techniques Reference Document for the Refining of Mineral Oil and Gas (2014)
For a base oil production, in aromatic extraction units (Chapter 2.3., 4.3.), the use of NMP and furfural is recommended. The NMP in comparison with furfural is preferred as a less toxic solvent with better degradability in the wastewater treatment plants. The NMP is presented such as less polluting solvent and its higher selectivity is leading to a higher refining yield and lower solvent ratio which both result in a lower energy consumption of some 30-40 %.

Based on this BREF the BAT conclusions were approved by the **Commission Implementing Decision 2014/738/EU establishing best available techniques (BAT) conclusions, under Directive 2010/75/EU of the European Parliament and of the Council on industrial emissions, for the refining of mineral oil and gas.**
The preference of the NMP use is defined by the BAT 22 as follows:
„Design (new plants) or implement changes (into existing) so that the plant operates a solvent extraction process with the use of a less hazardous solvent: e.g. converting furfural or phenol extraction into the n-methylpyrrolidone (NMP) process".

Above mentioned Implementing Decision was approved on October 9, 2014 so the period, when BAT 22 has to be implemented, ends in October 2018.

Based on the presented facts, the proposal concerning the inclusion of NMP into the Annex XIV seems to be inconsistent with the IPPC legislation in compliance with the EU Better regulation strategy. This situation is not clear for industry because EC requires using the NMP as the BAT under IPPC directive and proposes to limit significantly the use of such substance by authorisation under REACH regulation in the same time. So from our point of view such proposal appears at least questionable.

Regarding this we request ECHA and European Commission to further analyse the proportionality of prioritising this substance for Annex XIV inclusion at the current stage with regard to the collision with the IPPC regulatory framework. Based on the results of this analysis the best way forward should be discussed.