

**MSC/M/53/2017
(Adopted in MSC-54)**

**Minutes
of the 53rd Meeting of the Member State Committee (MSC-53)
25-26 April 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 53rd meeting of the Member State Committee (MSC) (for the full list of attendees and further details see Section II of the minutes).

Item 2 - Adoption of the Agenda

The Agenda was adopted as modified by the MSC Secretariat with removal of an item under information documents on update on the ongoing guidance activities (final Agenda is attached to these minutes as Section III). The Chairman informed MSC that the information slides will be uploaded to MSC S-CIRCABC after the meeting and requested MSC to provide their suggestions to SECR on the format of the update.

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-53.

Item 4 - Administrative issues

- **Outlook for MSC-54**

The Chairman presented an outlook on the potential length of the next meeting which is expected to require approximately 5 plenary days. The Chairman also presented an early stage estimation for the length of the MSC-55 meeting in September.

Item 5 – Minutes of the MSC-52

The minutes of MSC-52 were adopted as modified at the meeting.

Item 6 - Substance evaluation - 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 four substance evaluation cases (see Section V for more detailed identification of the cases). WP was launched on 30 March 2017 and closed on 10 April 2017. By the closing date, unanimous agreement was reached on three draft decisions (DD). For one DD WP was terminated by the MSC Chairman on the basis of Article 20.6 of the MSC Rules of Procedure.

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-UK-034/2015 A reaction mass of: O,O-di(1-methylethyl)trithio-bis-thioformate;O,O-di(1-methylethyl)tetrathio-bis-thioformate;O,O-di(1-methylethyl)pentathio-bis-thioformate (EC No. 403-030-6)

The MSC Chair had terminated the written procedure for MSC agreement seeking on this SEv draft decision prepared by the UK CA (eMSCA) and the case was brought to the meeting to discuss how to reflect the reporting of non-extractable residues for the two sediment simulation tests that were requested – sediment simulation test OECD 308 and surface water simulation test OECD 309.

The UK CA took the justification for stopping the written procedure into account and amended the DD before the meeting. MSC unanimously agreed with the DD as amended and made available to MSC before the meeting. MSC slightly amended the DD made available before the meeting and then unanimously agreed.

One member raised the question on how to best spike sediments with the test substance when conducting a sediment simulation study since this topic is of relevance to another

SEV case anticipated for MSC-54. MSC agreed that the general topic is best discussed first in the PBT Expert group.

d. General topics

• Update to MSC working procedures on evaluation

SECR presented a proposal for MSC to update its working procedures for processing draft decisions under substance and dossier evaluation. With this proposed update the 60-day agreement seeking period for MSC would finish at the end of the plenary week, leaving out the one-week period after the plenary meeting currently reserved for an urgent written procedure. SECR suggested to use those seven days in advance of MSC decision on a case, mainly the gain would be needed for preparing for written procedure but similarly more time is also gained for cases to be presented at a meeting.

SECR proposed to start implementing the new timelines for the MSCA consultation rounds affecting meetings from 2018 February (MSC-58) onwards. The first impact would be on the consultation round starting on 26 October 2017 (where PfAs for the DDs are due by 27th November 2017). With this proposed change all the legal deadlines remain unchanged. However, SECR will need to take the change into account when preparing the evaluation timelines for the meetings of 2018 onwards, and consequently communicate the deadlines to the eMSCAs (SEv) as well as to all MSCAs (DEv).

MSC adopted the updates to its working procedures and the plan for their implementation as presented.

• Appeals update (partly closed session)

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 substance evaluation and authorisation processes. MSC took note of the information received.

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 seven dossier evaluation cases (see Section VI for more detailed identification of the cases). WP was launched on 31 March 2017. By the closing date 10 April 2017 MSC reached unanimous agreement on seven DDs. Three members abstained from voting on one case.

The MSC member from Germany requested the floor to explain why they had abstained from voting on the case TPE-008/2017. In the member's view, similarly to the reasons for their abstention in previous MSC written procedure, 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. The MSC member emphasized that a statement of non-compliance (SONC) would be more efficient than starting a new decision making procedure to ask 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)

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

CCH-003/2017 Dimethyl ether (EC No. 204-065-8)

Session 1 (open)

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

Two PfAs were submitted, both proposing to include a request for the developmental neurotoxicity cohorts (DNT, cohorts 2A and 2B) in the extended one-generation reproductive toxicity study (EOGRTS, OECD TG 443), due to narcosis observed after exposure to the registered substance dimethyl ether, and additional information provided on its analogue diethyl ether which lead to a concern for developmental neurotoxicity.

The Registrant included in his written comments to PfAs a consideration that MSC had come to a general conclusion on narcosis in a previous CCH case. The MSC Chairman explained that MSC agreement seeking is case-specific and a conclusion on one particular case cannot be readily generalised, and furthermore, that these two compliance checks are quite different.

The Registrant disagreed with the two PfAs submitted on inclusion of the DNT cohorts arguing: (a) the narcotic effects are directly related to the test concentration and are caused by a non-specific mode of action; (b) the highest safe test concentration (due to explosiveness) is lower than the concentration causing anaesthetic effects in previously conducted studies; (c) no difference in sensitivity between the young and the adult animals is expected; (d) in his view, the read-across information from diethyl ether is not relevant: the impairment of learning and memory occur at levels showing narcotic effects and exceeding the highest safe test concentration.

SECR stressed that the transient, non-specific narcotic effects do not constitute triggers for inclusion of cohorts 2A and 2B in the design of the requested EOGRTS.

At the meeting, the Registrant's representatives reiterated their written arguments and noted that due to animal welfare considerations, they would consider all available information for possible waiving of the EOGRT testing with or without additional cohort. They highlighted that the Registrant considers the reference made to diethyl ether (DEE) for close structural analogue irrelevant, and noted that for DME no toxicity results or other abnormal neuropathology have been observed in 2-year chronic study with 2000 ppm where decreased responsiveness was seen. Furthermore, they argued the mode of action (MoA) is unclear and considered that anaesthetic properties are linked to reversible changes of ion channels with no receptor involvement. For an adverse outcome pathway (AOP) a molecular initiating event is needed, and no such is seen below the concentration causing the anaesthetic effects. No difference in developing species exposed to DME is identified at usual concentrations. Finally, they referred to explosive properties of the substance limiting the possibility to test DME at potentially narcotic concentrations thus the expected outcome will be of low relevance. Furthermore, in this context they noted from animal welfare perspectives that the proposed studies would require testing with the highest number of animals and therefore, should be considered only as a last resort.

SECR did not agree with the PfAs, as due to limited reporting on information regarding the disturbance of learning and memory after exposure to DEE, it is not possible to assess the reliability of the references. Furthermore no other effects than slight narcotic effects were reported at an exposure level of 2000 mg/kg/d and 3500 mg/kg/d in a 90-day oral study on DEE, and DME only causes narcotic effects at high dose levels. ECHA considers these effects are transient, reversible and non-specific. In SECR's view, the total evidence does not allow concluding on a specific mode(s) of action associated with DNT.

At the plenary, the MSC members of the PfA submitting countries provided some additional information from recent studies in support of the PfA arguments. They noted that REACH Regulation does not require a specific mechanism of action to be known for identification of a concern for neurotoxicity. In their view, it cannot be excluded that interaction with the GABA and NMDA receptors occurs in parallel to general lipid membrane disturbance. This consideration is further supported by read-across data from the structural analogue DEE and QSAR data which show that both DME and DEE can induce narcotic effects, are easily distributed in whole body and easily pass the brain-blood barrier.

SECR considered that narcotic substances are classified as STOT SE 3, while neurotoxic ones as STOT SE 1 or 2 based on the CLP criteria; therefore, the main difference depends on the nature of the effects, being transient or not. For this specific case, there is

insufficient supportive information that the effects are “more than transient in nature” or that narcosis as such has caused adverse effects in developing organisms.

Several MSC members disagreed with this interpretation of the CLP arguing that according to the legal text and the CLP guidance document, STOT classification in any of the 3 categories is based on adverse, severe effects and thus sufficient to trigger the cohorts’ inclusion. Further, it was pointed out that the decrease in responsiveness to sound in the dams in the TG 414 study was used to derive the NOAEL for maternal toxicity and thus considered adverse. Concerning the mechanisms of action for substances causing narcotic effects, some MSC members argued that it can be reasonably assumed that “specific” disruption of some function of receptors in the membrane lipid bi-layers (including GABA and NMDA) occur as a consequence of and in parallel with the “non-specific” diffusion into and disruption of bi-layer lipid cell membranes.

During the discussion, views were shared also with regard to: the sensitive life stages (in particular whether developing organisms are more sensitive than adults in this case, e.g. due to the sensitivity of the developing brain); difference between narcosis and anaesthesia (whether the anaesthesia causes permanent developmental effects and whether narcotic substances can be reasonably expected to do the same); adversity of DME narcotic effects comparing with the criteria for DNT triggering under REACH when focusing on the evidence from the substance itself (e.g. observed sluggishness and slight decrease in response to sound reported at 1 or 2% concentrations) and from DEE (whose structural analogy with DME was questioned by SECR and an adviser due to very different predicted metabolites, whereas the PfA-submitters pointed out the information on DEE was only supportive, but could be used to raise a concern since the two substances are similar when looking at a number of relevant phys-chem properties and both have been shown to induce narcotic effects in animals and humans); possibilities to test this explosive substance from a laboratory worker safety perspective (pointed out by the PfA-submitters to be possible to reach a level inducing mild narcotic effects), as well as on the interpretation of legislative and guidance criteria, mentioning narcosis as a potential trigger for DNT.

During the discussion on this case, an expert referred to a report entitled “Scientific review on the link between the narcotic effects of solvents and (developmental) neurotoxicity” recently submitted for an ECHA’s expert group consultation, pointing out that the report’s conclusions do not remove their concern about serious and severe effects caused by DME. However, the MSC Chairman reminded that neither the Registrant, nor the MSC members have seen this report which also does not refer directly to DME and therefore, it should not be used as a reference in this discussion.

Registrant’s representative agreed that ion channels might be influenced and some membranes affected at high concentrations, leading to possible slight and reversible effects; however, these he has considered as irrelevant for provoking any expectations for developmental neurotoxicity. He provided also further clarification on questions raised with regard to the self-classifications reported by other registrants for DME, inconsistency seen in the results of the reported teratogenicity and carcinogenicity studies, etc.

Several MSC members expressed their support or sympathy to the views expressed by the members of PfA-submitting Member States, while other MSC members supported the DD as presented by SECR. Few other members expressed their support to the SECR’s view.

Session 2 (closed)

During the MSC discussion it was acknowledged that clarification of the mechanism for narcotic effects of dimethyl ether was considered neither possible nor necessary for triggering of the DNT cohorts. However, emphasis was put on whether the narcotic effects observed were considered adverse.

SECR considered that narcosis is not a neurotoxicity finding because narcotic substances are classified as STOT SE 3 but neurotoxic substances as STOT SE 1 or 2. In this respect, the transient/ reversible nature of the effects was discussed. Furthermore, SECR explained that concerns stemming from anaesthetics cannot be considered for DME because it is not an anaesthetic substance and cannot be applied at anaesthetic concentrations as this results in lethality in test animals. Furthermore, anaesthetics for which a concern for DNT

has been hypothesised are structurally different from DME and cannot be considered as analogous substances. SECR also pointed to the difference between narcosis (drowsiness, reduced alertness, etc.) whereas anaesthesia is a state of planned unconsciousness and it is unknown whether the modes of action for narcosis and anaesthesia are linked. SECR further stressed that, according to ECHA Guidance, the adversity/ severity of the observed effects must be demonstrated to be considered as a particular concern for DNT. However, there is no evidence of association of adversity in adult animals or in developing animals for DME or an analogous substance at relevant doses/ concentrations.

Several members disagreed with this interpretation and argued that effects observed on DME itself raise a particular concern for DNT effects, further supported by data on diethylether, a close structural analogue. Furthermore they underlined that it has been shown that when reversible effects of different structurally diverse anaesthetics in adult animals have been observed, permanent adverse effects were also observed in offspring exposed during the critical period of neuronal development. It was further highlighted that narcotic effects also were observed after human exposure to DME above the substances explosion limit.

MSC did not reach a consensus conclusion on any of the above mentioned discussion points and on the amount and type of evidence needed for triggering a DNT concern leading to the inclusion of the DNT cohort into the EOGRTS design in this DD.

Members sharing the view that further investigation of potential DNT effects of DME is needed, informed the Committee that they could not agree with the DD and that they jointly had prepared a justification document for their foreseeable 'No' vote which comprises their arguments provided during the meeting discussions.

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

Seven MSC members, supported from the Norwegian member, voted against the draft decision and provided justification for their disagreement (see Section VII). Other five MSC members abstained from voting.

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

CCH-005/2017 3-p-cumenyl-2-methylpropionaldehyde (EC No. 203-161-7)

Session 1 (open)

Two representatives 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 among others two similar PfAs to ECHA's DD were submitted. The Registrant provided combined written comments on these PfAs, whereas he also expressed disappointment about the similarity. The Chairman clarified that REACH does not prohibit Member States to closely collaborate when preparing PfAs, and that such collaboration is often beneficial for all parties involved, irrespective who holds the pen on the text of the PfAs submitted.

One MSCA proposed two PfAs with regard to the classification and labelling (C&L) of the substance and requested the Registrant to apply self-classification and labelling on the registered substance for reproductive toxicity or else to provide a justification for not classifying and to shorten to 12 months (or less) the deadline for submission of this information. The PfA suggested that the Registrant's claim that the reproductive toxicity results seen in rats were irrelevant for humans could not be supported and that further evidence and details would need to be provided to justify this claim.

In his comments, the Registrant's representative indicated he did not self-classify for reproductive toxicity, arguing that the effects observed in rat are due to formation of a toxic metabolite (4-isopropyl benzoic acid) which is a proximate testicular toxicant in sensitive species, and due to significant differences in the relevant metabolic pathways between mice, rats, rabbits and humans, toxicologically significant systemic exposure to the toxic metabolite is unlikely in humans. In addition, the high margin of exposure (MoE) derived from a species with no relevance for humans did not justify classification of the registered substance for toxicity to reproduction. The Registrant's representatives further

suggested to provide additional information on these species' metabolisms that could be used to support their claim that further C&L is not needed and then, if still required, consider possible further testing in the most relevant species – rabbit.

SECR agreed that the concern for triggering the study at Annex IX would not remain if the Registrant could prove that the adverse effects seen in rats are not relevant to humans. However, additional data would be needed to support the claim that the adverse effects seen in rats are not relevant to humans and hence that Repr. 1B classification is not warranted. Some members agreed that the available evidence is not sufficient to conclude that testing on rat will be irrelevant to humans. Some further references to recent studies have been made for REG's further consideration of metabolites examined and produced in highest concentration in humans.

With regard to the EOGRTS request, a MSCA proposed to re-consider the need for the request at this point in time by either removing it or making it conditional, depending on the REG's respond to the C&L information request, or specifying the exact study design only after the receipt of the required information on 90-day sub-chronic toxicity study and on C&L.

As regards the request for sub-chronic toxicity study (90-day), an editorial PfA proposed to correct the text in the DD in order to align it with the current standard text wording when requesting sequential testing of the sub-chronic toxicity study (90-day) and the EOGRTS.

SECR agreed to parts of these PfAs and modified the DD for the meeting with regard to the 12-month deadline for the submission of the C&L information, and the current standard text wording when requesting sequential testing of the sub-chronic toxicity study (90-day) and the EOGRTS (which also deals with conditionality of the EOGRTS). The information requirement for EOGRTS, and the study design, will be re-assessed in the follow-up evaluation stage after the receipt of the currently requested information in an updated registration dossier. SECR noted that the conditions for triggering EOGRTS are met, and that considerations for dose-setting for the EOGRTS study are addressed in ECHA's guidance (R-7.6.2.3.2). The Registrants commented that he considered a two-step decision making process more appropriate as this approach would allow the Registrant to include updates from potential read-across from the EOGRTS results with a substance called Lilial (EC No. 201-289-8). However, MSC opted for the application of a consistent approach between decisions and keep the sequential testing with two deadlines for submission of additional information, since the compliance check deadline for providing the information on Lilial (by another registrant) already had passed and thus the study results could be available in 12 months.

Two other MSCAs submitted PfAs proposing to include a request for the DNT cohorts (cohort 2A and 2B) and the DIT cohort (cohort 3) since there is information on one or more endocrine disruptive (ED) mode(s) of action (MoA) of the substance, which justify the inclusion of these cohorts, if considered altogether: It was argued that effects on endocrine sensitive organs observed for the registered substance in the OECD TG 415 provided information on the substance interfering with the sex hormonal system (estrogen- and/or androgen signalling). These observations *in vivo* were combined with with the mechanistic *in vitro* study showing PXR activity. The *in vitro* PXR activity was argued to provide information on a mechanism of action which has a biologically plausible link to the observed effects on endocrine sensitive organs *in vivo*. The MSCAs further argued that clear e.g. "estrogenic" or "antiandrogenic" effect profiles cannot be expected, based on OECD validation report for TG 407 and examples from other substances such as tamoxifen and prochloraz, which also induce "blurred" *in vivo* profiles. The general information and the examples were used to illustrate that the observations *in vivo* in certain cases can provide information on interference with the sex hormonal system, i.e. indicating an ED MoA

Registrant disagreed with the inclusion arguing that the PXR assay used to justify inclusion is non-validated, non-GLP, and a non-specific *in vitro* assay. The PXR activation is an unspecific receptor-ligand effect observed at extremely high doses, and hence irrelevant. Furthermore, he argued that the effects observed in the OECD TG 415 can be explained by well-recognized biochemical MoA instead of an ED MoA.

As regards the potential inclusion of the DNT/DIT cohort in the EOGRTS design, the SECR explained that the REG has 12 months to provide requested (and other available) information and then to await in the following three months for possible ECHA's notification if new decision-making process is to be initiated, before the start of the EOGRT testing.

The MSC members from the two PfA-submitting countries expressed their disagreement with the currently requested EOGRTS design, as in their view, the "blurred *in vivo* effects profile" which could be due to multiple ED MOAs, as observed with some well-known EDs, and *in vitro* PXR results lead to their triggering based on an overall WoE. The PfA-submitting MSCA argued that even though PXR activation is not one of the classical endocrine disruptive mechanisms (like interaction with e.g. estrogen or androgen receptors), it is acknowledged as a novel important endocrine disruptive mechanism, since activation of PXR can lead to increased metabolism of steroid hormones like estrogens and androgens. Further that the *in vitro* PXR activity provides information on a mechanism of action which has a biologically plausible link to the observed effects on endocrine sensitive organs *in vivo* and that there is a clear line of information raising a particular concern for DNT and DIT.

Few members expressed their support to these PfAs; however, they also considered it appropriate to await for the result of 90-d study and the results from the EOGRTS for the structural similar substance Lillial before deciding on the design of the EOGRTS.

SECR agreed that there are adverse effects in some tissues, but expressed uncertainty with regard to the hormones involvement and toxic metabolite's MoAs.

Session 2 (closed)

In the following discussion, it was noted that DNT/DIT cohort inclusion is dependent on the 90-d study outcome and the potential additionally available information, including a read-across to Lillial study results. DNT/DIT inclusion will then be re-considered during the follow-up evaluation after the first 12 months deadline, and a new CCH decision-making process initiated if a change in the EOGRTS study design is warranted. An expert also pointed out that depending on how Registrant fulfilled the request to self-classify the substance or to justify no classification (also with a 12 month deadline) the EOGRTS may not be even triggered at this tonnage level (Annex IX).

A member also noted that although this approach could lead to some additional delay in a decision on the EOGRTS design it is acceptable to her MSCA, which considers this substance for potential CoRAP inclusion in 2022, depending on the results from the current decision-making.

MSC agreed unanimously to the DD as modified at the meeting. The Danish and Dutch members abstained from voting due to their disagreement with the approach chosen, as they consider available information sufficient to decide on the EOGRTS design and the inclusion of DNT and DIT cohorts already in this decision.

CCH-019/2017 Fatty acids, C16-18, compds. with C16-18-alkyl amines (List No. 800-984-9)

Session 1 (open)

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

SECR first summarised ECHA's DD, which comprised 17 requests and assessment of the read across approach suggested by the Registrant. It then explained that four PfAs to ECHA's DD had been submitted, two of which were discussed in the meeting and are outlined below.

The first PfA considered the proposed category read across with 8 substances acceptable. Since studies had been performed with a source substance with the highest level of saturation, the PfA suggested deleting several requests, the remaining ones being necessary if the identity of the registered substance was proven to have more than one double bond in the alkyl amines. A sub-chronic toxicity (90-day) study and bioaccumulation studies should still be requested.

The second PfA on biodegradation suggested deleting the alternatives of OECD testing guideline (TG) 301 on ready biodegradability, i.e. OECD TG 301A and OECD TG 301E, which analyse the dissolved organic carbon (DOC) dissipation in the test solution. It reasoned that using such DOC tests would overestimate the degradation potential due to the high adsorption potential of the test substance.

SECR had modified the DD based on the two above-mentioned PfAs and further modified the DD in advance of the meeting after receiving Registrant's comments on PfAs. The tentative amendments were thus included in the DD document submitted to the meeting.

The representatives of the Registrant confirmed their agreement with the first PfA, except for keeping requests for some studies. The Registrant had compiled in his written comments prior to the meeting further documentation to support the read across. The representatives of the Registrant pointed out that the read across category already included studies on aquatic effects, which would be sufficient to waive the long-term fish study. In particular, the Registrant claimed that the toxic fraction of the substance was not poorly soluble (CMC=36 mg/L) and that a short-term toxicity test on fish was already available, indicating no higher toxicity for fish than invertebrates or algae.

As for the second PfA, the representatives of the Registrant confirmed their agreement with it. They were of further view that also the ready biodegradability study (OECD TG 301) would not be necessary, as there were two available biodegradability studies for a source substance in the group of substances.

SECR clarified that after receiving the PfAs and comments from the Registrant on them the read across was considered plausible. The tentative amendments in the DD would result in requesting only studies on long-term toxicity to fish and toxicity to soil micro-organisms, because no information was available in the dossier and waivers deemed not acceptable.

A MSC member noted that the read across hypothesis does not include a justification on how the observed NOAEL from the available 28-day screening study can be used, with the application of an appropriate assessment factor, to extrapolate towards a DNEL for a 90 - day study. Possibly it would be needed to test a category member in a 90-day study as a worst-case source substance.

Another MSC member raised concern that the Registrant had made tests in river water, making it difficult to interpret the results. This is due to unknown adsorption processes, and any organic matter would significantly reduce concentrations in test media as well as toxicity. Thus, the Registrant should consider re-testing under proper conditions following the OECD TG.

The representatives of the Registrant responded, firstly, that use of existing short-term testing combined with STOT RE and results from most sensitive category member as source substance would provide a waiver to the 90-day study. Secondly, they claimed that the substance, being very adsorbing, is technically difficult to test for aquatic toxicity. Therefore, the Registrant had chosen to use river water as it occurs in the wild with suspended matter. In addition, for classification they had employed an additional (application/safety) factor of 10.

Session 2 (closed)

SECR first summarised views presented on the DNEL derivation, based on the category and using most sensitive category member as source substance. It considered that available studies and read across approach could be sufficient to waive the 90-day study. In particular, short-term testing has been done with category member substances being equally or more toxic than the registered substance.

SECR then drew attention to the testing in river water, containing SPM, where the Registrant deemed acceptable to apply a correction factor to attain nominal concentration information for the risk assessment. It considered the low or unquantifiable recovery rates in available studies. A MSC member considered it was difficult to conclude the value or validity of available results for the risk assessment. Another MSC member argued that testing could be done on selected, most reactive member substance(s) within the claimed category and suggested by the consortium.

MSC concluded that for this substance (but not necessarily all substances in the category as proposed by the Registrant) the read across was deemed to provide sufficient studies for most of the originally requested endpoints and, based on this, to remove selected requests from the draft decision. It decided to keep the request for the long-term toxicity testing on fish (OECD TG 210), while noting that this test may provide further information to support the interpretation of available category member data on algae and *Daphnia*. MSC also decided to keep requesting the description of the analytical methods, water solubility and effects on soil micro-organisms carbon transformation test. In addition, MSC modified the deadline from 30 months to 12 months, for providing and submitting the requested information in a dossier update.

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

TPE-006/2017 Cobalt dichloride (EC No. 231-589-4)

Session 1 (open)

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

SECR explained that one PfA to ECHA's DD was submitted on pre-natal developmental toxicity study (PNDT) in a second species. It requested stating that (a) acceptability of read-across for other cobalt substances has to be discussed case-by-case, and (b) the study does not automatically preclude the necessity to conduct a PNDT study in a second species for other cobalt substances, if not sufficiently justified for that particular case or substance. In addition, SECR presented the overall REACH regulatory context on cobalt substances by outlining the other REACH processes where cobalt substances are, or have been, discussed.

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

The representatives of the Registrant confirmed their written comments agreeing with the PfA and ECHA's interpretation of the read across approach. They explained that the carboxylates group of cobalt substances was not included in the read-across, as they have different toxicity profile via oral route due to gastric irritation at doses lower than those generating systemic toxicity. They also concurred that there were no agreed methods to assess dissolution of cobalt substances in aqueous media; however, they considered that potentially useful methods were used in discussions with regulatory bodies for nickel and lead substances for restriction cases. They expressed their view that bioaccumulation was a useful way to understand dissolution.

A stakeholder representative welcomed the read-across approach for cobalt substances but asked for clarification regarding classification as there were some substances in the group that were not classified as CMR. SECR informed that the cobalt group comprised 28 substances, of which five have harmonised classification which include *Carc. 1B*; *Muta. 2* and *Repro. 1B* (fertility).

Session 2 (closed)

An expert to a MSC member clarified the PfA submitted and suggested to amend the draft decision to reflect that in the dossier data on human health is rated with a non-assignable reliability. MSC also considered that under the current hypotheses toxicity is governed by the cobalt ion and bioavailability of cobalt correlates with the release of cobalt in the gastric environment; therefore, cobalt dichloride could in this context, be considered an appropriate candidate to perform a PNDT study. MSC further concluded that there might be additional effects which should be considered in the hazard identification, depending on the nature of the counter ion and further factors eventually influencing absorption/toxicity (e.g. role of transporters, nutritional state, and feedback mechanisms). A MSC member reminded that substances in this category need to follow the agreed strategy. MSC concluded to have the considerations above included in the DD.

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

d. Decision making process - General topics

- **Update to MSC working procedures on evaluation**

Please see under item 6d

- **Appeals update (partly closed session)**

See under 6.2.d.

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

- **Introduction of the preliminary prioritisation results in preparation for the 9th draft recommendation**

SECR presented to MSC the outcome of its preliminary work in preparation for the 9th draft recommendation for inclusion of priority substances in Annex XIV. Five substances added to the Candidate List in the last two SVHC identification rounds (June 2016 and January 2017) have been preliminary assessed with regard to their priority for recommending them for inclusion in Annex XIV. These five substances with their respective preliminary priority scores were added to the prioritisation assessment table which includes all other substances with a prior addition to the Candidate List not yet recommended. The main aim was to give an early view on how the newly added substances rank among the other Candidate List substances but also to signal to industry that – if needed - registrations should be updated. Some first observations on those results were shared, however, it was noted that MSC will discuss this topic again in a year’s time. At that time any updates of the dossiers received until the end of 2017 will be assessed by SECR. MSC was also reminded that its actual work on the MSC opinion on the 9th draft recommendation for priority substances will start only once the 8th recommendation has been finalised and submitted to the Commission.

As SECR had indicated that letters to some registrants will be sent in order to clarify intermediate status of their substances, an industry observer was wondering if such letters had been used previously in the context of prioritisation work. In responding SECR highlighted the importance of having intermediate status clarified as early as possible, and that this is indeed not the first time. A further question was raised whether SVHCs identified in June 2017 will also be included into the prioritisation assessment. SECR clarified that a small time gap has been introduced between SVHC identification and prioritisation assessment, to allow for dossier updates, and hence substances added to the Candidate List by January 2017 are the last ones to be included for the assessment in the 9th round of prioritisation. Another NGO observer inquired how the prioritisation will work for substances that are causing effects in the environment, which may not score high in the assessment, but which have RMOAs suggesting a need for further regulatory action. In responding SECR explained that RMOAs are not discussed in MSC but nothing prevents MS’s to consider other risk management options if risks are expected.

Item 9 – SVHC identification

- **Status report on SVHC identification proposals of four phthalates referred to COM**

- **Envisaged updates in the candidate list**

The MSC observer from the Commission informed MSC about the recent REACH Committee decisions on the SVHC identification proposals of DEHP, BBP, DBP and DIBP under Article 57 (f) due to their endocrine disruptive (ED) effects to human health and the further actions to be undertaken in this regard. As MSC did not reach unanimous agreement on the additional SVHC identification of these substances in December 2014, the MSC opinions, minority positions and other supporting documentation were referred to the Commission in the beginning of 2015 for further decision making. MSC was informed that in these cases, the Commission’s proposal to additionally identify DEHP, BBP, DBP and DIBP as SVHCs due to their probable adverse ED effects to human health was supported by qualified majority of the REACH Committee. The final decision is expected to be published in the Official Journal in the following weeks. Consequently, the Commission will inform ECHA about the outcome of these SVHC identification proposals and the existing

Annex IV list entries for DEHP, BBP, DBP and DIBP will be updated accordingly in due course.

SECR informed MSC about the forthcoming updates in the Candidate list (CL), possibly already in May as a follow-up action of the above-mentioned COM decision on the four phthalates, including the revised terminology for all Article 57(f) cases, and in June for those cases receiving unanimous agreement during MSC-54. In case the COM decision on the four phthalates does not become available in sufficient time in May, then the items mentioned above for the possible May update will be combined with the June update of the Candidate List.

Item 10 – Any other business

• Meeting dates of 2018

SECR informed MSC about meeting dates for the 5 plenary meetings in 2018.

Concern was raised about June meeting dates due to overlap of another international meeting but SECR explained that many factors went into consideration including availability of facilities and support functions, as well as the sequence of legal deadlines in advance of these meetings. Hence it was not possible to reconsider the meeting dates.

A stakeholder observer requested some elaboration for having only one meeting during autumn (in October, whereas previously in September and October). The Chairman explained that few if any substance evaluation cases had been submitted for the September meetings and therefore these meetings had been relatively short, and that the aim is to spread out all evaluation cases more evenly across meetings.

Tentative meeting dates for 2018 are 5-9 February, 23-27 April, 11-15 June, 8-12 October and 10-14 December.

• Presentation on disseminated substance total tonnage band – an introduction

SECR introduced the principles of reporting the total tonnage band for disseminated substances. The aim is to provide a meaningful indication of the approximate volume of the substance that the general public would be exposed to based on latest available, non-confidential data. At the substance level all eligible dossiers according to REACH are considered. In the tonnage band calculation the sum of manufactured and imported tonnages are included minus directly exported and intermediate use tonnages.

It was asked whether there will be a need to split the lowest total tonnage band to better reflect nanomaterials volumes. SECR explained that it will be included in the registered dossier if the substance was produced as nanomaterial but it does not foresee that specific tonnage bands will be disseminated.

• Status update on ad-hoc scoping group on UVCBs

The Dutch alternate member informed MSC of an ad-hoc scoping group meeting on UVCBs that will take place immediately after the plenary meeting, in line with the action point from MSC-52. The aim is to discuss and identify the most crucial aspects on testing of UVCBs. The possible approaches in hazard and risk assessment will be considered and as an outcome a potential path forward will be presented in MSC-54.

• Brief report from Workshop on the implementation of the ECHA integrated regulatory strategy (28 February-1 March 2017)

SECR presented a report on the main topics discussed in the workshop.

MSC was informed that the report on the workshop outcome will be published on May 22 (tentative date).

• ECHA Interact – update on the progress of a project on improvement of collaboration between ECHA and external actors

SECR presented the progress on ECHA Interact project which was introduced in MSC-50. Different work packages for this year were highlighted. Tools will be developed to make ECHA's document management system available for external users to simplify work collaboration. The idea is that access to relevant information and functionalities will be

provided according to user needs. IT security-related concerns are taken into consideration and currently in discussion. Further updates on the progress will be shared at a later stage.

- **Suggestions from members**

No suggestions have been received by members under this agenda item.

Item 11– Adoption of conclusions and action points

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

II. List of attendees

Members/Alternate members	ECHA staff
ALMEIDA, Inês (PT)	AJAO, Charmaine
ANDRIJEWSKI, Michal (PL)	ANDERSSON, Niklas
COCKSHOTT, Amanda (UK)	BELL, David
COPOIU, Oana (RO)	BERCARU, Ofelia
COSGRAVE, Majella (IE)	BICHLMAIER, Ingo
DE KNECHT, Joop (NL)	BONNOMET, Vincent
DEIM, Szilvia (HU)	BRAUNSCHWEILER, Hannu
DUNAUSKIENE, Lina (LT)	BRENNAN, Eoin
FINDENEGG, Helene (DE)	BROERE, William
FRANZ, Michel (FR)	CARTON DE TOURNAI, Laure-Anne
GYMANOU, Panagiotis (CY)	DE WOLF, Watze
HORSKA, Alexandra (SK)	DELOFF-BIALEK, Anna
HUMAR-JURIC, Tatjana (SI)	DREVE, Simina
JANTONE, Anta (LV)	HERBATSCHEK, Nicolas
KOUTSODIMOU, Aglaia (EL)	HUUSKONEN, Hannele
KREKOVIĆ, Dubravka (HR)	JAAGUS, Triin
KULHANKOVA, Pavlína (CZ)	JOHANSSON, Matti
LONDESBOROUGH, Susan (FI)	KARHU, Elina
LUNDBERGH, Ivar (SE)	KREUZER, Paul
LØFSTEDT, Magnus (DK)	LEPPÄRANTA, Outi
MARTÍN, Esther (ES)	NAUR, Liina
PISTOLESE, Pietro (IT)	O'FARRELL, Norah
REIERSON, Linda (NO)	RÖNTY, Kaisu
STESSEL, Helmut (AT)	SOSNOWSKI, Piotr
VANDERSTEEN, Kelly (BE)	STILGENBAUER, Eric
VESKIMÄE, Enda (EE)	THUVANDER, Ann
WAGENER, Alex (LU)	TRNKA, Jan Peter
Representatives of the Commission	VAHTERISTO, Liisa
KOBE, Andrej (DG ENV)	VASILEVA, Katya
Observers	WALKER, Lee
ANNYS, Erwin (Cefic)	
DROHMANN, Dieter (ORO)	
HÖK, Frida (ChemSec)	
LOONEN, Helene (EEB)	
TAYLOR, Katy (ECEAE)	
WAETERSCHOOT, Hugo (Eurometaux)	

Proxies

- KULHANKOVA, Pavlina (CZ) also acting as proxy of DIMCHEVA, Tsvetanka (BG)
- PISTOLESE, Pietro (IT) also acting as proxy of BORG, Ingrid (MT)
- FINDENEGG, Helene also acting as proxy of DUNAUSKIENE, Lina (LT) for short periods during the meeting
- LONDESBOROUGH, Susan (FI) also acting as proxy of COCKSHOTT, Amanda (UK) on 26 April from 13:30 onwards
- STESSEL, Helmut (AT) also acting as proxy of KULANKOVA, Pavlina (CZ) on 26 April from 14:30 onwards

Experts and advisers to MSC members

- ATTIAS, Leonello (IT) (expert to PISTOLESE, Pietro)
- BARTHELEMY BERNERON, Johanna (FR) (expert to FRANZ, Michel)
- DANIHELOVA, Martina (SK) (expert to HORSKA, Alexandra)
- GRINCEVICIUTE, Otilija (LT) (expert to DUNAUSKIENE, Lina)
- HOLMER, Marie Louise (DK) (expert to LØFSTEDT, Magnus)
- INDANS, Ian (UK) (expert to COCKSHOTT, Amanda)

KOZMIKOVA, Jana (CZ) (expert to KULHANKOVA, Pavlina)
LE, Elisa (FR) (adviser to FRANZ, Michel)
MALKIEWICZ, Katarzyna (SE) (expert to LUNDBERGH, Ivar)
RISSANEN, Eeva (FI) (adviser to LONDESBOROUGH, Susan)
ROSENTHAL, Esther (DE) (expert to FINDENEGG, Helene)
TOBIASSEN, Lea Stine (DK) (adviser to LØFSTEDT, Magnus)
ZELJEZIC, Davor (HR) (expert to KREKOVIĆ, Dubravka)

Case owners:

Representatives of the Registrants were attending under the agenda item 7b for TPE-006/2017, CCH-003/2017, CCH-005/2017 and CCH-019/2017.

Apologies:

BORG, Ingrid (MT)
CONWAY, Louise (IE)
DIMCHEVA, Tsvetanka (BG)
MIHALCEA UDREA, Mariana (RO)
PALEOMILITOU, Maria (CY)
TYLE, Henrik (DK)
WIJMENGA, Jan (NL)

III. Final Agenda



MSC/A/053/2017

Agenda

53rd meeting of the Member State Committee

25-26 April 2017
ECHA Conference Centre
Annankatu 18, in Helsinki, Finland

25 April: starts at 9 am
26 April: ends at 3:30 pm

Item 1 – Welcome and Apologies

Item 2 – Adoption of the Agenda

MSC/A/053/2017
For adoption

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

Item 4 – Administrative issues

- Outlook for MSC-54

For information

Item 5 – Minutes of the MSC-52

- Draft minutes of MSC-52

MSC/M/52/2017
For adoption

Item 6 – Substance evaluation - Decision making process

Closed session for 6c, partly closed session for 6d

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

ECHA/MS-53/2017/004
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*):**

For discussion followed by agreement seeking under 6c:

MSC code	Substance name	EC No.
<i>none</i>		

For discussion

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

A case returned from written procedure for agreement seeking in the meeting

SEV-UK-034/2015	A reaction mass of: O,O-di(1-methylethyl)trithio-bis-thioformate; O,O-di(1-methylethyl)tetrathio-bis-thioformate; O,O-di(1-methylethyl)pentathio- bis-thioformate	403-030-6 ECHA/MSC-53/2017/015
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For agreement

d. General topics

- Update to MSC working procedures on evaluation

ECHA/MSC-53/2017/009

For adoption

- Appeals update¹

For information

Item 7 – Dossier evaluation

Day 1 for item 7b

Closed session for 7c, partly closed session for 7d

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

ECHA/MSC-53/2017/002

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-53/2017/003

For discussion followed by agreement seeking under 7c:

Compliance checks

MSC code	Substance name	EC No. / Doc.
CCH-003/2017	Dimethyl ether	204-065-8 ECHA/MSC-53/2017/005-006
CCH-005/2017	3-p-cumenyl-2-methylpropionaldehyde	203-161-7 ECHA/MSC-53/2017/007-008
CCH-019/2017	Fatty acids, C16-18, compds. with C16-18-alkyl amines	800-984-9 ECHA/MSC-53/2017/011-012

Testing proposal examinations

MSC code	Substance name	EC No.
TPE-006/2017	Cobalt dichloride	231-589-4 ECHA/MSC-53/2017/013-014

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

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

Cases as listed above under **7b**

For agreement

d. Decision making process - General topics

- Update to MSC working procedures on evaluation

ECHA/MSC-53/2017/009

For adoption

- Appeals update¹

For information

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

- Introduction of the preliminary prioritisation results in preparation for the 9th draft recommendation

ECHA/MSC-53/2017/010

For information

Item 9 – SVHC identification

- Status report on SVHC identification proposals of four phthalates referred to COM
- Envisaged updates in the candidate list

For information

Item 10 – Any other business

- Meeting dates of 2018
- Presentation on disseminated substance total tonnage band – an introduction
- Status update on ad-hoc scoping group on UVCBs
- Brief report from Workshop on the implementation of the ECHA integrated regulatory strategy (28 February-1 March 2017)
- ECHA Interact – update on the progress of a project on improvement of collaboration between ECHA and external actors
- Suggestions from members

ECHA/MSC-53/2017/001

For information

Item 11 – Adoption of main conclusions and action points

- Table with conclusions and action points from MSC-53

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/2017/008)

IV. Main Conclusions and Action Points



Main conclusions and action points MSC-53, 25-26 April 2017 (adopted at MSC-53)

CONCLUSIONS / DECISIONS / MINORITY OPINIONS	ACTIONS REQUESTED
Item 5 – Minutes of the MSC-52	
MSC adopted the draft minutes as modified at the meeting.	MSC-S to upload final version of the minutes on MSC S-CIRCABC by 28 April 2017 and on ECHA website without undue delay.
Item 6 - 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.
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-UK-034/2015 A reaction mass of: O,O-di(1-methylethyl)trithio-bis-thioformate;O,O-di(1-methylethyl)tetrathio-bis-thioformate;O,O-di(1-methylethyl)pentathio- bis-thioformate (EC No. 403-030-6)	MSC-S to upload on MSC S-CIRCABC the final ECHA decision of the agreed case.
d. General topics	
<ul style="list-style-type: none"> Update to MSC working procedures on evaluation 	
MSC agreed to the suggested changes to the working procedures for dossier and substance evaluation, and agreed these are applicable for the MSC meeting rounds in 2018 (first time for MSC-59).	MSC-S to upload the revised working procedures to S-CIRCABC by 5 May 2017. MSC-S to upload the revised working procedures to ECHA's website in early Jan 2018.
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 a testing proposal examination and a compliance check when amendments were proposed by MS-CA's (Session 2, closed)	
MSC reached unanimous agreement on the following ECHA draft decisions (as modified in the meeting): Compliance checks	MSC-S to upload on MSC S-CIRCABC the final ECHA decisions of the agreed cases.

CONCLUSIONS / DECISIONS / MINORITY OPINIONS	ACTIONS REQUESTED
<p>CCH-005/2017 3-p-cumenyl-2-methylpropionaldehyde (EC No. 203-161-7)</p> <p>CCH-019/2017 Fatty acids, C16-18, compds. With C16-18-alkyl amines (EC No. 800-984-9)</p> <p>Testing proposal examinations</p> <p>TPE-006/2017 Cobalt dichloride (EC No. 231-589-4)</p>	
<p>MSC could not reach unanimous agreement on the following draft decision, as submitted to the meeting:</p> <p>CCH-003/2017 Dimethyl ether (EC No. 204-065-8)</p>	<p>MSC members who voted against the draft decision to provide their finalised justification(s) in writing to the MSC-S by 2 May 2017; otherwise, the draft justification(s) as provided at the time of the vote will be considered as the final justification.</p> <p>MSC-S to refer the decision to the Commission for further decision making, without undue delay once minutes of MSC-53 are agreed.</p>
<p>d. Decision making process - General topics</p> <ul style="list-style-type: none"> Update to MSC working procedures on evaluation 	
<p>See under 6d</p>	
<p>Item 10 – Any other business</p>	
<p>MSC took note of the delay in submission of the slides on the status update on Guidance developments (information document).</p>	<p>MSC-S to upload the slides on MSC S-CIRCABC by 27 April 2017.</p> <p>MSC to send any comment on the format of the update to the MSC Functional Mailbox by 12 May 2017.</p>
<p>Item 11– Adoption of main conclusions and action points</p>	
<p>MSC adopted the main conclusions and action points of MSC-53 at the meeting.</p>	<p>MSC-S to upload the main conclusions and action points on MSC S-CIRCABC by 27 April 2017.</p>

V. Substance evaluation cases agreed by MSC in written procedure (WP) in advance of the meeting:

MSC ID number	Substance name used in draft decision	EC/List number
SEV-DK-015/2014	1,2-benzenedicarboxylic acid, benzyl C7-9-branched and linear alkyl esters	271-082-5
SEV-DK-015/2015	Reaction product: bisphenol-A-(epichlorhydrin); epoxy resin (average molecular weight \leq 700)	500-033-5
SEV-NO-030/2015	Bis(α,α -dimethylbenzyl) peroxide	201-279-3

VI. Dossier evaluation cases agreed by MSC in the written procedure (WP) in advance of the meeting:

Compliance checks (CCH)

MSC ID number	Substance name used in draft decision	EC or List number
CCH-007/2017	Octene, hydroformylation products, low-boiling	273-110-1
CCH-008/2017	2-ethylhexyl 10-ethyl-4-[[2-[(2-ethylhexyl)oxy]-2-oxoethyl]thio]-4-octyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate	248-227-6
CCH-009/2017	1,1,1,3,5,5,5-heptamethyltrisiloxane	217-496-1
CCH-010/2017	bis(nonylphenyl)amine	253-249-4
CCH-011/2017	reaction mass of (1S,1'R)-2-[1-(3',3'-dimethyl-1'-cyclohexyl) ethoxy] [...]propanoate	604-250-7

Testing proposal examinations (TPE)

MSC ID number	Substance name used in draft decision	EC or List number
TPE-003/2017	2-ethylhexyl 10-ethyl-4-[[2-[(2-ethylhexyl)oxy]-2-oxoethyl]thio]-4-octyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate	248-227-6
TPE-008/2017	Phenol, isopropylated, phosphate (3:1)	273-066-3

VII. Statements as regards agenda item 7

Justification for voting against ECHA draft decision on CCH-003/2017 for Dimethyl ether, EC No. 204-065-8, CAS No. 115-10-6

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

The members of the Member State Committee (MSC) for the countries named above did not for the reasons set out below agree with the draft decision from ECHA on dimethyl ether, EC nr. 204-065-8, CAS nr. 115-10-6 (CCH-003/2017),

Dimethyl ether is registered under REACH in the tonnage band more than 1000 tonnes per year per manufacturer. 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, inhalation route are proposed to be requested. As regards EOGRTS, the basic configuration without extension of cohort 1B to produce the F2 generation is proposed to be requested.

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

Justification for particular concern for developmental neurotoxicity (DNT):

Substance specific information concerning narcotic effects of dimethyl ether:

The registered substance is a gas, and has been shown to induce narcotic effect in rats and in humans.

In a rat 2 weeks whole body inhalation study with exposure to 0%, 1% and 5% of dimethyl ether, 6 hrs/day, 5 days/week, sluggishness for a short time post exposure was observed in the 1% exposure group, whereas a narcotic/"borderline anaesthetic" effect (uncoordinated and unresponsive to loud noises) was observed in the 5% exposure group (Short-term repeated dose inhalation toxicity study, ECHA registration dossier).

In a rat OECD TG 414 whole body inhalation study with exposure to 0, 1250, 5000, 20000 and 40000 ppm (app. 0%, 0.125%, 0.5%, 2% and 4%) of dimethyl ether, days 6-15 of gestation, 6 hours daily, dams exposed to 40000 ppm showed no response to sound stimulus during exposure and gained significantly less weight during the early exposure period than did the control dams. In the dams exposed to 20000 ppm, there was a slight decrease in response to sound, whereas the response in the 5000 ppm group was equivocal (OECD TG 414, ECHA registration dossier). It should be noted that the decrease in responsiveness to sound was used to derive the NOAEL for maternal toxicity in this study (concluded to be 1250ppm by the authors) and is thus considered adverse.

Further, in a human exposure study reported at the TOXNET, HSDB, narcotic effects was also observed after exposure to dimethyl ether. Human subjects were exposed to 50.000, 75.000, 82.000, 100.000, 144.000 and 200.000 ppm (5%, 7.5%, 8.2%, 10%, 14.4% and 20%) for approximately 60 minutes. The number of subjects in each group is not reported. The observed effects ranged from feelings of mild intoxication and slight lack of attention at the lowest exposure levels (50.000 and 75.000 ppm). At 82.000 ppm, some incoordination was observed, and a complaint was made of indistinct vision. At 100.000 ppm, distinct signs of incoordination developed after 21 minutes of exposure. After 64 minutes, balancing of the head required a special effort, estimation of time was lost, simple multiplication and memory was affected. At 144.000 ppm, the subject lost consciousness after 26 minutes. Inhalation of 200.000 ppm caused unconsciousness in 17 minutes (TOXNET, HSDB, only summary available). It cannot be excluded that the effects observed in this study could also occur at lower concentrations, especially if humans are exposed to dimethyl ether for a longer duration.

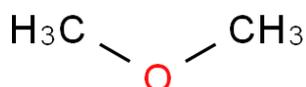
Substance specific information concerning sedative/narcotic effects of diethyl ether (structural analogue of dimethyl ether):

The effects observed on dimethyl ether itself raise a particular concern for DNT effects and justify the inclusion of the DNT cohort in the requested EOGRTS.

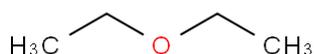
However, this is further supported by data on diethyl ether, CAS no. 60-29-7, which is a close structural analogue of the same congeneric series. Diethyl ether also induces sedative /narcotic effects, and has previously been used as an anaesthetic (Zardooz et al., 2010, Glowa 1993).

The two substances are close structural analogues:

Dimethyl ether (CAS no.115-10-6) (Registered substance):



Diethyl ether (CAS no. 60-29-7) (Analogue):



Both substances are gasses with very high vapour pressures (513300 Pa for dimethyl ether and 71860 Pa for diethyl ether, according to the Danish QSAR database²). The logKow of dimethyl ether (0.1, experimental, according to the Danish QSAR database) is lower than the logKow for diethyl ether (0.89, experimental, according to the Danish QSAR database). Further, they both induce sedative/narcotic effects, with diethyl ether even have been used as an anaesthetic agent.

Like other anaesthetics dimethyl (and diethyl) ether are expected to interact with membrane lipids and hydrofobic regions of specific membrane-bound proteins affecting the neuronal function (NEG and NIOSH, 1993). In addition, the NEG and NIOSH report from 1993 concludes that long term exposure to low concentrations of diethyl ether in the air may give symptoms on the central nervous system (CNS). Symptoms that have been reported are sleepiness, dizziness, irritability, headache and psychic disturbances (NEG and NIOSH, 1993).

Narcotic effects (of dimethyl ether and diethyl ether) justify the concern for Developmental neurotoxicity (DNT):

We noted that the proposal without DNT as submitted to MSC in the draft decision has been based on ECHA's considerations that narcotic effects reported for dimethyl ether (and in general) are reversible, non-specific and occur at high doses, and for those reasons do not justify the concern for DNT. In our view those factors do not in this particular case remove the concerns for DNT. It has been shown that when reversible effects of different structurally diverse anaesthetics in adult animals have been observed, permanent adverse effects were also observed in off spring exposed during the critical period of neuronal development (e.g. Zou et al 2011, Kang et al. 2016 and other review papers). Concerning the mechanisms of action for substances causing narcotic effects it can be reasonably assumed that "specific" disruption of some function of receptors in the membrane lipid bi-layers (including GABA and NMDA) occur as a consequence of and in parallel with the "non-specific" diffusion into and disruption of bi-layer lipid cell membranes.

This is in line with the report provided by ECHA "Scientific review on the link between the narcotic effects of solvents and (developmental) neurotoxicity" and other references, e.g. Martin et al. 1995, which show that diethyl ether and other structurally diverse substances used for anaesthesia disrupt glutamatergic neurotransmission through an action at NMDA receptors and Huidobro-Toro et al. 1987, which show that Diethyl ether potentiate GABA-dependent chloride flux. Interactions with GABA and NMDA receptors are recognised as molecular initiating events in accepted adverse outcome pathways for development of DNT (OECD 2016).

During the MSC discussion we noted that it was acknowledged that clarification of the mechanism for narcotic effects of dimethyl ether was considered neither possible nor necessary for triggering of the DNT cohorts. However, emphasis was put on whether the narcotic effects observed were considered adverse.

In general narcotic effects (including central nervous system depression, drowsiness, narcosis, reduced alertness, loss of reflexes, lack of coordination, vertigo, headache (from observation in humans) or lethargy, lack of coordination, ataxia, loss of righting reflex (in tested animals) are the criteria to classify the hazardous property as STOT SE according to CLP. If the effects are transient STOT SE Cat 3 applies, if the effects are not transient STOT SE Cat 1 or 2 should be considered. Therefore, in our view narcotic effects as other neurotoxic effects are considered adverse and by default meet the criteria for triggering of DNT according to REACH. This is further supported by the specific mentioning of narcotic effects as an example of substance specific findings raising a particular concern that can be used to trigger the DNT cohorts in the ECHA guidance R.7.a (see below).

This is further justified because dimethyl ether has a very high vapour pressure (see above) and hence an intrinsic property related to a high exposure potential via inhalation

Furthermore we noted that the registrant considers that due to explosive properties of dimethyl ether, investigation of DNT effects is technically not possible at doses causing narcotic effects. According to the registrant, the highest dose to be tested is 1.65% (50% of Lower Explosive Limit) and the lowest concentration causing narcotic effects is 5%. However we observe that slight narcotic effects were reported around 1.65%; i.e. sluggishness at 1% in a 14-day repeated dose toxicity study, and slight decrease in response to sound in the dams exposed to 20000 ppm/2%, whereas the response in the 5000 ppm/0.5% group was reported as equivocal in the PNDT study.

Based on the above, the triggers to include the DNT 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 proportional to the concern and respecting animal welfare considerations. It is in this regard noted that inclusion of the investigations of the DNT cohorts do not increase the number of animals included in the requested EOGRTS.

REACH standard information requirements:

The triggers relevant for the inclusion of the DNT cohorts 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) (...) may be required by the Agency in accordance with Article 40 or 41, in case of particular concerns on (developmental) neurotoxicity (...) justified by (...)

- existing information on the substance itself derived from relevant available in vivo or non-animal approaches (e.g. abnormalities of the CNS, evidence of adverse effects on the nervous (...) system in studies on adult animals or animals exposed prenatally), or

-..., or

- existing information on effects caused by substances structurally analogous to the substance being studied, suggesting such effects or mechanisms/modes of action".

ECHA guidance:

According to the ECHA guidance (R.7.a, 2016), narcosis is an example of substance specific findings which may indicate a particular concern justifying inclusion of the

developmental neurotoxicity cohorts (p. 412 on inclusion of Cohorts 2A and 2B): "REACH specifies that an extended one-generation reproductive toxicity study including Cohorts 2A and 2B (developmental neurotoxicity cohorts) shall be proposed by the registrant or may be required by ECHA if a particular concern on (developmental) neurotoxicity".

And further on p.413 under "Examples of substance specific findings which may indicate a particular concern justifying inclusion of the developmental neurotoxicity cohort": "any signs of behavioral or functional adverse effects on the nervous system in adult studies e.g. repeated-dose and acute toxicity studies and neurotoxicity studies, not likely to be secondary to general toxicity.

- clinical and/or behavioral signs (such as abnormal gait, narcosis, seizures or any other altered activity) if seen in absence of general toxicity"

Animal welfare considerations:

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

References:

Danish QSAR database: <http://qsar.db.food.dtu.dk/db/index.html>

ECHA Registration dossier: <https://echa.europa.eu/da/registration-dossier/-/registered-dossier/15974/7/6/3/?documentUUID=b45ff5e7-cf66-4fa4-a44c-b67951618588>

Glowa 1993, Behavioral and neuroendocrine effects of diethyl ether exposure in the mouse, *Neurotoxicology and teratology*, vol.15, pp.215-221, 1993.

Huidobro-Toro et al. 1987, Neurochemical Actions of Anesthetic Drugs on the γ -Aminobutyric Acid Receptor-Chloride Channel Complex, *The Journal of pharmacology and experimental therapeutics*, Vol. 242, No. 3

Kang et al. 2016. Neurogenesis and developmental anesthetic neurotoxicity. *Neurotoxicol Teratol.* 2016 Oct 14.

Martin et al. 1995. Volatile anesthetics and glutamate activation of N-methyl-D-aspartate receptors *Biochemical Pharmacology*, Vol. 49, No. 6, pp. 809-817, 1995.

NEG and NIOSH, 1993, NEG and NIOSH, Basis for an Occupational Health Standard for Ethyl Ether. p.14. *Arbete och Halsa* 30 (2002) Available from, as of October 31, 2007: <https://www.cdc.gov/niosh/docs/93-103/pdfs/93-103.pdf>

OECD 2016: Annex 1, REPORT OF THE OECD/EFSA WORKSHOP ON DEVELOPMENTAL NEUROTOXICITY (DNT): THE USE OF NON-ANIMAL TEST METHODS FOR REGULATORY PURPOSES, ENV/JM/WRPR(2016)87/ANN1,

TOXNET, HSDB, only summary available: <https://toxnet.nlm.nih.gov/cgi-bin/sis/search/a?dbs+hsdb:@term+@DOCNO+354>

Zardooz et al., 2010. Plasma corticosterone, insulin and glucose changes induced by brief exposure to isoflurane, diethyl ether and CO₂ in male rats, *Physiol. Res.* 59. 973-978, 2010.

Zou et al 2011. Inhalation anesthetic-induced neuronal damage in the developing rhesus monkey *Neurotoxicol Teratol.* 2011 Sep-Oct;33(5):592-7.