RAC/M/41/2017
Final
12 September 2017

Minutes of the 41st Meeting of the Committee for Risk Assessment (RAC 41)

29 May starting at 09.00
2 June suspended at 12.30
8 June resumed at 9.00
9 June ended at 13.00

Part I Summary Record of the Proceedings

1. Welcome and apologies

The Chairman, Tim Bowmer, welcomed all the participants to the 41st meeting of the Committee for Risk Assessment (RAC 41). Apologies were received from three Members.

The participants were informed that the meeting would be recorded solely for the purpose of writing the minutes and that this recording would be destroyed once no longer needed. He added that the recordings from the 40th meeting had already been destroyed. The Chairman noted that the minutes would be published on the ECHA website and would include a full list of participants as given in Part III of these minutes.

2. Adoption of the Agenda

The Chairman reviewed the agenda for the meeting (RAC/A/41/2017), informing RAC that agenda item 10.2b.3 (EDC_Olon) has been withdrawn and postponed to the next meeting. The Committee agreed that the following item proposed by the Secretariat could be added to the agenda:

a) A short report from the authorisation Rapporteurs' workshop held on the evening of 30 May

The agenda and the list of all meeting documents, including conclusions and action points are attached to these minutes as Annexes I and II, respectively. No points were raised under any other business.

3. Declarations of conflicts of interests to the Agenda

The Chairman requested all participants to declare any potential conflicts of interest to any of the agenda items. Ten Members declared potential conflicts of interest, each to specific agenda items, the majority related to concurrent employment of Members at agencies submitting dossiers to RAC but who had not been involved in the preparation. In the event of a vote, these Members were requested to refrain from voting on the respective agenda items, as stated in Article 9.2 of the RAC Rules of Procedure. Where Members declared that they had contributed to the preparation of a substance dossier for consideration by RAC, or similar potential conflict, they were asked to refrain from voting and the Chairman noted that he would consider additional mitigation measures. The list of persons declaring potential conflicts is attached to these minutes as Annex III.

4. Appointment of (co-) rapporteurs

a) Appointment of (co-)rapporteurs for CLH dossiers, restriction dossiers, authorisation applications, DNEL/dose-response relationships, Article 95 (3) requests and Article 77 (3) (c) requests (closed session).

The Secretariat collected the names of volunteers for rapporteurships as stated in the restricted room document RAC/41/2017/01.

The Committee agreed upon the proposed appointments of the Rapporteurs for the intentions and/or newly submitted CLH and restriction dossiers, as well as the forthcoming Applications for Authorisation (AfAs).

5. Report from other ECHA bodies and activities

a) Report on RAC-40 action points, written procedures and an update on other ECHA bodies

The Chairman informed the Committee that all action points from the previous meeting RAC-40 had been completed. He explained that the usual report covering the developments in the ECHA Management Board, the Socio-Economic Assessment Committee, Member State Committee, the Forum and the Biocidal Products Committee had been compiled and distributed to RAC as a meeting document (RAC/41/2017/02). The summary of all consultations, calls for expression of interest in rapporteurships and written procedures (room document RAC/41/2017/03) is also available in the usual meeting document on S-CIRCABC (see Annex IV).

The Chairman also informed the Committee that the final minutes of RAC-40 had been adopted via written procedure and were uploaded to S-CIRCABC and will be published on the ECHA website, and thanked those Members who had provided comments on the draft.

b) RAC workplan for all processes

The Chairman presented the updated RAC work plan for Q1-Q4/2017, covering the four processes of Restriction, Authorisation, Harmonised Classification and Labelling of substances and evaluation of Occupational Exposure Limits (Article 77(3) (c) requests. He informed Members that they could find the expected schedules for Restriction, Occupational Exposure Limit (OEL) and Authorisation dossiers in the work plan. In addition, the scheduling to be considered for each Harmonised Classification and Labelling (CLH) dossier are given in the relevant section.

6 Requests under Article 77 (3)(c)

The Chairman informed the Committee that following a request from the Commission, dated 15 March 2017, the Executive Director had requested RAC to draw up opinions on the evaluation of the scientific relevance of Occupational Exposure Limits (OELs) for MOCA and arsenic acid and its inorganic salts. The aim of the opinions (on each of the two substances) is to support the Commission, by providing scientific advice, in taking action on the Proposal to amend Directive 2004/37/EC (3rd amendment). The opinions should include a recommendation to the Advisory Committee on Safety and Health at Work (ACSH) in line with the Occupational Safety and Health (OSH) legislative procedures and considering the format used by the Scientific Committee on Occupational Exposure Limits in drafting their opinions. These are urgent requests as both opinions are intended for adoption at RAC-41. The deadline for forwarding the opinions to the Commission was 29 May, which was the first day of RAC-41.

a) 2,2'-dichloro-4,4'-methylenedianiline (MOCA)

The Chairman informed the Committee that due to the imposed short deadline for this particular case, the ECHA Secretariat had drafted the report and developed the opinion in close collaboration with the Rapporteur. In accordance with the mandate of 15 March, RAC was requested to form an opinion on MOCA based on the published RAC and SCOEL opinions on the

dose-response function and the consideration of OELs for MOCA respectively. During the first RAC commenting round on the draft opinion (4-12 May), comments were received from eight RAC members and referred mainly to the structure of the opinion and the need to clarify the "recommendation" further. A subsequent version of the opinion was prepared, revising and restructuring the draft opinion as far as possible within the constraints of the mandate and a second commenting round was launched (by 23 May). Five mainly editorial comments were received from RAC members. The Chairman invited the Rapporteur to present the draft opinion

The Committee agreed that in line with SCOEL a health based OEL could not be assigned to MOCA because it was considered to be a non-threshold genotoxic carcinogen with respect to risk characterisation. The Committee agreed that the major exposure route for MOCA was the dermal route and therefore, to indicate and assess exposure to MOCA, the measurement of residues in urinary samples of workers were more appropriate than concentrations in air only. However, biomonitoring should be complemented with air monitoring and, when appropriate, measurements of skin and surface contamination in order to identify exposure sources. Furthermore, as exposure via the dermal route makes a substantial contribution to body burden, a skin notation was warranted. The Committee agreed a Biological Guidance Value (BGV) corresponding to the limit of detection of the biomonitoring method and proposed this to ACSH. It was further pointed out that MOCA is listed on Annex XIV of REACH as a Substance of Very High Concern as a result of its carcinogenic properties and that ECHA had received only one (upstream) application, indicating that continued use is limited.

RAC adopted the opinion by consensus. The Chairman thanked the Rapporteur for the presentation of the arguments and the Committee Members for their written comments.

b) arsenic acid and its inorganic salts

The Chairman informed the Committee that similar to the previous case, due to the imposed short deadline, ECHA Secretariat had drafted the report and developed the opinion in close collaboration with the Rapporteur. A new opinion was developed based on the published RAC dose response relationship and recent published reviews and primary literature. During the first consultation round (4 May -15 May) three sets of comments were received from RAC members. A revised draft opinion was circulated, taking the comments into account and a second consultation was launched (by 23 May), during which five comments were received. The Chairman invited the Rapporteur to present the draft opinion

The Chairman informed the Committee that arsenic acid and its inorganic salts was a specific CLP entry and covered a set of As(V) compounds; this meant that the exposure and risk sections of the opinion were different to what might be expected from a review of inorganic arsenic compounds as a whole. The Committee agreed that a health-based OEL could not be established for arsenic acid and its inorganic salts because the available data did not allow the identification of any threshold for the genotoxic and carcinogenic effects of arsenic acid and its inorganic salts. The Committee agreed that inhalation was the primary route of occupational exposure, and that non-occupational exposure occurs mainly through food and drinking water in areas with high levels of arsenic in drinking water sources. The use and exposure assessment carried out indicated that the main occupational exposures to As(V) are to be expected in the removal, recycling and/or disposal of chromated copper arsenate (CCA) treated timber and in the extraction of copper and zinc from ores. The Committee agreed to recommend a Biological Guidance Value (BGV) of 10 µg As/L urine (for the sum of As^{3+}, As^{5+} and the methylated metabolites DMA and MMA) and proposed this but noted that dietary sources, especially seafood may have a significant impact on total levels. Absorption by the dermal route was considered to be low compared to the other routes thus a skin notation was not warranted.

RAC adopted the opinion by consensus. The Chairman thanked the Rapporteur for the presentation of the arguments and the Committee Members for their comments.

7. Requests under Article 95(3)

a) OEL-DNEL methodology request

The Secretariat presented an outline approach on how the last task (task 2) of the joint ECHA-SCOEL Task Force on carcinogens and their treatment as threshold, practical-threshold or non-threshold substances can be approached. The task is intended for completion by December 2017. A renewed Joint Task Force has been set up, consisting of 6 SCOEL members and 8 RAC members. The RAC members of the Joint Task Force will meet on 14 June to discuss the concept of practical thresholsd among themselves, followed by the first joint RAC-SCOEL Task Force meeting on this topic which will be held, on 15 June.

8. Harmonised classification and labelling (CLH)

8.1 General CLH issues

The Secretariat gave a brief presentation on the fast track procedure to refresh the RAC Members and Stakeholders on its working. The fast track procedure was implemented at RAC 30 in September 2014 as a procedure to increase the efficiency in the Committee's processing of the opinions without compromising the quality and the transparency of the process. Fast track agreement means that following adequate scrutiny by the Rapporteur and commenting members, selected hazard classes are proposed for agreement through a list without further debate in the Committee.

8.2 CLH dossiers

A. Hazard classes for agreement without plenary debate[1] (see section B below for hazard classes form the same substances debated in plenary)

RAC reviewed an 'A-listing' of hazard classes for two substances and being informed by the Secretariat of the appropriate scrutiny by Rapporteurs and commenting RAC Members in both cases, agreed these without plenary debate. The details for the two substances are given below in section B.

B. Substances with hazard classes for agreement in plenary session

a) phenyl bis(2,4,6-trimethylbenzoyl)-phosphine oxide

The Chairman reported that phenyl bis(2,4,6-trimethylbenzoyl)-phosphine oxide is used as a photoinitiator. It has an existing entry to Annex VI of the CLP Regulation for skin sensitisation (Skin. Sens. 1; H317) and for environmental hazards (Aquatic Chronic 4; H413). The legal deadline for the adoption of an opinion is 5 January 2018.

The Dossier Submitter (DE) proposed to modify the existing skin sensitisation classification to Skin Sens. 1A; H317 and to remove the environmental classification.

[1] Following adequate scrutiny by the Rapporteur and commenting Members and taking the comments from the Public Consultation into account, selected hazard classes are proposed for agreement through a list ('fast-track') without further debate in Committee.

Based on the effects in two GPMT tests demonstrating strong potency for skin sensitisation the Committee supported the Dossier Submitter's (DS) proposal for sub-categorisation of phenyl bis(2,4,6-trimethylbenzoyl)-phosphine oxide into category 1A. As the substance belongs to a strong potency class the generic concentration limit of 0.1% applies.

As to the environmental classification, the Committee discussed the BCF study results used as basis for the DS proposal to remove the existing aquatic chronic classification. Contrary to the DS, RAC was of the opinion that the non-GLP BCF study did not contain enough information to assess its reliability for classification purposes and hence did not support removal of the aquatic classification.

RAC adopted the opinion by consensus. The Chairman thanked the Rapporteurs for the presentation of the arguments and the Committee Members for their comments.

b) diisohexyl phthalate (DIHP)

The Chairman reported that diisohexyl phthalate has currently no Annex VI entry. The legal deadline for the adoption of an opinion is 8 January 2018.

The Dossier Submitter (SE) proposed to classify DIHP as Repr. 1B; H360FD. In the absence of relevant toxicity data for DIHP itself, the proposal was based on read across from a chemical category comprising a number of structurally similar ortho-phthalates (carbon side chains from 3-6 carbon atoms) with similar physicochemical, biological, and toxicological properties.

The Committee discussed the proposal and based on the data on other phthalates in the category that showed effects both for fertility (reduced number of viable offspring, effects on male reproductive organs) and development (reduced anogenital distance, testicular malformations/degeneration) and taking into account that DIHP is one of branched constituents of 1,2-benzenedicarboxylic acid, dihexyl ester, branched and linear, which is classified as Repr. 1B; H360FD, supported the proposal for classifying DIHP into category 1B for fertility and development (Repr. 1B; H360FD).

RAC adopted the opinion by consensus. The Chairman thanked the Rapporteur for the presentation of the arguments and the Committee Members for their comments.

c) N,N-diethyl-m-toluamide; DEET

The Chairman welcomed the expert accompanying the Cefic stakeholder observer and reported that DEET is an active substance in biocidal products. It is used and an active ingredient in insect repellent products. It has an existing Annex VI entry as Acute Tox. 4*; H302 (minimum classification), Eye Irrit. 2; H319, Skin Irrit. 2; H315 and for aquatic hazards as Aquatic Chronic 3; H412. The legal deadline for the adoption of an opinion is 18 December 2017.

The Dossier Submitter (SE) proposed to confirm the acute oral toxicity classification and to remove the aquatic chronic classification. CMR hazards and STOT SE were also assessed in the CLH report although no classification for these hazard classes was proposed. These hazards were open for comments during the public consultation.

The Committee concurred with the DS proposal for oral acute toxicity (Acute Tox. 4; H302) via fast track. The Committee also agreed that no classification for germ cell mutagenicity was warranted due to insufficient data, since no reliable *in vivo* study was available.

As to carcinogenicity, RAC agreed to no classification based on the low incidence of the findings (with no dose-response relationship) in male rats and no increases in tumour incidence in mice, as well as epidemiological data, which showed no cause-effect relationship.

The Committee supported the DS proposal for no classification for toxicity to reproduction based on studies in dogs, rats, rabbits and hamsters.

As regards specific target organ toxicity following single dose exposure (STOT SE), the Committee discussed the human evidence (several clinical case reports of dermal and oral exposure, in some cases involving deliberate intake via the oral route) and the animal data (namely neurotoxic effects observed in the dog studies) provided in the CLH report. One member suggested that more weight be given to human evidence which were consistent with the neurotoxic effects seen in dogs and therefore could suggest that classification as STOT SE 1 was warranted. Other members were of the view that human data were of limited value due to confounding factors and the low number of case reports relative to the wide scale on which this substance is being used. The industry expert confirmed the limitations of the human evidence. He noted that the self-reported cases had to be seen in the context of a large population who had been exposed (around 5 billion applications of DEET), the fact that confounding factors could not be excluded and that in some cases there was deliberate consumption.

As regards the animal data, clinical signs of neurotoxicity were observed in the three dog studies (two 8-week oral studies and a one-year oral study) at below the guidance value for classification for STOT SE category 1, effects seen in rats and rabbits did not fulfil the criteria for classification. It was noted that since the neurotoxic effects in dogs were observed at doses much lower than the LD50 in rats and not resulting in mortality of dogs, classification for STOT SE could in principle be adopted without concern for double classification. RAC however noted that the dog studies had some limitations (for example the small number of animals used in each study, doses too close to each other to allow for conclusion on a dose-effect relationship); in addition, there were no histopathology findings from the dog studies. Although the possibility that the ptyalism and emesis observed might have been caused by irritation of the stomach, evidence was lacking.

In conclusion, RAC supported the proposal by the dossier submitter for no classification for STOT SE.

RAC agreed to the DS proposal for removal of the existing aquatic chronic classification based on the application of the surrogate approach, where toxicity results from the existing aquatic toxicity studies for this rapidly degradable and non-bioaccumulative substance are compared with the respective classification criteria.

RAC adopted the opinion by consensus. The Chairman thanked the Rapporteur for the presentation of the arguments and the Committee Members for their comments.

d) benzo[rst]pentaphene

e) dibenzo[b,def]chrysene, dibenzo[a,h]pyrene

The Chairman reported that benzo[rst]pentaphene and dibenzo[b,def]chrysene are polycyclic aromatic hydrocarbons (PAHs) contained in certain petroleum streams and elastomer/rubber materials, and potentially also in plastics, lacquers/varnishes, or coatings. None of the two substances has a harmonised classification in Annex VI to the CLP Regulation. The legal deadline for the adoption of opinions are 27 December 2017 for benzo[rst]pentaphene and 29 December 2017 for dibenzo[b,def]chrysene.

The Dossier Submitter (DE) evaluated the experimental data available for both substances and, in combination with information from structurally and mechanistically similar substances, proposed a classification as mutagen (Muta. 2; H341) and carcinogen (Carc. 1B; H350) for both.

The Committee supported the DS proposal to classify both substances as Muta. 2 based on positive in vivo (micronucleus assay, DNA adduct formation, tumour initiating activity) and in vitro studies (bacterial and mammalian cell gene mutation assays). In addition, this is supported by chemical structure activity relationship to known mutagens (e.g. B[a]P and chrysene). One RAC Member asked for the clarification of the justification for the category 2 classification noting that chrysene is classified as Muta 2 (H341), but B[a]P as Muta 1B (H340). The Rapporteur justified this decision by lack of data in the CLH dossier on these two read across substances, and thus on data in support of 1B classification.

As to carcinogenicity, the Committee concurred with the DS proposal to classify benzo[rst]pentaphene and dibenzo[b,def]chrysene as carcinogens (Carc. 1B; H350) based on positive results (local tumour formation) in numerous studies in two species (mice and rats), further supported by the classification of the two structurally similar PAHs, chrysene and B[a]P.

RAC adopted the opinion by consensus. The Chairman thanked the Rapporteurs for the presentation of the arguments and the Committee Members for their comments.

f) 4,4'-sulfonylbisphenol, polymer with ammonium chloride (NH4Cl), pentachlorophosphorane and phenol

The Chairman reported that the substance has an existing Annex VI entry as Aquatic Chronic 4; H413. The Dossier Submitter (DE) proposed to remove the existing harmonised classification. The legal deadline for the adoption of an opinion is 8 December 2017.

RAC supported the DS proposal to remove the existing aquatic chronic classification based on new aquatic chronic data that did not reveal any toxic effects below the water solubility limit.

RAC adopted the opinion by consensus. The Chairman thanked the Rapporteur for the presentation of the arguments and the Committee Members for their comments.

g) titanium dioxide

The Chairman welcomed the experts accompanying the regular stakeholders from Cefic and Eurometaux, the representative of an occasional stakeholder from Cosmetic Europe accompanied by the expert and the representatives of occasional stakeholders from Industrial Minerals Association Europe (IMA-Europe) and from European Council of Producers and Importers of Paints (CEPE) and the representatives of the Dossier Submitter from France.

The Chairman reported that titanium dioxide (TiO_2) is a high production volume (HPV) chemical manufactured and imported in the European Economic Area at 1,000,000 – 10,000,000 tonnes per year. Products/articles in which titanium dioxide is incorporated are numerous and include paints, coatings, plastics, rubbers, papers, plasters, adhesives, coated fabrics and textiles, glassware, ceramics, electro-ceramics, electronic components, catalysts, welding, floor coverings, roofing, but also food additives (E171), pharmaceuticals, and cosmetics. The meeting was informed that titanium dioxide was classified by IARC (2010) in Category 2B (possibly carcinogenic to humans). The legal deadline for the adoption of an opinion is 27 November 2017.

Titanium dioxide has no existing Annex VI entry. The Dossier Submitter (France) proposed to classify the substance as Carc. 1B via the inhalation route (H350i). This proposed classification was the one subject to the Public Consultation.

At RAC 40, key issues related to the properties of poorly soluble low-toxicity (PSLT) particles, the implications of lung overload and the scope of the Annex VI entry were discussed.

At the present meeting, the discussion was conducted over two sessions (RAC 41a and 41b). At RAC-41A, as an exception to the usual rule and in order to allow for a wider debate, presentations were invited from , Cefic, Eurometaux, EUCheMS, and the Dossier Submitter, i.e. in addition to those of the Rapporteurs and Secretariat.

In their introduction the Secretariat reminded the Committee that the scope of their mandate was to provide an opinion on harmonised classification and labelling of titanium dioxide on the basis of available information as provided in the CLH report and that received during the public consultation.

Industry representatives noted that a "catch all" classification should not be proposed for substances with chemical activity strongly connected to structural form and surface area. According to industry, the rat model is unique in developing lung tumours following chronic overload particle exposures to poorly soluble particles (PSPs), and thus is not a suitable model of relevance for humans. They argued that human interstitial macrophages were less responsive to an inflammatory stimulus than alveolar macrophages. They further noted that the Lee et al., 1985 study included in the CLH report should not be considered as valid for classification because the study produced tumours under conditions where the clearance half-life from lung was greater than 1 year. According to industry the Heinrich et al., 1995 study should also not be considered as relevant because it was a non-guideline study. Industry was of the view that neither of the studies conformed with the CLP/OECD guidelines. According to industry, the epidemiological studies in PSP production workers and coal miners demonstrate no correlation with exposure and lung cancers.

The DS presented their proposal and the justification for classification as Carc. 1B. The DS found the human evidence inadequate to prove lack of carcinogenicity in humans due to gaps in the record (e.g. unknown cause of death, incomplete information on confounding factors such as smoking history of workers, lack of exposure measures), concerns that the follow-up time was not long enough and the high exclusion rate (of possibly highly exposed workers). The DS considered the rat model sufficient and adequate to predict lung carcinogenesis in humans. The DS considered the Lee et al. 1985 study comparable to OECD guidelines and the tested concentrations used in this study and in the Henrich et al. 1995 study relevant for hazard assessment. According to the DS, a Carc. 1B classification was justified by sufficient evidence in animals and inadequate evidence in humans with a relevant MoA showing similarities in the adverse outcome pathway (AOP) between human and rat. The DS also referred to other publications in the scientific literature which supported the classification for carcinogenicity.

The Rapporteurs introduced the RAC 41b meeting with the summary of the epidemiological studies available in the CLH report or provided during the public consultation (1 case report study, 3 case-control studies, 5 cohort studies and 2 review papers - Thompson et al. (2016) and Hext et al. (2005) both papers referred to during the PC). A few members expressed their view that the human data was adequate and sufficient to conclude that there was no association between human TiO_2 exposure and lung cancer. The DS commented that there was an association even if there was no clear evidence of a dose-relationship, and taking into account the limitations of the epidemiological data, the human data was inadequate to prove lack of carcinogenic effect in humans. RAC considered that the exposure levels in epidemiological studies were much lower than those causing cancer in animals, but exposure comparisons were compromised as RAC did not have the weighted average data from epidemiological studies. The rapporteurs also pointed out that whether the particles were of inhalable/respirable size would also affect the dose metrics. RAC concluded that the epidemiological data was not sufficient to

conclude on a carcinogenicity classification as the exposure data was inconclusive and that the epidemiological data could not overrule the outcome of the animal studies.

After concluding on the epidemiological studies the Rapporteur presented the animal data and considerations related to category 2 and no classification via the inhalation route. RAC concluded during RAC41a that the data did not meet the criteria for category 1A or 1B. RAC also accepted that it had been 'conclusively proven' that such a hazard was not applicable following exposure via the oral or dermal routes. According to industry the critical points were related to lung particle overload and to the relevance of the observed tumours in rats to humans. A RAC member questioned the relevance of the rat data as there were physiological differences in particle distribution in lung alveoli and interstitium between rats and humans suggesting lower cancer potential in humans. It was also noted that although humans were normally considered the most sensitive species by default, in this case there was evidence to suggest that humans were actually less sensitive to the effects of inhaled poorly soluble particles. In addition, since TiO_2 was considered a low potency threshold carcinogen in rats, this raised the question of how low could the potency be and the findings still be relevant to humans and whether the evidence of qualitative similarities was sufficient to conclude on relevance to humans. The Rapporteur stated that the normal alveolar clearance half-time was shorter in rats than in humans. The Rapporteur also pointed out that there were only quantitative differences in particle distribution in lung alveoli and interstitium between rats and humans. The DS commented that the tested TiO_2 particles should not be defined as PSLT (poorly soluble low toxicity) particles because TiO_2 is not of low toxicity considering its surface reactivity. At least TiO_2 was assumed to have the same MoA as PSLT particles. However, additional MoA are expected in particular for fibre-like TiO2. The DS further commented that the kinetic data were of limited quality and obtained using other particles (not TiO_2) and thus should not be used as such to conclude for TiO2. The industry commented that data on other PSLT particles and the association between cancer and exposure levels in coal miners should be looked at. The Rapporteur commented that the coal miner data showed that the carcinogenic concentrations tested in the Heinrich et al. (1995) rat study resulted in rat lung burdens that were achievable in humans at workplaces and therefore these concentrations in this study were not considered unrealistically high and irrelevant to humans. The Rapporteur also pointed out that only the tested TiO_2 were considered as PSLT particles whereas TiO_2 with WHO fibre characteristics were considered as particles with higher cancer potency different from PSLT particles. The DS commented that they did not have data on all forms of TiO_2 and therefore it was not possible to conclude that humans would be less sensitive to any specific forms of TiO_2. Industry questioned whether RAC had sufficient data on different TiO_2 forms to be able to conclude on classification, whether classification was appropriate as the critical issue concerned lung overload and whether dusts in general should be classified.

Two RAC members were of the view that the lung tumour frequency in rats was rather high and therefore TiO_2 should not be considered as a weak carcinogen. Several RAC members commented that the human relevance of the observed lung tumours in rats could not be excluded even if there were quantitative differences between rats and humans. It was also pointed out by a RAC member that the rat was normally the preferred test species and it had not been brought up during the OECD guidance development that rat should not be used as the test animal for lung carcinogenicity. Another RAC member pointed out by referring to the CLP criteria and Guidance that the human relevance did not need to be demonstrated in order to classify based on positive animal data, as substances which induced tumours in animals were considered also to be presumed or suspected human carcinogens unless there was strong evidence that the mechanism of tumour formation was not relevant for humans. Another RAC member noted that according to the CLP Guidance the existence of a secondary mechanism of action with the implication of a practical threshold above a certain dose level may lead to a

downgrading of a Category 1 to Category 2 classification thereby supporting Carc. 2 classification.

The session was closed briefly in order to give an opportunity for the dossier submitter to address the committee. The statement provided by the dossier submitter, is attached as an Annex to these minutes.

Following further discussion in which those members arguing for no-classification agreed that they could support the majority, RAC agreed by consensus on the harmonised classification for TiO_2 as Carc. 2; H351 (inhalation).

As the Rapporteur and several RAC members had during the opinion forming process noted that the CLP entry needed to express and clarify that the carcinogenic hazard category proposed was related to respirable particles of TiO_2 without WHO fibre characteristics and without surface coatings introducing specific chemical toxicity, the ECHA secretariat presented a suggestion that in addition to the adopted classification, a 'Note' could be added to the last column of the Annex VI entry. The note would introduce to the Manufacturers, Importers and Downstream Users an obligation to assess the available data on TiO_2 with WHO fibre characteristics or with surface coating and to self-classify these forms in a higher category if warranted by the data. In the absence of a note, the hazard classification of the entry would implicitly cover all forms of TiO_2. If these forms were simply excluded from the Annex VI entry, the harmonised classification would not capture the (undoubted but possibly underrated) hazardous properties of these forms of the substance and it could even be interpreted that these forms did not possess the hazardous properties of the harmonised classification. Two RAC members commented that this was a policy issue and not the responsibility of RAC. The Rapporteur commented that it would be important to ascertain that all different TiO_2 forms were not likely to have the same hazardous properties and therefore supported the 'Note' to the Annex VI entry. It was agreed that this issue would be addressed to the European Commission in the text of the Opinion to decide on the whether this would be appropriate.

On the issue of whether the reference to the inhalation route was sufficient, RAC further discussed whether the entry should be restricted to "respirable" particles. One RAC member clearly expressed that the restriction of the entry to respirable particles was not supported as there was no data to associate the carcinogenic hazard with certain particle sizes. Industry drew attention to the fact that the particle sizes tested in the underlying animal data were clearly reflective of "respirable" particles, and that the observed effects were clearly related to alveolar deposition in rats.

It was agreed that the scientific opinion of RAC justifying Carc. 2; H351 (inhalation) will be revised in accordance with the discussion and the conclusions, submitted to RAC for consultation and the final opinion adopted via a written procedure. The Chairman thanked the Rapporteurs for the presentation of the arguments and the Committee Members for their comments.

h) Fludioxonil (ISO)

The Chairman welcomed the expert accompanying the ECPA stakeholder observer and reported that fludioxonil (ISO) is a biocide with no harmonised classification, thus in accordance with Article 36(2) of CLP all hazard classes need to be assessed. The Dossier Submitter (DK) proposed to classify fludioxonil (ISO) as Aquatic Acute 1; H400 and Aquatic Chronic 1; H410 with an M factor of 1 for both endpoints. The legal deadline for the adoption of an opinion is 21 December 2017.

The Committee supported via fast track no classification for physical hazards, acute toxicity (all routes of exposure), skin corrosion / irritation, serious eye damage / eye irritation, respiratory

or skin sensitisation, STOT SE, STOT RE, germ cell mutagenicity, toxicity to reproduction and aspiration hazard.

The Committee agreed to the DS conclusion that increased incidences of hepatocellular tumours in rats and lymphoma in mice were not considered treatment-related with no evident dose-response relationship and with incidences within the HCD range and therefore no classification for carcinogenicity is warranted.

RAC agreed that fludioxonil is not readily biodegradable and not accumulative. The Committee supported the aquatic acute classification (Aquatic Acute 1; H400 with an M-factor of 1), and Aquatic Chronic 1, but contrary to the DS, agreed on an M-factor of 10 for aquatic chronic toxicity taking into account the results of a *Daphnia magna* chronic study with a 21d NOEC of 0.005 mg/L. The *Daphnia* study was considered relevant by RAC because, although not in line with the current OECD TG 211, it complied with the guideline in force when it was conducted.

RAC adopted the opinion by consensus. The Chairman thanked the Rapporteurs for the presentation of the arguments and the Committee Members for their comments.

i) pentapotassium 2,2',2'',2''',2''''-(ethane-1,2-diylnitrilo)pentaacetate (DTPA-K5)

j) N-carboxymethyliminobis(ethylenenitrilo)tetra(acetic acid) (DTPA-H5)

k) pentasodium (carboxylatomethyl)iminobis(ethylenenitrilo)tetraacetate (DTPA-Na5)

The Chairman welcomed the representative of the Dossier Submitters and reported that the three substances (acid or salt chelates) are potentially used in a wide number of industries including pulp and paper industries, laundry detergents, cleaners, soaps, and textiles. None of the substances has an existing entry in Annex VI to the CLP Regulation.

The Dossier Submitters from industry (Akzo Nobel Functional Chemicals BV for DTPA-H_5 and DTPA-K_5 and Dow Chemical Company Ltd for DTPA-Na_5) proposed to classify the substances as follows: DTPA-H_5 and DTPA-K_5 for developmental toxicity (Repr. 2; H361d), acute toxicity via inhalation (Acute Tox. 4; H332), for specific target organ toxicity after repeated inhalation exposure (STOT RE 2; H373) and for eye irritation (Eye Irrit. 2; H319). As regards DTPA-Na_5, the DS proposed to classify as Repr. 2; H361d, Acute Tox. 4; H332 and STOT RE 2; H373 (inhalation).

Based on similar molecular structures, a common mechanism of action altering the homeostasis of metal ions and similar physico-chemical properties, read-across to other chelates (DTPA's and EDTA's) was used for the evaluation of the three substances.

RAC discussed the proposals at its March meeting (RAC 40) and agreed on the acute toxicity classification via inhalation for all three dossiers (Acute Tox. 4; H332) based on the effects after single exposure observed in a 5-day repeated dose toxicity study in the rat performed with EDTA-Na_2H_2.

Using the weight of evidence RAC at its March meeting also supported the classification for eye effects of DTPA-H_5 and DTPA-K_5 as proposed by the DS – into category 2 (Eye Irrit. 2; H319).

At the present meeting, the Committee supported the conclusion by the DS that effects in two 28-day oral repeated dose toxicity studies in the rat performed with DTPA-K_5 and DTPA-Na_5 did not warrant classification for STOT RE via oral route. For the inhalation route of exposure, effects (namely epithelial necrosis in epiglottis) observed in a 5-day repeated dose toxicity study in the rat performed with EDTA-Na_2H_2 were considered not reversible and warranting the classification

further supported by the local effects seen in a 90-day study with EDTA-Na_2H_2. Whereas two Members were of the opinion that the observed effects might be better addressed through STOT SE classification, other Members thought that the respiratory tract irritation signs after repeated exposure would not fulfil the STOT SE criteria and using the weight of evidence approach supported the proposal to classify DTPAs in category 2 for repeated dose toxicity via inhalation.

In relation to toxicity to reproduction, no data were presented in the CLH dossiers on fertility, although one RAC member mentioned that there appears to be at least one fertility multi-generation (2004) study on sodium EDTA (apparently negative).. In response to some RAC Members' questions the Dossier Submitter's representative clarified that no data on fertility impairment on the three substances or other chelates (DTPA's and EDTA's) were available to the DS but noted that – as expressed in the CLH dossiers - the potential mode of action (induced zinc deficiency) observed in developmental toxicity studies is assumed to affect also male fertility. However, in absence of data no classification can be proposed.

As regards developmental toxicity, the Committee agreed to classify the three substances into category 1B based on serious malformations and other developmental effects (retardation) observed also in lower doses, above historical controls and without severe maternal toxicity in a developmental toxicity study in rats with DTPA-Na_5 (key study), supported by effects in two additional studies in rats and mice showing a consistent developmental toxicity. The proposed mode of action (developmental toxicity induced by maternal zinc deficiency) was considered plausible and relevant to human. The understanding of the MOA supports the fact that the developmental toxicity was not a non-specific consequence of a maternal effect.

RAC adopted the opinion by consensus. The Chairman thanked the Rapporteur for the presentation of the arguments and the Committee Members for their comments.

9. Restrictions

9.1 General restrictions issues

a) Report from the Restriction workshop held in Helsinki 17-18 May 2017

RAC was informed about this workshop held just before its plenary meeting and which had a bearing on the work of the Committee. Member States expressed their view during the workshop that the 71 recommendations agreed to date have contributed to improving the efficiency and effectiveness of the restriction process. An additional eight potential new recommendations were made during the workshop. However, it was also noted that the restrictions process still remains more resource intensive than other processes, such as SVHC identification. In addition, it is clear that Member States are progressing in making new proposals and that matters are speeding up.

9.2 Restriction Annex XV dossiers

a) Conformity check and key issues discussion

1) Lead and its compounds in shot

The Chairman welcomed the dossier submitters' representatives from ECHA. He informed the participants that the dossier was submitted in April 2017, the conformity check process was launched in the Committees on 17 May 2017 and the RAC commenting round finished on 23 May 2017 (there were two supporting comments received from RAC members).

The dossier submitters' representative (ECHA) provided a brief introductory presentation on the dossier. The dossier proposes restriction on the use of lead shots over wetlands. The

harmonisation of the conditions of use of lead in shot in wetlands is a priority at EU level, as national legislation has already been enacted by some Member States (or regions in some Member States) further to international action through the Agreement on the Conservation of African-Eurasian Migratory Waterbirds (AEWA) under the auspices of the UN Environment Programme (UNEP) to which the EU is a Party.

The RAC Rapporteurs presented the outcome of the conformity check and the recommendations to the dossier submitter and proposed to the Committee that the dossier can be considered in conformity from the RAC point of view. After a short discussion, the Committee agreed that the dossier does conform to the Annex XV requirements. In addition, the rapporteurs presented the key issues identified by them in the dossier.

The Committee discussed different aspects of the proposed restriction, such as scope, enforceability of the proposed restriction, calculated benefits from the restriction and proposed restriction implementation measures by the applicant. Some RAC members questioned whether the REACH Regulation is the appropriate EU regulation to restrict possession of lead gunshot for persons in wetlands. Other RAC members asked, why the scope of the restriction proposal is limited to wetlands only. The Secretariat responded to that that ECHA drafted the restriction proposal based on the request by the Commission.

The Chairman informed the Committee that the public consultation on this restriction proposal will be launched on 21 June 2017.

b) Opinion development

1) Diisocyanates

The Chairman welcomed the Dossier Submitter's representatives from Germany, the SEAC Rapporteur (following via WebEx), an industry expert accompanying a regular stakeholder observer and an occasional stakeholder observer from EuPC. He reminded the participants that this restriction proposal had been resubmitted by Germany in February 2017 and had been considered in conformity by RAC in its March plenary. The proposal limits the use of diisocyanates in industrial and professional applications to those cases where a combination of technical and organisational measures as well as a minimum standardised training package have been implemented. Information how to get access to this package is communicated throughout the supply chain. Exemptions are defined for cases where the content of diisocyanates in the substance or mixture placed on the market or used is less than 0.1% by weight, as well as for mixtures containing diisocyanates at higher levels than 0.1% by weight which fulfil criteria that show that the potential risks using such products are very low. The Rapporteurs had developed the first draft opinion on this dossier, taking into account the discussion on key issues held at RAC-40, which was made available to RAC on 18 May. The commenting round ended on 23 May with comments received from 4 RAC members. At this RAC-41 meeting, the Committee was invited to discuss the first draft opinion and to provide feedback sufficient to enable the Rapporteurs to formulate a next version of the draft opinion.

The Rapporteurs presented the first draft opinion, in which they mainly had focused on the hazard, exposure and risk. The Rapporteurs explained to the Committee that the main goal of the proposed restriction is to prevent new cases of respiratory sensitisation to diisocyanates among workers/professionals (and indirectly exposed residents). Diisocyanates are classified as Resp. Sens. 1 and Skin Sens 1 (CLP). Exposure to methylendiisocyanates (MDI), toluene diisocyanates (TDI) and hexamethylene diisocyanates (HDI) may be the cause for most of the diisocyanate-related asthma cases. RAC agreed with the conclusion of the Rapporteurs to include all diisocyanates in the scope of the restriction. One RAC member questioned if monoisocyanates

should have been included in the scope of the restriction. An industry expert, however, explained that the uses of monoisocyanates are different compared to diisocyanates and that is why they have not been covered in the scope. Furthermore, there is no direct evidence for monoisocyanate-induced asthma but they indicated that more information would be provided in the Public Consultation. Another RAC member asked why consumer use is not mentioned in the scope of the restriction. The Dossier Submitter representatives responded that they did not find any data that would indicate that there is a risk for consumers and that there is a need for protecting consumers.

The Committee agreed that the restriction should be taken forward with Occupational Asthma (OA) as the main concern. RAC also agreed that the exposure assessment conducted by the Dossier Submitter based on air monitoring data from three databases (ISOPA, MEGA (IFA), HSE) and from relevant literature, and on biomonitoring data is a reasonable estimate of an overall exposure to diisocyanates in the EU. Finally, the Committee agreed with the conclusion of the Rapporteurs that the Dossier Submitter's approach to base the risk characterisation on incidence of OA cases and their calculation of the number of diisocyanate OA cases in the EU is accepted and that therefore the identified risk to users is not adequately controlled and needs to be addressed.

The Chairman informed the Committee that the second draft opinion should be developed by the Rapporteurs by early August 2017.

2) Lead in PVC

The Chairman welcomed the Dossier Submitter's representatives from ECHA, an industry expert accompanying a regular stakeholder observer and an occasional stakeholder observer from EuPC. He reminded the participants that this restriction proposal had been submitted by ECHA in February 2017 and had been considered in conformity by RAC in its March plenary. The dossier proposes a restriction of lead compounds in PVC articles in concentrations equal to or greater than 0.1% (w/w) with a 15 year derogation for certain building and construction articles produced from recycled PVC (with a higher restriction limit of 1% (w/w) and a 10-year derogation for PVC silica separators in lead acid batteries.

The Rapporteurs had developed the first draft opinion on this dossier, taking into account the discussion on key issues held at RAC-40, which was made available to RAC on 18 May. The commenting round ended on 23 May with comments received from 1 RAC member. At this AC-41 meeting, the Committee was invited to discuss the first draft opinion and to provide feedback sufficient to enable the Rapporteurs to formulate a next version of the draft opinion.

The Rapporteurs presented the first draft opinion, in which they mainly had focused on the hazard, exposure and risk. With regard to the scope of the proposed restriction, the Rapporteurs noted that the purpose of the restriction and the reasons for derogations are clear (although a derogation for recycling should be reworded to ensure that it does not allow any intentional addition of lead stabilisers during the process for articles supplied to the EU market) and that the grouping of all lead compounds is appropriate, prevents substitution and facilitates enforcement based on Pb content. The Rapporteurs explained to the Committee that they are waiting for the Forum advice on the proposal, including their view on the need to mention mixtures in the scope. The industry experts also highlighted that they will be providing comments regarding the scope and derogations in the ongoing public consultation. Finally, the Committee agreed with the conclusion of the human health hazard assessment, i.e. that a threshold for neurodevelopmental effects in children (as well as renal effects in adults) has not been established. However, this may be the subject of further contributions of information from industry (within the public consultation).

The Chairman informed the Committee that the second draft opinion should be developed by the Rapporteurs by early August 2017.

10. Authorisation

10.1 General authorisations issues

a) New applications received during the May 2017 submission window

The ECHA Secretariat informed the Committee that five applications for authorisation were received during the May 2017 submission window. Three out of the five are upstream applications on the uses of chromium (VI) substances in the aviation sector. One of the new applications is on the downstream use of chromium trioxide in piston rods for vehicles shock absorbers. And the remaining application is also submitted by a downstream user of 1,2-dichloroethane (EDC) for manufacturing of beads for filtration units to treat nuclear wastes.

In addition the ECHA Secretariat informed the Committee that in the August 2017 submission window it is expected to receive two review reports on the uses of two phthalates (DBP and DEHP). In the November 2017 submission window it is likely that one review report on the use of lead chromate pigments will be submitted to ECHA, as well as one new application for authorisation on the downstream use of diglyme. The Committee briefly discussed the scope of the review reports.

b) Review reports

The ECHA Secretariat presented to the Committee the main principles of the evaluation process for review reports as well as the modified templates, which will be used by the applicants for submission of the review reports. The process for handling review reports in terms of its content and evaluation by RAC is very similar to the applications for authorisation process. In terms of content and timelines of the review reports it is the same as for the applications for authorisation. However scope of the review report has to fall within the limits of its original scope or it can be narrowed down or split into several (more narrow) uses. Review reports have to specify all the changes in the original application reports, if it concerns hazards (DNEL, dose-response relationship, new intrinsic properties defined in Annex XIV etc.), or exposure (process modifications, OCs/RMMs, monitoring etc.), or R&D activities to identify or to implement suitable alternatives (reflected in the analysis of alternatives), or business activities, changes to the NUS (reflected in the socio-economic analysis). In addition to the chemical safety report, the analysis of alternatives and the socio-economic analysis, a new format of an explanatory note is added to the package to be submitted by the applicants. The explanatory note is high level document to facilitate reading and to understand changes and progress made. Two RAC Members expressed their view on the scope of the review reports and the templates used for the review reports during the brief plenary discussion. They were of view that the Committee opinion templates would also need review in order to avoid unnecessary repetition in the opinions, and changes in the order of various parts of the opinions. The ECHA Secretariat responded that the opinion templates are also being reviewed as part of the preparation for the review reports process.

c) Review periods longer than 12 years

The ECHA Secretariat presented the Commission proposal of "Criteria for setting a review period longer than 12 years ("longer review period")". During the discussion RAC members pointed out that recommending a longer review period should be limited to specific Downstream User (DU)

applications only, to be recommended on a case-by-case basis. It could e.g. be applicable to DU installations with a very long life span, which are very difficult to change and also possibly use low quantities of Annex XIV substances.

Some members raised concerns that longer review period conflicts with the general authorisation principle of REACH which is to encourage industry to replace Annex XIV substances with safer alternatives.

The Commission confirmed that it will be always a case-by-case decision and that all the listed criteria have to be fulfilled to grant very long review period. Although the Commission should further clarify some elements in the paper, overall RAC foresees no major difficulties to use these criteria in practice.

The Secretariat will compile the views of RAC and SEAC and communicate them to the Commission. The paper will be subject for further discussion in the next REACH committee meeting in June 2017.

d) AfA DNEL/DR: Carcinogenicity dose-response relationship - development of:

1. Coal tar pitch, high temperature (CTPHT)

2. Anthracene oil

RAC noted the presentation by the ECHA Consultant.

The RAC Rapporteur after examination of the draft report submitted by the ECHA contractor and the presentation recognised that the report needs some improvement as to the inclusion and review of data (e.g. data used for justifying the classification of CTPHT and anthracene oil as carcinogens and the inclusion in Annex XIV) and previous regulatory assessments for CTPHT, anthracene oil and particularly on benzo[a]pyrene, as done by international or national bodies. As to the proposed recommendation for a risk, the RAC Rapporteur would like to see some options presented in the next draft, including justifications, so that RAC can take an informed decision.

RAC discussed the proposed approach and Members acknowledged the difficulties of the task, considering that both substances are UVCBs (i.e. substances of unknown or variable composition, complex reaction products or biological materials). One RAC member shared her knowledge about biomonitoring of workers exposure, suggesting to use 1-hydroxyperene as a potential biomarker in exposure assessment of workers exposed to anthracene oil.

The Cefic expert acknowledged that both substances are well-known carcinogens, therefore, with regards to some comments, no new carcinogenicity studies are expected. He also suggested the ECHA contractor to examine other relevant literature sources, which are available on the subject, especially those produced in the Netherlands in 2006 (DECOS) and Germany in 2010 (AGS). The latter is based on 39 epidemiology studies and those should be taken into account. In choosing the marker component RAC should consider what data are predominantly available. Usually benzo[a]pyrene is used as an exposure indicator and workplace measurements on the 16 EPA PAHs would be rare under OSH. The Cefic expert expressed his wish to receive the draft reports made by the ECHA contractor at an earlier stage in order to provide the comments of industry in the development of the notes. This was agreed.

One RAC Member emphasised the need to consider DRs set by other Committees, e.g.SCOEL published an opinion on BaP in 2016 and also FIOH agreed on a target value for BaP.

Another RAC Member highlighted the need for a very practical, very transparent and scientifically sound approach, which should include the use of epi data.

The Cefic expert reminded that the effects observed in epidemiological studies over more than 100 years are based on the total composition, not BaP alone, but usually BaP serves as the marker component for the exposure estimate.

One RAC Member informed the Committee that EFSA used PAH 4 as a marker of the oral exposure, and concluded that PAH 4 or PAH 8 would be more suitable exposure indicators for the oral (and dermal) route. Hence, she proposed for RAC to not rush to a conclusion and explore this approach. This view was supported by another two Committee members. Industry pointed out that BaP would be the only component available in workplace monitoring studies and therefore anything else was unlikely to be found in Applications for Authorisation in the future. This was noted by RAC as an important practical consideration in developing a DR.

RAC concluded its discussion with the following advice to the ECHA contractor, which should be considered by them in development of the draft notes: (1) to describe and use existing risk assessments by international and national bodies, (2) clearly describe and assess the epidemiological studies upon which the previous assessments are based, (3) to assess advantages and disadvantages of proposed basic markers for CTPHT for various routes of exposure (benzo[a]pyrene vs. PAH4/8), (4) oral route indirect exposure markers (PAH 4/8), (5) 1-hydroxypyrene as a potential biomarker in exposure assessment of workers exposed to anthracene oil. It was noted that BaP concentrations in anthracene oil might be too low to be useful as a marker.

10.2 Authorisation applications

The Secretariat presented a short report from the authorisation Rapporteurs' workshop held on the evening of 30 May (see Annex VI).

a) Discussion on key issues

The Secretariat in cooperation with the RAC Rapporteurs provided general information regarding the new application for authorisation listed below.

The Chairman noted that from this case onwards, and in order to increase transparency of the process, all the questions to the Applicant as well as the answers received will be published with the final opinion. This new change was welcomed by one stakeholder observer (Eurometaux), who considered this as a positive step towards the increase of the transparency of the process, as well as the quality of the information provided by the Applicants.

1. PC_SC_Saes (2 uses)

This is an application with a narrow, well-defined scope regarding the following two uses of sodium and potassium chromates.

> Use 1: Use of Sodium and Potassium chromate in the fabrication of alkali metal dispensers for production of photocathodes
>
> Use 2: Use of alkali metal dispensers containing sodium and potassium chromate for production of photocathodes

The two substances are used alternatively for the same uses and identical application conditions. The number of sites relevant for the application is one for Use 1, and several sites / wide network

of customers for Use 2. The number of workers exposed is <10 for Use 1, but not specified for Use 2. The tonnage used is <20 kg per year and the Applicant requested a review period of 7 years.

The Secretariat in cooperation with the RAC Rapporteur provided general information regarding this new application. In the presentation of the case, the Secretariat outlined the key issues identified by the Rapporteur and asked the Committee for comments and further suggestions.

The Committee discussed these key issues. Where needed, RAC will request further clarifications from the Applicants on the issues identified and discussed by the Committee.

b) Agreement on Draft Opinions

1. Diglyme_Acton, use 2 (1 use)

The Rapporteurs presented the draft opinion for the use 2 of the application for authorisation submitted by the Acton Technologies Limited: Use of bis(2-methoxyethyl) ether (diglyme) as a carrier solvent in the application of sodium naphthalide etchant for fluoropolymer surface modification whilst preserving article structural integrity (downstream user processes). The annual volume of the substance used is up to 10 tonnes and the Applicant requested a 12-year review period. This use describes the use of the substance by 5 downstream users.

The discussion during the plenary focused mainly on the proposed conditions for the authorisation, including the requirement to do regular workers exposure monitoring and monitoring of the procedures affecting the dermal exposure potential through the wipe testing. RAC members asked if the wipe testing can be recommended as condition without knowing if a relevant analytical technique has been developed. The Rapporteurs replied that conditions should stimulate industry to develop new techniques if such do not exist yet. The wipe testing is requested to help the Applicant to improve housekeeping rules to reduce dermal exposure, to complement the other conditions aiming at reduction of the exposure. The RAC agreed with Rapporteurs suggestion on frequency of the regular measurement program (twice a year) and reduction of this frequency once adequate control and effectiveness of the procedures have been demonstrated. RAC members shared the Rapporteurs' concerns on the length of tasks when use of the full face mask is required.

RAC agreed by consensus on the draft opinion as proposed by the Rapporteurs. In particular, RAC is of the opinion that the applicant has not demonstrated adequate control for workers at the sites of DUs 1, 3 and 4. The applicant did however demonstrate adequate control for workers at the sites of DUs 2 and 5 and for the general population exposed via the environment at all sites. In conclusion RAC is of the opinion that for the use applied for, adequate control has NOT been demonstrated for workers.

Regarding the RMMs to control the exposure of workers, RAC concluded that, the currently employed RMMs are not sufficient to control their exposure and not all possible engineering controls are currently implemented at the DU 1, 3 and 4 sites, especially in relation to minimising the potential for dermal exposure. They are of the opinion that additional and/or improved engineering controls are needed in order to reduce current dermal exposures. The RMMs have to be implemented within a year from issuing of the decision. The DUs have to continue or develop and implement monitoring programs in order to ensure the robust evaluation of exposures to diglyme, resulting directly from performance of tasks, or from contamination of surfaces. RAC recommends also improvement of RMMs for reduction of emissions to the environment and for reduction of workers exposure at DUs 2 and 5 in conditions for review report.

Due to the lack of adequate control for workers and the significant uncertainties described regarding exposure assessment, risk management measures and operational conditions, RAC recommended to SEAC to consider a review period of no longer than 4 years.

2. EDC_Bayer (1 use)

The Rapporteur presented the draft opinion on the application for authorisation submitted by BAYER Pharma AG for the use of 1,2-dichloroethane (EDC) as an industrial solvent in the manufacture of the high-grade pure final intermediate of Iopromide, the Active Pharmaceutical Ingredient for the X-ray contrast medium Ultravist®. The application covers one site with 130 + 50 external (maintenance) exposed workers. The annual tonnage used ranges between 100-1,000 tonnes/year (recycling rate – 93%). The requested review period is 13 years.

RAC agreed by consensus on the draft opinion as proposed by the Rapporteurs. In particular, RAC was of the opinion that the RMMs and OCs described in the application are appropriate and effective in limiting the risk to workers and the general population. However, considering the data set not covering all tasks, shortcomings in the RMMs for some tasks (e.g. filling of big bags, sampling) and planned expansion of the production - RAC decided to recommend additional monitoring arrangements for the authorisation, as described in the draft opinion. RAC agreed to give no advice to SEAC on the length of the review period.

3. EDC_Olon (2 uses)

The item was postponed to RAC 42.

4. MOCA_Reachlaw (1 use)

The Rapporteur presented the draft opinion on the application for authorisation submitted by the only representative of a company located in China for the industrial use of 2,2'-dichloro-4,4'-methylenedianiline (MOCA) as a curing agent/chain extender in cast polyurethane elastomer production. It is reported to be used at 89 sites, of which an estimated 89% are automatic and the remaining 11% are manually operated. The use thus has a broad scope. An estimated 213 workers are exposed. The volume of the substance used is approximately 500 tonnes per year. The requested review period is 12 years.

RAC agreed by consensus on the draft opinion as proposed by the Rapporteur. In particular, RAC was of the opinion that the RMMs and OCs are not appropriate in limiting the risks to workers and the general population due to the broad scope of the application, describing a wide variety of work practices and RMMs used, including also sites where good practices are not observed (work with open system, LEV not used for the tasks with potential for exposure). Not all exposure situations were covered by the measured data submitted. These elements were identified as the main source of uncertainty affecting the risk characterisation and human health impact assessment. Although risk characterisation is based on biomonitoring data, the applicant has not been able to define minimum standards for OCs and RMMs, which should be in place in order to achieve the exposure levels described. However, the biomonitoring results presented were at a level comparable with the data described in the literature. There were also concerns noted related to the MOCA residue in the end-products and lack of consistent approach to testing of the products. RAC noted shortcomings in treatment of contamination from the air extracted through used LEV - in many cases air is released to the atmosphere with no removal of contamination.

In the conditions proposed, RAC defined minimum standards for OCs and RMMs, including also good housekeeping, which should be in place in order to achieve the exposure levels described. RAC discussed the requirement for the biomonitoring to be done by the applicant twice a year

until the monitored exposure levels are repeatedly below the detection limit. In addition to the additional conditions and monitoring arrangements for the authorisation, as described in the draft opinion, RAC recommended to SEAC to consider a review period of no longer than 7 years.

5. CT_ZFL (2 uses)

The Rapporteurs presented draft opinions on a downstream user application for two uses of chromium trioxide:

- Functional chrome plating with the annual tonnage of 20 kg,
- Surface treatment for applications in the aeronautics and aerospace industries (unrelated to Functional chrome plating or Functional chrome plating with decorative character) with the annual use of 43 kg.

Use 1 covers treatment of large parts often of unique shape so it is not possible to use closed, automated process; small parts are moved from bath to bath manually. The main form of application is dipping or immersion of parts in a tank or through a series of tanks containing solutions in closed or open systems. Additional tasks include preparing and control of the solution in the bath, cleaning, maintenance and waste management.

Use 2 covers the same steps as in use 1 with the exception of pre-treatment which is not needed for use 2.

Both uses are conducted in one site and the Applicant requested the review period of 12 years.

RAC agreed on the draft opinions as proposed by the Rapporteurs. RAC was of the opinion that RMMs and OCs are appropriate in limiting the risk to workers, but noted some areas for improvement. Hence, the Committee recommended additional conditions for the authorisation (namely to cover tank 51). This is in line with the Applicant's intention confirmed during the trialogue. RAC decided to recommend additional conditions and monitoring arrangements for review reports, namely that the applicant shall add the tasks as described in WCS 2, WCS 3, WCS 12 and WCS 14 to the planned occupational exposure measurements. The measurements shall be undertaken according to standard sampling and analytical methods. In addition, the Applicant shall refine the assessment of indirect exposure and risk to humans via the environment beyond the default assumptions outlined by them, using measurements of emissions of Cr(VI) to wastewater.

RAC agreed to give no advice to SEAC on the length of the review period. RAC agreed on the draft opinions by consensus.

6. SD_ZFL (1 use)

The Rapporteurs presented draft opinions on a downstream user application for one use of sodium dichromate for surface treatment of metals such as aluminium, steel, zinc, magnesium, titanium, alloys, composites, sealing of anodic films. The annual tonnage is 10 kg.

The use is conducted in one site and the Applicant requested the review period of 12 years.

RAC agreed on the draft opinions as proposed by the Rapporteurs. RAC was of the opinion that RMMs and OCs are appropriate in limiting the risk to workers, but noted some areas for improvement. Hence, the Committee recommended additional conditions for the authorisation (namely to cover tank 51). This is in line with the Applicant's intention confirmed during the trialogue. RAC decided to recommend additional conditions and monitoring arrangements for review reports, namely that the applicant shall add the tasks as described in WCS 2, WCS 3, WCS 4, WCS 14 and WCS 16 to the planned occupational exposure measurements. The

measurements shall be undertaken according to standard sampling and analytical methods. In addition, the Applicant shall refine the assessment of indirect exposure and risk to humans via the environment beyond the default assumptions outlined by them, using measurements of emissions of Cr(VI) to wastewater.

RAC agreed to give no advice to SEAC on the length of the review period. RAC agreed on the draft opinions by consensus.

7. **CT_Haas (1 use)**
8. **SD_Haas (1 use)**
9. **PD_Haas (1 use)**
10. **SC_Aviall (2 uses)**

The RAC Rapporteurs presented the draft opinions on the four upstream (importer) applications for authorisation prepared with the support of the Global Chromates Consortium for Aerospace (GCCA). Three of the applications have been submitted by Haas Group International SCM Ltd, with one application for the use of chromium trioxide (CT) for chemical conversion treatment and slurry coating by aerospace companies and their suppliers and one application for the use of sodium dichromate (SD) and one application for the use of potassium dichromate (PD) for sealing after anodizing by aerospace companies and their suppliers. The fourth application has been submitted by Aviall Services Inc. as the lead Applicant and Haas Group International as the co-Applicant for two uses of sodium chromate (SC): Use 1: Formulation of mixtures of sodium chromate for sealing after anodizing, chemical conversion coating, pickling and etching applications by aerospace companies and their suppliers. Use 2: Use of sodium chromate for sealing after anodizing, chemical conversion coating, pickling and etching applications by aerospace companies and their suppliers. A review period of 12 years or more is requested for all five uses covered in these applications for authorisation. The 8-weeks public consultation on the alternative substances and technologies closed on 9 January 2017 with a total of 12 comments received for these five consultations. A RAC consultation on the applications for authorisation has ended on 4 January 2017 with no comments received from the RAC members. A trialogue meeting was held on 28 March 2017. One RAC member submitted comments during the RAC consultation on the draft opinions prior to this plenary meeting.

Following the presentation, RAC Members noted uncertainties with regard to risks to humans and environment.

Regarding formulation (SC), RAC agreed on the draft opinion as proposed by the Rapporteurs with modifications as proposed during the meeting. RAC is of the opinion that the RMMs and OCs are not appropriate and effective in limiting the risk to workers and the general population. Considering the uncertainties relating to the risks, RAC decided to recommend additional conditions and monitoring arrangements for the authorisation and review report, specifying that the monitoring would be done at least annually. RAC also concluded that the monitoring frequency for this authorisation may be reduced to at least every three years once exposure to humans and releases to the environment have been reduced to as low a level as technically and practically possible and where it is demonstrated that OCs and RMMs function appropriately.

In addition, RAC agreed to give no advice to SEAC on the length of the review period for the use of sodium chromate in formulation.

For the surface treatment and coating (CT, SC, SD, PD), RAC agreed on the draft opinions as proposed by the Rapporteurs with modifications as proposed during the meeting. RAC was of the opinion that the RMMs and OCs are not appropriate and effective in limiting the risk to workers and the general population. Considering the uncertainties relating to the risks, RAC decided to recommend additional conditions and monitoring arrangements for the authorisation

and review report, as described in the draft opinions. For the uses on surface treatment and coating, RAC agreed to give no advice to SEAC on the length of the review period, except for the CT Haas, where RAC recommends to SEAC to consider a review period of no longer than 7 years.

The Committee agreed on the draft opinion on these applications for authorisation by consensus. The Secretariat will send out the draft opinions to the Applicants for commenting.

11. SD_Colle (1 use)

The Rapporteurs presented the draft opinion on the application for authorisation submitted by a downstream user for the use of sodium dichromate as mordant in wool dyeing.

This application for authorisation relates to the use of sodium dichromate at two sites in Italy (Gruppo Colle s.r.l. and Color Fibre s.r.l.). The function of sodium dichromate is to fix the dye on the fabric by forming a coordination complex which is then attached to the fabric. Sodium dichromate is supplied as an aqueous solution (46% water) in 1,000 L tanks. The tanks are placed and stored in a dedicated area with waterproof soil and containment vessel in case of accidental release. The dyeing process is a closed batch process at both sites. Dosing of sodium dichromate occurs by using an automated closed chemical dosing system. The dyeing phase lasts approximately 45 min at temperatures of about 70 °C to 98 °C and at pressures from 0.8 to 2 atm. According to the applicant sodium dichromate is completely consumed under normal reaction conditions and any unreacted Cr(VI) is reduced to Cr(III) by adding a reducing agent to the dyeing vessel after finishing the dyeing process. Workers wear PPE for those task with potential exposure to sodium dichromate, e.g. at the connection of the sodium dichromate tank to the dosing system. A total number of 9 workers are exposed to sodium dichromate in both sites. Excess cancer risk levels are estimated to be below 1.714×10^{-3} for workers and 1.73×10^{-10} for the general population.

RAC agreed by consensus on the draft opinion as proposed by the Rapporteurs. In particular, RAC was of the opinion that the RMMs and OCs are appropriate in limiting the risks to workers and the general population. RAC recommended additional monitoring arrangements for the review report, and gave no advice to SEAC on the length of the review period.

12. CT_Hansgrohe (2 uses)

The Rapporteurs presented the draft opinions on the application for authorisation submitted by a downstream user on the following two uses:

Use 1: The use of chromium trioxide for electroplating of different types of substrates with the purpose to create a long-lasting high durability surface with bright (shiny) or matte look (Functional plating with decorative character),

Use 2: The use of chromium trioxide for a pre-treatment step (etching) in the electroplating process. The scope of the application was well defined.

The substance is used by the applicant on their two sites. Chrome plating is carried out in two modular automated lines and in one manual plating unit. The chrome plating process is integrated into a complex electroplating process, which in the manual process involves 10 steps and in the automated lines combines up to 30 successive treatments plus rinsing baths. Number of workers exposed during the Use 1: 69. The etching is integrated with the plating steps that avoids handling and prevents any contamination of the etched surface. Number of workers exposed during the Use 2 operations: 26. The Applicant requested a 12 years review period.

RAC agreed by consensus on the draft opinions as proposed by the Rapporteurs. In particular, RAC was of the opinion that the RMMs and OCs are appropriate and effective and in line with

the hierarchy of control. RAC agreed to recommend additional monitoring arrangements for the review report with regard to air emissions, and gave no advice to SEAC on the length of the review period. During the discussion the RAC members noted that in this case it is not necessary to set frequency of measurements of the chromium (VI) air emissions in the draft opinions. This is because the applicant could demonstrate very low emissions of chromium (VI) to the air (below the limit of detection) in the application for authorisation.

c) Adoption of final opinions

1. Diglyme_ISOCHEM (1 use)

The Rapporteur presented the draft Final opinion on the application for authorisation submitted by a downstream user for the industrial use of diglyme as a process solvent in the manufacturing of an intermediate for an active pharmaceutical ingredient (API). The annual volume of the substance used is 22-35 tonnes and the applicant requested a 12 years review period.

Taking into consideration the information submitted by the applicant in the consultation on the draft opinion, RAC concluded that the RMMs and OCs described in the application are appropriate and effective in limiting the risks. However, RAC recommended additional conditions and monitoring arrangements for the authorisation: the applicant must i) continue monitoring exposure (dermal and inhalation), in order to assess newly implemented technical improvements; and ii) implement further RMMs for loading-unloading, sampling and storage in order to minimise exposure and reduce the remaining uncertainties related to the exposure estimation.

Taking into account the moderate to high uncertainty related to the exposure assessment, RAC agreed to recommend to SEAC a no longer than 7 years review period.

The Committee adopted the Final opinion by consensus.

11. AOB

1) Results of the Second Forum Pilot Project on Authorisation

The Forum Secretariat presented the results of the second Forum Pilot Project on Authorisation which will be published soon on ECHA's website. A representative of the Austrian enforcement authority also presented to RAC more concrete Austrian experience gained during inspections. During the discussion it was suggested that further cooperation between RAC and Forum could be useful, for instance regarding the enforceability of the additional conditions and monitoring arrangements recommended by RAC in authorisations.

Part II. Main Conclusions and action points

RAC 41
29 May – 2 June 2017 and 8 - 9 June 2017

(Adopted at the meeting)

Agenda point	
Conclusions / agreements / adoptions	**Action requested after the meeting (by whom/by when)**
2. Adoption of the Agenda	
The Agenda (**RAC/A/41/2017**) was adopted.	**SECR** to upload the adopted Agenda to the RAC CIRCABC and to the ECHA website as part of the RAC-40 minutes.
4. Appointment of (co-)rapporteurs	
RAC appointed the new (co-)rapporteurs for the CLH, Restrictions and AfA dossiers.	**SECR** to upload the list of appointed (co-) rapporteurs to CIRCA BC confidential.
5. Report from other ECHA bodies and activities	
a) Report on RAC-40 action points, written procedures and other ECHA bodies **SECR** presented document **RAC/41/2017/01** and document **RAC/41/2017/02.**	**SECR** to upload the document to the CIRCABC non-confidential website.
b) RAC work plan for all processes SECR presented the update for Q3-4/2017 and Q1-2/2018 work plan for RAC covering the Classification and Labelling, Restriction, Authorisation and Art. 77(3)(c) request processes.	**SECR** to upload the presentation to non-confidential folder of the RAC-41 meeting on S-CIRCABC.
6. Requests under Article 77 (3)(c)	
a) MOCA RAC adopted by consensus the opinion on the evaluation of the scientific relevance of occupational exposure limit for MOCA.	**SECR** to make an editorial check of the opinion document in consultation with the Rapporteur. **SECR** to forward the adopted opinion and to COM by 29 May 2017 and publish it on the ECHA website.
b) Arsenic acid and its inorganic compounds RAC adopted by consensus the opinion on the evaluation of the scientific relevance of occupational exposure limit for arsenic acid and its inorganic compounds.	**SECR** to make an editorial check of the opinion document in consultation with the Rapporteur. **SECR** to forward the adopted opinion and its annexes to COM by 29 May 2017 and publish it on the ECHA website.
7. Requests under Article 95 (3)	

8. Harmonised classification and labelling (CLH)

A. Substances with hazard classes for agreement by A-listing following the usual scrutiny but without plenary debate

Please mention any ATE values for acute toxicity, together with the applicable route of exposure, where these were agreed by RAC through fast-tracking.

fludioxonil (ISO): no classification for the following hazards: physical hazards, acute toxicity (all routes of exposure), STOT SE, skin corrosion / irritation, serious eye damage / eye irritation, respiratory or skin sensitisation, STOT RE, germ cell mutagenicity, toxicity to reproduction

N,N-diethyl-M-toluamide, deet: Acute Tox. 4; H302

B. Substances with hazard classes for agreement in plenary session

Please mention any ATE values for acute toxicity, together with the applicable route of exposure, where these were agreed by RAC, including those agreed through fast-tracking.

1. phenyl bis(2,4,6-trimethylbenzoyl)-phosphine oxide
2. diisohexyl phthalate
3. N,N-diethyl-m-toluamide; DEET
4. benzo[rst]pentaphene
5. dibenzo[b,def]chrysene, dibenzo[a,h]pyrene
6. 4,4'-sulfonylbisphenol, polymer with ammonium chloride (NH4Cl), pentachlorophosphorane and phenol
7. titanium dioxide
8. Fludioxonil (ISO)
9. pentapotassium 2,2',2'',2''',2''''-(ethane-1,2-diylnitrilo)pentaacetate (DTPA-K5)
10. N-carboxymethyliminobis(ethylenenitrilo)tetra(acetic acid) (DTPA-H5)
11. pentasodium (carboxylatomethyl)iminobis(ethylenenitrilo)tetraacetate (DTPA-Na5)

1. phenyl bis(2,4,6-trimethylbenzoyl)-phosphine oxide

RAC adopted by consensus the opinion with a proposal for the harmonised classification and labelling as indicated in Table 1 below. [Skin Sens. 1A; H317, Retain: Aquatic Chronic 4; H413]	**Rapporteurs** to revise the opinion in accordance with the discussion in RAC and to provide it to SECR. **SECR** to make an editorial check of the opinion documents in consultation with the Rapporteurs. **SECR** to forward the adopted opinion and its annexes to COM and publish it on the ECHA website.

2. diisohexyl phthalate

RAC adopted by consensus the opinion with a proposal for the harmonised classification and labelling as indicated in Table 1 below. [Repr. 1B; H360FD]	**Rapporteur** to revise the opinion in accordance with the discussion in RAC and to provide it to SECR. **SECR** to make an editorial check of the opinion documents in consultation with the Rapporteur. **SECR** to forward the adopted opinion and its annexes to COM and publish it on the ECHA website.
3. N,N-diethyl-m-toluamide; DEET	
RAC adopted by consensus the opinion with a proposal for the harmonised classification and labelling as indicated in Table 1 below. [Acute Tox. 4; H302 Remove: Aquatic Chronic 3; H412]	**Rapporteurs** to revise the opinion in accordance with the discussion in RAC and to provide it to SECR. **SECR** to make an editorial check of the opinion documents in consultation with the Rapporteurs. **SECR** to forward the adopted opinion and its annexes to COM and publish it on the ECHA website.
4. benzo[rst]pentaphene	
RAC adopted by consensus the opinion with a proposal for the harmonised classification and labelling as indicated in Table 1 below. [Muta 2; H341, Carc. 1B; H350]	**Rapporteurs** to revise the opinion in accordance with the discussion in RAC and to provide it to SECR. **SECR** to make an editorial check of the opinion documents in consultation with the Rapporteurs. **SECR** to forward the adopted opinion and its annexes to COM and publish it on the ECHA website.
5. dibenzo[b,def]chrysene, dibenzo[a,h]pyrene	
RAC adopted by consensus the opinion with a proposal for the harmonised classification and labelling as indicated in Table 1 below. [Muta 2; H341, Carc. 1B; H350]	**Rapporteurs** to revise the opinion in accordance with the discussion in RAC and to provide it to SECR. **SECR** to make an editorial check of the opinion documents in consultation with the Rapporteurs. **SECR** to forward the adopted opinion and its annexes to COM and publish it on the ECHA website.
6. 4,4'-sulfonylbisphenol, polymer with ammonium chloride (NH4Cl), pentachlorophosphorane and phenol	

RAC adopted by consensus the opinion with a proposal for the harmonised classification and labelling as indicated in Table 1 below. [n.c., due to removal of Aquatic Chronic 4; H413]	**Rapporteur** to revise the opinion in accordance with the discussion in RAC and to provide it to SECR. **SECR** to make an editorial check of the opinion documents in consultation with the Rapporteurs. **SECR** to forward the adopted opinion and its annexes to COM and publish it on the ECHA website.
7. titanium dioxide	
RAC agreed on the harmonised classification and labelling as indicated in Table 2 below. [Carc. 2; H351 (inhalation)]	**Rapporteurs** to revise the opinion in accordance with the discussion in RAC and to provide it to SECR. **SECR** to launch a RAC commenting round for the final version of the opinion. **SECR** to launch a written procedure / put the final opinion for adoption at RAC 42.
8. Fludioxonil (ISO)	
RAC adopted by consensus the opinion with a proposal for the harmonised classification and labelling as indicated in Table 1 below. [Aquatic Acute 1; H400, M=1, Aquatic Chronic 1; H410, M=10]	**Rapporteurs** to revise the opinion in accordance with the discussion in RAC and to provide it to SECR. **SECR** to make an editorial check of the opinion documents in consultation with the Rapporteurs. **SECR** to forward the adopted opinion and its annexes to COM and publish it on the ECHA website.
9. pentapotassium 2,2',2'',2''',2''''-(ethane-1,2-diylnitrilo)pentaacetate (DTPA-K5)	
RAC adopted by consensus the opinion with a proposal for the harmonised classification and labelling as indicated in Table 1 below. [Repr. 1B; H360D, STOT RE 2; H373 (inhalation) *Agreed at RAC 40*: Acute Tox. 4; H332, Eye Irrit. 2; H319]	**Rapporteur** to revise the opinion in accordance with the discussion in RAC and to provide it to SECR. **SECR** to make an editorial check of the opinion documents in consultation with the Rapporteur. **SECR** to forward the adopted opinion and its annexes to COM and publish it on the ECHA website.
10. N-carboxymethyliminobis(ethylenenitrilo)tetra(acetic acid) (DTPA-H5)	
RAC adopted by consensus the opinion with a proposal for the harmonised classification and labelling as indicated in Table 1 below. [Repr. 1B; H360D, STOT RE 2; H373 (inhalation) *Agreed at RAC 40*: Acute Tox. 4; H332, Eye Irrit. 2; H319]	**Rapporteur** to revise the opinion in accordance with the discussion in RAC and to provide it to SECR. **SECR** to make an editorial check of the opinion documents in consultation with the Rapporteur. **SECR** to forward the adopted opinion and its annexes to COM and publish it on the ECHA website.

11. pentasodium (carboxylatomethyl)iminobis(ethylenenitrilo)tetraacetate (DTPA-Na5)	
RAC adopted by consensus the opinion with a proposal for the harmonised classification and labelling as indicated in Table 1 below. [Repr. 1B; H360D, STOT RE 2; H373 (inhalation) *Agreed at RAC 40*: Acute Tox. 4; H332]	**Rapporteur** to revise the opinion in accordance with the discussion in RAC and to provide it to SECR. **SECR** to make an editorial check of the opinion documents in consultation with the Rapporteur. **SECR** to forward the adopted opinion and its annexes to COM and publish it on the ECHA website.
9. Restrictions	
9.2 Restriction Annex XV dossiers	
a) Conformity check	
1) Lead in shot RAC agreed that the dossier conforms to the Annex XV requirements. RAC took note of the recommendations to the dossier submitter.	**Rapporteurs** to consider the following aspects, while drafting the opinion: - Scope of the restriction related to the definition of wetlands in the Ramsar Convention vs designated Ramsar Sites, - Possession of gunshot in or near wetlands, - The human health impact and consistency with the lead in PVC dossier, - How to reflect that Member States having stricter legislation covering non-wetland areas would not have to repeal their existing laws. **SECR** to compile the RAC and SEAC final outcomes of the conformity check and upload this to S-CIRCABC IG. **SECR** to inform the dossier submitter on the outcome of the conformity check.
b) Opinion development	
1) Diisocyanates The Rapporteurs presented and RAC discussed the first draft opinion. RAC agreed to include all diisocyanates in the scope of the restriction. RAC agreed that the restriction is taken forward with Occupational Asthma as the main concern.	**Rapporteurs** to take the discussion into account in the second draft opinion.

RAC agreed that the exposure assessment conducted by the DS based on air monitoring data from three databases and from relevant literature, and on biomonitoring data is a reasonable estimate of an overall exposure to diisocyanates in the EU. RAC agreed that there is identified risk to the workers that is not adequately controlled.	
2) Lead in PVC The Rapporteurs presented and RAC discussed the first draft opinion. RAC agreed with the conclusion of the human health hazard assessment, i.e. that a threshold for neurodevelopmental effects in children (as well as renal effects in adults) has not been established. This may be the subject of further contributions of information from industry.	**Rapporteurs** to take the discussion into account in the second draft opinion.
10. Authorisation	
10.1 General authorisation issues	
a) New applications received during the May 2017 submission window	
RAC noted the information presented by the Secretariat.	
b) Review reports	
RAC noted the information presented by the Secretariat. RAC discussed review reports presented by the Secretariat.	**SECR** to consider discussion on the review reports.
c) Review periods longer than 12 years	
RAC noted the information presented by the Secretariat. RAC discussed review reports presented by the Secretariat.	**SECR** to consider discussion on the review periods.
d) AfA DNEL/DR	
1. Carcinogenicity dose-response relationship and DNEL setting for the reprotoxic properties of coal-tar pitch, high temperature (CTPHT)	

2. Carcinogenicity dose-response relationship of anthracene oil RAC noted the presentation by the ECHA Consultant. RAC discussed the proposed approach and provided advice regarding the way forward, in particular: - to describe and use existing risk assessments by international and national bodies; - clearly describe and assess the epidemiological studies upon which the previous assessments are based; - to assess advantages and disadvantages of proposed basic markers for CTPHT various routes of exposure (benzo[a]pyrene vs. PAH4/8); - oral route indirect exposure markers (PAH 4/8); - 1-hydroxypyrene as a potential biomarker in exposure assessment of workers exposed to anthracene oil.	**ECHA Consultant** to consider the plenary discussion in drafting of the notes.
10.2 Authorisation applications	
a) Discussion on key issues	
1. PC_SC_Saes (2 uses) RAC discussed the key issues for this application for authorisation and provided advice as needed to the Rapporteur, also in relation to the conformity.	**SECR** to inform SEAC about the outcome of the discussion.
b) Agreement on Draft Opinions	
1. Diglyme_Acton (1 use) RAC agreed on the draft opinion as proposed by the Rapporteurs. RAC is of the opinion that RMMs and OCs are not sufficient to control workers exposure and not all possible engineering controls are currently implemented. RAC is of the opinion that additional and/or improved engineering controls are needed in order to reduce current dermal exposures. RAC is of the opinion that for the use applied for, the applicant has not demonstrated adequate control of the risk for workers (at the sites of DU 1, DU 3 and DU 4). The applicant did demonstrate adequate control of the risk of the general population exposed via the environment (all sites). RAC decided to recommend additional monitoring arrangements for the authorisation and for review reports, as described in the draft opinion (wipe testing initially at least twice a year).	**Rapporteurs** together with **SECR** to do the final editing of the draft opinion. **SECR** to send the draft opinion to the applicant for commenting.

RAC recommends to SEAC to consider a review period of no longer than 4 years.	
2. EDC_Bayer (1 use) RAC agreed on the draft opinion as proposed by the Rapporteurs. RAC is of the opinion that the RMMs and OCs described in the application are appropriate and effective in limiting the risk to workers and the general population. RAC decided to recommend additional monitoring arrangements for the authorisation, as described in the draft opinion. RAC also agreed to add a condition for annual environmental monitoring related to the expected increase in the production. RAC agreed to give no advice to SEAC on the length of the review period.	**Rapporteurs** together with **SECR** to do the final editing of the draft opinion (to include a condition for monitoring for the environment). **SECR** to send the draft opinion to the Applicant for commenting.
4. MOCA_Reachlaw (1 use) RAC agreed on the draft opinion as proposed by the Rapporteur. RAC is of the opinion that the RMMs and OCs are <u>not</u> appropriate and effective in limiting the risk to workers and the general population. RAC decided to recommend additional conditions and monitoring arrangements for the authorisation, as described in the draft opinion. RAC recommends to SEAC to consider a review period of no longer than 7 years.	**Rapporteur** together with **SECR** to do the final editing of the draft opinion. **SECR** to send the draft opinion to the Applicant for commenting.
5. CT_ZFL (2 uses) RAC agreed on the draft opinions as proposed by the Rapporteurs. RAC is of the opinion that RMMs and OCs are appropriate in limiting the risk to workers. In line with the Applicant's intention (confirmed during the trialogue) RAC recommended additional conditions for the authorisation (namely to cover tank 51) RAC decided to recommend additional conditions and monitoring arrangements for review reports, as described in the draft opinions. RAC agreed to give no advice to SEAC on the length of the review period.	**Rapporteurs** together with **SECR** to do the final editing of the draft opinions. **SECR** to send the draft opinions to the Applicant for commenting.
6. SD_ZFL (1 use) RAC agreed on the draft opinion as proposed by the Rapporteurs.	**Rapporteurs** together with **SECR** to do the final editing of the draft opinion. **SECR** to send the draft opinion to the Applicant for commenting.

RAC is of the opinion that RMMs and OCs are appropriate in limiting the risk to workers. In line with the Applicant's intention (confirmed during the trialogue) RAC recommended additional conditions for the authorisation (namely to cover tank 51) RAC decided to recommend additional conditions and monitoring arrangements for review reports, as described in the draft opinion. RAC agreed to give no advice to SEAC on the length of the review period.	

7. CT_Haas (1 use) **8. SD_Haas (1 use)** **9. PD_Haas (1 use)** **10. SC_Aviall (2 uses)** <u>Formulation</u> (SC) RAC agreed on the draft opinion as proposed by the Rapporteurs with modifications as proposed during the meeting. RAC is of the opinion that the RMMs and OCs are not appropriate and effective in limiting the risk to workers and the general population. Considering the uncertainties relating to the risks, RAC decided to recommend additional conditions and monitoring arrangements for the authorisation and review report, specifying that the monitoring would be done at least annually. RAC also concluded that the monitoring frequency for this authorisation may be reduced to at least every three years once exposure to humans and releases to the environment have been reduced to as low a level as technically and practically possible and where it is demonstrated that OCs and RMMs function appropriately. RAC agreed to give no advice to SEAC on the length of the review period. <u>Surface treatment and coating (CT, SC, SD, PD)</u> RAC agreed on the draft opinions as proposed by the Rapporteurs with modifications as proposed during the meeting. RAC is of the opinion that the RMMs and OCs are not appropriate and effective in limiting the risk to workers and the general population. Considering the uncertainties relating to the risks, RAC decided to recommend additional conditions and monitoring arrangements for the authorisation and review report, as described in the draft opinions. RAC agreed to give no advice to SEAC on the length of the review period, except for the CT Haas, where RAC recommends to SEAC to consider a review period of no longer than 7 years.	**Rapporteurs** together with **SECR** to do the final editing of the draft opinions. **SECR** to send the draft opinions to the Applicant for commenting.

11. SD_Colle (1 use) RAC agreed on the draft opinion as proposed by the Rapporteurs. RAC is of the opinion that the RMMs and OCs are appropriate and effective in limiting the risk to workers and the general population. RAC decided to recommend additional conditions and monitoring arrangements for the review report, as described in the draft opinion. RAC agreed to give no advice to SEAC on the length of the review period.	**Rapporteurs** together with **SECR** to do the final editing of the draft opinion. **SECR** to send the draft opinion to the Applicant for commenting.
12. CT_Hansgrohe (2 uses) RAC agreed on the draft opinions as proposed by the Rapporteurs. RAC is of the opinion that RMMs and OCs are appropriate and effective and in line with the hierarchy of control. RAC decided to recommend additional monitoring arrangements for the review report with regard to air emissions, as described in the draft opinions. RAC agreed to give no advice to SEAC on the length of the review period.	**Rapporteurs** together with **SECR** to do the final editing of the draft opinions. **SECR** to send the draft opinions to the Applicant for commenting.
c) Adoption of final opinions	
Diglyme ISOCHEM (1 use) RAC adopted the final opinion following the Applicants' comments on the draft opinion. RAC concludes that adequate control has been demonstrated for workers' exposures, as well as for the general population exposed via the environment. RAC is of the opinion that the RMMs and OCs are appropriate and effective in limiting the risk to workers and the general population exposed via the environment. RAC decided to recommend additional monitoring arrangements for the authorisation and the review reports, as described in the draft opinion (including the installation of closed sampling, modification in transferring system, implementation of adequate housekeeping / cleaning procedures and practices). RAC decided to recommend to SEAC a review period no longer than 7 years.	**Rapporteur** together with **SECR** to do the final editing of the opinion. **SECR** to send the final opinion to the EC, MSs and the Applicants.

11. AOB: Results of Second Forum Pilot Project on Authorisation	
RAC noted and discussed the report on the Second Forum Pilot Project presented by the Forum Secretariat and Austrian experience in enforcing REACH authorisation decisions presented by a Forum member.	**SECR** to consider discussion (enforceability) in further development of the AfA process, in particular the technical suitability of conditions.
12. Action points and main conclusions of RAC-41	
SECR to upload the adopted action points to CIRCA BC.	

Table 1: CLH opinions which were adopted at RAC-41

RAC-41

1. Pentapotassium 2,2',2'',2''',2''''-(ethane-1,2-diylnitrilo)pentaacetate
2. N-carboxymethyliminobis(ethylenenitrilo)tetra(acetic acid)
3. Pentasodium (carboxylatomethyl)iminobis(ethylenenitrilo)tetraacetate
4. benzo[rst]pentaphene
5. Dibenzo[b,def]chrysene
6. 4,4'-sulfonylbisphenol, polymer with ammonium chloride (NH4Cl), pentachlorophosphorane and phenol
7. Fludioxonil (ISO)
8. Diisohexyl phthalate
9. Phenyl bis(2,4,6-trimethylbenzoyl)-phosphine oxide
10. N,N-diethyl-m-toluamide; DEET
11. Titanium dioxide

Pentapotassium 2,2',2'',2''',2''''-(ethane-1,2-diylnitrilo)pentaacetate ("DTPA-K5")

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard state-ment Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	No current Annex VI entry										
Dossier submitter's proposal	TBD	pentapotassium 2,2′,2″,2‴,2⁗-(ethane-1,2-diylnitrilo)pentaacetate	404-290-3	7216-95-7	Repr. 2 STOT RE 2 Acute Tox. 4 Eye Irrit. 2	H361d H373 (Inhalation) H332 H319	GHS08 GHS07 Wng	H361d H332 H373 H319			
RAC opinion	TBD	pentapotassium 2,2′,2″,2‴,2⁗-(ethane-1,2-diylnitrilo)pentaacetate	404-290-3	7216-95-7	Repr. 1B STOT RE 2 Acute Tox. 4 Eye Irrit. 2	H360D H373 (Inhalation) H332 H319	GHS08 GHS07 Dgr	H360D H373 H332 H319			
Resulting Annex VI entry if agreed by COM	TBD	pentapotassium 2,2′,2″,2‴,2⁗-(ethane-1,2-diylnitrilo)pentaacetate	404-290-3	7216-95-7	Repr. 1B STOT RE 2 Acute Tox. 4 Eye Irrit. 2	H360D H373 (Inhalation) H332 H319	GHS08 GHS07 Dgr	H360D H373 H332 H319			

***N*-carboxymethyliminobis(ethylenenitrilo)tetra(acetic acid) ("DTPA-H5")**

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard state-ment Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	No current Annex VI entry										
Dossier submitter's proposal	TBD	*N*-carboxymethyliminobis(ethylenenitrilo)tetra(acetic acid)	200-652-8	67-43-6	Repr. 2 STOT RE 2 Acute Tox. 4 Eye Irrit. 2	H361d H373 (Inhalation) H332 H319	GHS08 GHS07 Wng	H361d H373 H332 H319			
RAC opinion	TBD	*N*-carboxymethyliminobis(ethylenenitrilo)tetra(acetic acid)	200-652-8	67-43-6	Repr. 1B STOT RE 2 Acute Tox. 4 Eye Irrit. 2	H360D H373 (Inhalation) H332 H319	GHS08 GHS07 Dgr	H360D H373 H332 H319			
Resulting Annex VI entry if agreed by COM	TBD	*N*-carboxymethyliminobis(ethylenenitrilo)tetra(acetic acid)	200-652-8	67-43-6	Repr. 1B STOT RE 2 Acute Tox. 4 Eye Irrit. 2	H360D H373 (Inhalation) H332 H319	GHS08 GHS07 Dgr	H360D H373 H332 H319			

Pentasodium (carboxylatomethyl)iminobis(ethylenenitrilo)tetraacetate ("DTPA-Na5")

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard state-ment Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	No current Annex VI entry										
Dossier submitter's proposal	TBD	pentasodium (carboxylatomethyl)iminobis(ethylenenitrilo)tetraacetate	205-391-3	140-01-2	Repr. 2 STOT RE 2 Acute Tox. 4	H361d H373 (Inhalation) H332	GHS08 GHS07 Wng	H361d H373 H332			
RAC opinion	TBD	pentasodium (carboxylatomethyl)iminobis(ethylenenitrilo)tetraacetate	205-391-3	140-01-2	Repr. 1B STOT RE 2 Acute Tox. 4	H360D H373 (Inhalation) H332	GHS08 GHS07 Dgr	H360D H373 H332			
Resulting Annex VI entry if agreed by COM	TBD	pentasodium (carboxylatomethyl)iminobis(ethylenenitrilo)tetraacetate	205-391-3	140-01-2	Repr. 1B STOT RE 2 Acute Tox. 4	H360D H373 (Inhalation) H332	GHS08 GHS07 Dgr	H360D H373 H332			

Benzo[rst]pentaphene

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard state-ment Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	No current Annex VI entry										
Dossier submitters proposal	TBD	benzo[*rst*]pentaphene	205-877-5	189-55-9	Carc. 1B Muta. 2	H350 H341	GHS08 Dgr	H350 H341			
RAC opinion	TBD	benzo[*rst*]pentaphene	205-877-5	189-55-9	Carc. 1B Muta. 2	H350 H341	GHS08 Dgr	H350 H341			
Resulting Annex VI entry if agreed by COM	TBD	benzo[*rst*]pentaphene	205-877-5	189-55-9	Carc. 1B Muta. 2	H350 H341	GHS08 Dgr	H350 H341			

Dibenzo[b,def]chrysene

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard state-ment Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	No current Annex VI entry										
Dossier submitters proposal	TBD	dibenzo[*b,def*]chrysene; dibenzo[a,h]pyrene	205-878-0	189-64-0	Carc. 1B Muta. 2	H350 H341	GHS08 Dgr	H350 H341			
RAC opinion	TBD	dibenzo[*b,def*]chrysene; dibenzo[a,h]pyrene	205-878-0	189-64-0	Carc. 1B Muta. 2	H350 H341	GHS08 Dgr	H350 H341			
Resulting Annex VI entry if agreed by COM	TBD	dibenzo[*b,def*]chrysene; dibenzo[a,h]pyrene	205-878-0	189-64-0	Carc. 1B Muta. 2	H350 H341	GHS08 Dgr	H350 H341			

4,4'-sulfonylbisphenol, polymer with ammonium chloride (NH4Cl), pentachlorophosphorane and phenol

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	**International Chemical Identification**	**EC No**	**CAS No**	**Classification**		**Labelling**			**Specific Conc. Limits, M-factors**	**Notes**
					Hazard Class and Category Code(s)	**Hazard statement Code(s)**	**Pictogram, Signal Word Code(s)**	**Hazard state-ment Code(s)**	**Suppl. Hazard statement Code(s)**		
Current Annex VI entry	604-083-00-X	4,4'-sulfonylbisphenol, polymer with ammonium chloride (NH_4Cl), pentachlorophosphorane and phenol	439-270-3	260408-02-4	Aquatic Chronic 4	H413		H413			
Dossier submitters proposal	604-083-00-X	4,4'-sulfonylbisphenol, polymer with ammonium chloride (NH_4Cl), pentachlorophosphorane and phenol	439-270-3	260408-02-4	**Remove** Aquatic Chronic 4	**Remove** H413		**Remove** H413			
RAC opinion	604-083-00-X	4,4'-sulfonylbisphenol, polymer with ammonium chloride (NH_4Cl), pentachlorophosphorane and phenol	439-270-3	260408-02-4	**Remove** Aquatic Chronic 4	**Remove** H413		**Remove** H413			
Resulting Annex VI entry if agreed by COM	Removal of the existing entry from Annex VI										

Fludioxonil (ISO)

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	No current Annex VI entry										
Dossier submitters proposal	TBD	fludioxonil (ISO); 4-(2,2-difluoro-1,3-benzodioxol-4-yl)-1H-pyrrole-3-carbonitrile		131341-86-1	Aquatic Acute 1 Aquatic Chronic 1	H400 H410	GHS09 Wng	H410		M=1 M=1	
RAC opinion	TBD	fludioxonil (ISO); 4-(2,2-difluoro-1,3-benzodioxol-4-yl)-1H-pyrrole-3-carbonitrile		131341-86-1	Aquatic Acute 1 Aquatic Chronic 1	H400 H410	GHS09 Wng	H410		M=1 M=10	
Resulting Annex VI entry if agreed by COM	TBD	fludioxonil (ISO); 4-(2,2-difluoro-1,3-benzodioxol-4-yl)-1H-pyrrole-3-carbonitrile		131341-86-1	Aquatic Acute 1 Aquatic Chronic 1	H400 H410	GHS09 Wng	H410		M=1 M=10	

Diisohexyl phthalate

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard state-ment Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	No current Annex VI entry										
Dossier submitters proposal	TBD	diisohexyl phthalate	276-090-2	71850-09-4	Repr. 1B	H360FD	GHS08 Dgr	H360FD			
RAC opinion	TBD	diisohexyl phthalate	276-090-2	71850-09-4	Repr. 1B	H360FD	GHS08 Dgr	H360FD			
Resulting Annex VI entry if agreed by COM	TBD	diisohexyl phthalate	276-090-2	71850-09-4	Repr. 1B	H360FD	GHS08 Dgr	H360FD			

Phenyl bis(2,4,6-trimethylbenzoyl)-phosphine oxide

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard state-ment Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	015-189-00-5	Phenyl bis(2,4,6-trimethylbenzoyl)-phosphine oxide	423-340-5	162881-26-7	Skin Sens. 1 Aquatic Chronic 4	H317 H413	GHS07 Wng	H317 H413			
Dossier submitters proposal	015-189-00-5	Phenyl bis(2,4,6-trimethylbenzoyl)-phosphine oxide	423-340-5	162881-26-7	**Modify** Skin Sens. 1A **Remove** Aquatic Chronic 4	**Retain** H317 **Remove** H413	**Retain** GHS07 Wng	**Retain** H317 **Remove** H413			
RAC opinion	015-189-00-5	Phenyl bis(2,4,6-trimethylbenzoyl)-phosphine oxide	423-340-5	162881-26-7	**Modify** Skin Sens. 1A **Retain** Aquatic Chronic 4	**Retain** H317 H413	**Retain** GHS07 Wng	**Retain** H317 H413			
Resulting Annex VI entry if agreed by COM	015-189-00-5	Phenyl bis(2,4,6-trimethylbenzoyl)-phosphine oxide	423-340-5	162881-26-7	Skin Sens. 1A Aquatic Chronic 4	H317 H413	GHS07 Wng	H317 H413			

N,N-diethyl-m-toluamide; DEET

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	616-018-00-2	N,N-diethyl-m-toluamide; deet	205-149-7	134-62-3	Acute Tox. 4* Skin Irrit. 2 Eye Irrit. 2 Aquatic Chronic 3	H302 H315 H319 H412	GHS07 Wng	H302 H315 H319 H412			
Dossier submitters proposal	616-018-00-2	N,N-diethyl-m-toluamide; deet	205-149-7	134-62-3	**Retain** Skin Irrit. 2 Eye Irrit. 2 **Modify** Acute Tox. 4 **Remove** Aquatic Chronic 3	**Retain** H315 H319 **Modify** H302 **Remove** H412	**Retain** GHS07 Wng	**Retain** H315 H319 **Modify** H302 **Remove** H412			
RAC opinion	616-018-00-2	N,N-diethyl-m-toluamide; deet	205-149-7	134-62-3	**Retain** Skin Irrit. 2 Eye Irrit. 2 **Modify** Acute Tox. 4 **Remove** Aquatic Chronic 3	**Retain** H315 H319 **Modify** H302 **Remove** H412	**Retain** GHS07 Wng	**Retain** H315 H319 **Modify** H302 **Remove** H412			
Resulting Annex VI entry if agreed by COM	616-018-00-2	N,N-diethyl-m-toluamide; deet	205-149-7	134-62-3	Acute Tox. 4 Skin Irrit. 2 Eye Irrit. 2	H302 H315 H319	GHS07 Wng	H302 H315 H319			

Table 2: CLH opinions not (yet) adopted at RAC-41, but with agreed hazard classes

Titanium dioxide

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard state-ment Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	No current Annex VI entry										
Dossier submitters proposal	TBD	titanium dioxide	236-675-5	13463-67-7	Carc. 1B	H350i	GHS08 Dgr	H350i			
RAC opinion	TBD	titanium dioxide	236-675-5	13463-67-7	Carc. 2	H351 (inhalation)	GHS08 Dgr	H351 (inhalation)			
Resulting Annex VI entry if agreed by COM	TBD	titanium dioxide	236-675-5	13463-67-7	Carc. 2	H351 (inhalation)	GHS08 Dgr	H351 (inhalation)			

Part III. List of Attendees of the RAC-41 meeting

29 May – 2 June and 8-9 June 2017

RAC Members
ANDREOU Kostas
BARAŃSKI Bogusław
BIRO Anna
BJØRGE Christine
BRANISTEANU Radu
CARVALHO João
CHANKOVA-PETROVA Stephka
CHIURTU Elena (co-opted Member)
CZERCZAK Slawomir
DE LA FLOR TEJERO Ignacio
DUNAUSKIENĖ Lina
DUNGEY Stephen
GRUIZ Katalin
GUSTAFSON Anne-Lee
HAKKERT Betty
HUSA Stine
HÖLZL Christine
JANKOWSKA Elżbieta (co-opted Member)
KADIĶIS Normunds
KAPELARI Sonja
LECLOUX Helene
LEINONEN Riitta
LUND Bert-Ove
MARTINEK Michal
MENARD Anja
MOELLER Ruth
MULLOOLY Yvonne
MURRAY Brendan
NEUMANN Michael
PARIS Pietro
PASQUIER Elodie
POLAKOVICOVA Helena
PRONK Marja
RUCKI Marian
RUPPRICH Norbert
SANTONEN Tiina
SCHLÜTER Urs
SCHULTE Agnes
SMITH Andrew
SOGORB Miguel
SØRENSEN Peter Hammer
SPETSERIS Nikolaos
STAHLMANN Ralf
TOBIASSEN Lea Stine
TSITSIMPIKOU Christina
UŽOMECKAS Žilvinas
VAN DER HAAR Rudolf (co-opted Member)
VARNAI Veda Marija
VIEGAS Susana (co-opted Member)
Apologies, Members
AGAPIOU Agapios
ILIE Mihaela
RUBBIANI Maristella
Apologies, stakeholders
DOLORES Romano, EEB

Commission observers
GARCIA-JOHN Enrique, DG GROW
JAMERS An, DG GROW
HEIDORN Christian, DG ENV
VAN DER JAGT Katinka, DG ENV
RAC advisors
ESPOSITO Dania (Pietro Paris) CLH fludioxonil
LOIKKANEN Jarkko (Riitta Leinonen)
PAPPONEN Hinni (Riitta Leinonen)
PECZKOWSKA Beata (Boguslaw Baranski)_2,4,6-trimethylbenzoyl-phosphine oxide
ROMOLI Debora (Pietro Paris)
STOCKMANN-JUVALA Helene (Tiina Santonen)
SUUTARI Tiina (Riitta Leinonen)
THOMAS Sally (Andrew Smith)_two PAHs
WOUTERSEN Marjolijn (Betty Hakkert)_CLH DEET

Stakeholders observers
ANNYS Erwin, Cefic
BARRY Frank, ETUC
BRZUSKA Karolina (Cosmetics Europe); occasional stakeholder observer, CLH TiO2
DOOME Roger (IMA-Europe); occasional stakeholder observer, CLH TiO2
De KORT Patrick (EuPC); occasional stakeholder observer, CLH TiO2
LEROY Didier (CEPE); occasional stakeholder observer, CLH TiO2
MUNARI Tomaso, EuCheMS
ROBINSON Janice (EuPC); occasional stakeholder observer, CLH TiO2
ROWE Rocky, ECPA
TILLIEUX Geoffroy (EUPC;occasional stakeholder observer, restrictions)
VEROUGSTRAETE Violaine, Eurometaux
Dossier submitters
CHARLES Sandrine (FR, TiO2)
HINDLE Stuart (Akzo/DOW) (DE, DTPAs)
MICHEL Cécile (FR, TiO2)
ROUW Aarnout (DE, diisocyanates)
WALENDZIK Gudrun (DE, diisocyanates)

Industry experts
ALBUQUERQUE Ruth (ECPA, Syngenta, fludioxonil)
BATTERSBY Rodger (Eurometaux, EBRC Consulting GmbH, titanium dioxide)
BOENIGK Winfried (Cefic, Ruetgers Group, DCHT)
CAVALLERO Alain (Cefic, European Stabiliser Producer Association ESPA, Lead in PVC)
McCUNNAY Robert J (EuPC, Harward Medical School, TiO2)
LÜCKE-BRUNK Gudrun (Cefic, Covestro Deutschland AG, diisocyanates)
TREMBLAY Raphael (Cosmetics Europe, Procter&Gamble, TiO2)
WARHEIT David (Cefic, Chemours, titanium dioxide)
WHITTLE Edward (Cefic, SC Johnson, DEET)
Invited experts
LINHART Igor (University of Chemistry and Technology, Prague, dose-response)
LISKOVA Lenka (Výzkumný Ústav Organických Syntéz (VUOS), dose-response))
NOVOTNY Tomas (EcoMole Ltd, dose-response)
PRICHYSTALOVA Radka (Technical University of Ostrava, dose-response)

REMOTE PARTICIPANTS
RAC Members:
DUNGEY Steve
LECLOUX Helene
SOGORB Miquel
SMITH Andrew
SOERENSEN Peter Hammer
Advisers
McCABE Laura (adviser to Andrew Smith)
SEAC Members (AfA and restriction rapporteurs)
CSERGO Robert
FANKHAUSER Simone
FIORE Karine
KRAJNC Karmen
LUEDEKE Andreas
LUIT Richard
Forum member
ANWANDER Eugen

Dossier submitters		JONES Stella
Denmark		KANELLOPOULOU Athanasia
CHRISTENSEN Anne Munch (fludioxonil)		KARJALAINEN Ari
France		KIVELÄ Kalle
CHARLES Sandrine (titanium dioxide)		KOKKOLA Leila
		KOSK-BIENKO Joanna
MICHEL Cécile (titanium dioxide)		KOULUOMPOS Vasileios
ROUSSELLE Christophe (titanium dioxide)		LAPENNA Silvia
Germany		LINNA Risto
AVERBECK Frauke (diisocyanates)		LIOPA Elīna
BERNHEIM Teresa (diisocyanates)		LOGTMEIJER Christiaan
GUHE Christine (diisocyanates)		LUDBORŽS Arnis
HEESCHE-WAGNER Kerstin (diisocyanates)		MARQUEZ-CAMACHO Mercedes
PROG Matthias (diisocyanates)		MAZZOLINI Anna
ROTHER Dag (diisocyanates)		MERKOURAKIS Spyridon
		MUSHTAQ Fesil
Sweden		MÜLLER Gesine
BIRGANDER Pernilla (DEET)		NATHANAIL Alexis
Commission		NICOT Thierry
BERTATO Valentina		NYGREN Jonas
JAMERS An		ORISPÄÄ Katja
MORRIS Alick-James		O´ROURKE Regina
LUVARA Giuseppina		PELTOLA Jukka
ROZWADOWSKI Jacek		PENNESE Daniele
Van Der JAGT Katinka		PERAZZOLA Chiara
EFSA		PREVEDOUROS Konstantinos
LODI Federica		REGIL Pablo
VETTORI Vittoria Maria		RODRIGUEZ-IGLESIAS Pilar
		ROGGEMAN Maarten
ECHA staff		SADAM Diana
BERGES Markus		SIMOES Ricardo
BLAINEY Mark		SIMPSON Peter
BOWMER Tim, Chairman		SOSNOWSKI Piotr
BROECKAERT Fabrice		UPHOFF Andreas
DVOŘÁKOVÁ Dana		HELLSTEN Kati
ERICSSON Gunilla		HOPLAND Eivind
GIGIOLI Roberto		HENRICHSON Sanna

Part IV. LIST OF ANNEXES

ANNEX I Final Agenda of the RAC-41 meeting

ANNEX II List of documents submitted to the Members of the Committee for Risk Assessment for the RAC-41 meeting

ANNEX III Declarations of conflicts of interest to the Agenda of the RAC-41 meeting

ANNEX IV Administrative issues and information items

ANNEX V Statement provided by the Dossier Submitter of the TiO_2 CLH proposal

ANNEX VI Rapporteur's preparatory workshop on the Authorisation Applications

29 May 2017
RAC/A/41/2017

Final Agenda
41st meeting of the Committee for Risk Assessment

29 May – 2 June 2017
and
8-9 June 2017

ECHA Conference Centre (Annankatu 18, Helsinki)

Monday 29 May starts at 09.00
Friday 2 June breaks at 12.30
Thursday 8 June resumes at 9.00
Friday 9 June ends at 13.00

Item 1 – Welcome and Apologies

Item 2 – Adoption of the Agenda

RAC/A/41/2017
For adoption

Item 3 – Declarations of conflicts of interest to the Agenda

Item 4 – Appointment of (co-)rapporteurs

a) Appointment of (co-)rapporteurs for CLH dossiers, restriction dossiers, authorisation applications, DNEL/dose-response relationships, Article 95 (3) requests and Article 77 (3) (c) requests

RAC/41/2017/01
Restricted room document
For agreement

Item 5 – Report from other ECHA bodies and activities

a) Report on RAC 40 action points, written procedures and update on other ECHA bodies

RAC/41/2017/02

RAC/41/2017/03
Room document

For information

b) RAC workplan for all processes

For information

Item 6 – Requests under Article 77 (3)(c)

a) MOCA

For adoption

b) Arsenic acid and its inorganic salts

For adoption

Item 7 – Requests under Article 95 (3)

a) OEL-DNEL methodology

For information/discussion

Item 8 – Harmonised classification and labelling (CLH)

8.1 General CLH issues

a) Evaluation fast track procedure

For discussion

8.2. CLH dossiers

A. Hazard classes for agreement without plenary debate (fast-track)

1. fludioxonil (ISO): no classification for the following hazards: physical hazards, acute toxicity (all routes of exposure), STOT SE, skin corrosion / irritation, serious eye damage / eye irritation, respiratory or skin sensitisation, STOT RE, germ cell mutagenicity, toxicity to reproduction
2. N,N-diethyl-M-toluamide, deet: acute toxicity

B. Hazard classes for agreement with plenary debate

1. phenyl bis(2,4,6-trimethylbenzoyl)-phosphine oxide
2. diisohexyl phthalate
3. N,N-diethyl-m-toluamide; DEET

4. benzo[rst]pentaphene
5. dibenzo[b,def]chrysene, dibenzo[a,h]pyrene
6. 4,4'-sulfonylbisphenol, polymer with ammonium chloride (NH4Cl), pentachlorophosphorane and phenol
7. titanium dioxide
8. Fludioxonil (ISO)
9. pentapotassium 2,2',2'',2''',2''''-(ethane-1,2-diylnitrilo)pentaacetate (DTPA-K5)
10. N-carboxymethyliminobis(ethylenenitrilo)tetra(acetic acid) (DTPA-H5)
11. pentasodium (carboxylatomethyl)iminobis(ethylenenitrilo)tetraacetate (DTPA-Na5)

For discussion and adoption

Item 9 – Restrictions

9.1 General restriction issues

a) Report from the Restriction workshop held in Helsinki 17-18 May 2017

For information

9.2 Restriction Annex XV dossiers

a) Conformity check and key issues discussion
   1) Lead and lead compounds in shots

For agreement

b) Opinion development

   1) Diisocyanates
   2) Lead and lead compounds in PVC

For discussion

Item 10 – Authorisation

10.1 General authorisation issues

a) New applications received during the May 2017 submission window
b) Review reports

For information

c) Review periods longer than 12 years

RAC/41/2017/04
Room document
For discussion

d) AfA DNEL/DR: Carcinogenicity dose-response relationship - development of:
   1. Coal tar pitch, high temperature (CTPHT)
   2. Anthracene oil

RAC/41/2017/05

For discussion

10.2 Authorisation applications

a) Discussion on key issues

1. PC_SC_Saes (2 uses)

For discussion

b) Agreement on draft opinions

1. Diglyme_Acton (1 use)
2. EDC_Bayer (1 use)
3. ~~EDC_Olon (2 uses)~~
4. MOCA_Reachlaw (1 use)
5. CT_ZFL (2 uses)
6. SD_ZFL (1 use)
7. CT_Haas (1 use)
8. SD_Haas (1 use)
9. PD_Haas (1 use)
10. SC_Aviall (2 uses)
11. SD_Colle (1 use)
12. CT_Hansgrohe (2 uses)

For discussion and agreement

c) Adoption of final opinions

For discussion and adoption

Item 11 – AOB

1) Results of the Second Forum Pilot Project on Authorisation

For information

Item 12 – Action points and main conclusions of RAC-40

Table with Conclusions and Action points from RAC-41

For adoption

Annex II (RAC 41)

Documents submitted to the Members of the Committee for Risk Assessment for the RAC 41 meeting.

Document number	Title
RAC/A/41/2017	Final Draft Agenda
RAC/A/41/2017 Restricted	Draft outline agenda
RAC/41/2017/01 Restricted room document	Appointment of (co-)rapporteurs for CLH dossiers, restriction dossiers, authorisation applications, DNEL/dose-response relationships, Article 95 (3) requests and Article 77 (3) requests
RAC/41/2017/02	Report from other ECHA bodies
RAC/41/2017/03 Room document	Administrative issues
RAC/41/2017/04	Review periods longer than 12 years
RAC/41/2017/05	AfA DNEL/DR: Carcinogenicity dose-response relationship – development of coal tar pitch, high temperature (CTPHT) and anthracene oil

ANNEX III (RAC-41)

The following participants, including those for whom the Chairman declared the interest on their behalf, declared potential conflicts of interest with the Agenda items (according to Art 9 (2) of RAC RoPs)

AP/Dossier / DS	RAC Member	Reason for potential CoI / Working for
ALREADY DECLARED AT PREVIOUS RAC PLENARY MEETING(S)		
Applications for Authorisation		
All chromates	Urs SCHLÜTER	Institutional & personal involvement; asked to refrain from voting in the event of a vote on this group of substances - other mitigation measures may be applied by the Chairman.
Harmonised classification & labelling		
Titanium dioxide **(FR)**	Nathalie PRINTEMPS	Working for the CA submitting the dossier and involved in its preparation; asked to refrain from voting in the event of a vote on this substance - other mitigation measures may be applied by the Chairman.
Restrictions		
Diisocyanates **(DE)**	Agnes SCHULTE	Working for the CA submitting the dossier and involved in the preparation; asked to refrain from voting in the event of a vote on this substance - other mitigation measures may be applied by the Chairman.
	Norbert RUPPRICH	Working for the CA submitting the dossier; and involved in the preparation; asked to refrain from voting in the event of a vote on this substance - other mitigation measures may be applied by the Chairman.
	Urs SCHLÜTER	Working for the CA submitting the dossier and involved in the preparation; asked to refrain from voting in the event of a vote on this substance - other mitigation

AP/Dossier / DS	RAC Member	Reason for potential CoI / Working for
		measures may be applied by the Chairman.
	Michael NEUMANN	Working for the CA submitting the dossier; asked to refrain from voting in the event of a vote on this substance - no other mitigation measures applied.
Lead in PVC	none	

New dossiers

AP/Dossier / DS	RAC Member	Reason for potential CoI / Working for
NEW		
Article 77.3(c)		
none		
Restrictions		
none		
Applications for Authorisation		
none		
Harmonised classification & labelling		
Titanium dioxide **(FR)**	Miguel A. SOGORB	Working as a project leader for a research project on nanomaterials (involving TiO2) – no mitigation measures applied.
N,N-diethyl-m-toluamide, DEET **Diisohexyl phthalate** **(SE)**	Bert-Ove LUND	Working for the CA submitting the dossier but not personally involved in the preparation of the dossier; asked to refrain from voting in the event of a vote on these substances - no other mitigation measures applied.
	Anne-Lee GUSTAFSON	Working for the CA submitting the dossier but not personally involved in the preparation of the dossier; asked to refrain from voting in the event of a vote on these substances - no other mitigation measures applied.
1) benzo[rst]pentaphene **2) dibenzo[b, def]chrysene ; dibenzo[a,h]pyrene** **3) phenyl bis(2,4,6-trimethylbenzoyl-)phosphine oxide**	Agnes SCHULTE	Working for the CA submitting the dossier; involved in the preparation of 1) and 2) (PAHs); asked to refrain from voting in the event of a vote on this substance - no other mitigation measures applied.

AP/Dossier / DS	RAC Member	Reason for potential CoI / Working for
4) 4,4'-sulfonylbisphenol, polymer with ammonium chloride (NH4Cl), pentachlorophosphorane and phenol **(DE)**		
Fludioxonil (ISO) **(DK)**	Peter Hammer SØRENSEN	Working for the CA submitting the dossier but has not been involved personally in the preparation; asked to refrain from voting in the event of a vote on this substance - no other mitigation measures applied.
	Lea Stine TOBIASSEN	Working for the CA submitting the dossier but has not been involved personally in the preparation; asked to refrain from voting in the event of a vote on this substance - no other mitigation measures applied.

Annex IV

Helsinki, 22 May 2017

RAC/41/2017/03

ROOM DOCUMENT

41ST MEETING OF THE COMMITTEE FOR RISK ASSESSMENT

29 May – 2 June 2017
and
8 – 9 June 2017

Helsinki, Finland

Concerns: **Administrative issues and information items**

Agenda Point: **5a**

Action requested: **For information**

ADMINISTRATIVE ISSUES AND INFORMATION ITEMS

1 Status report on the RAC-40 Action Points

The RAC-40 action points due for RAC-41 are completed.

2 Outcome of written procedures & other consultations

2.1 Written procedures for adoption of RAC opinions / minutes of the meeting

Opinions / minutes adopted via written procedure	Deadline	Report on the outcome
Written procedure for adoption of the minutes of RAC-40	8 May 2017	Closed

2.2 RAC consultations (status by 22 May 2017)

Subject / document	Deadline	Status / follow-up
Harmonised classification and labelling		
N,N-diethyl-m-toluamide; DEET	26 April 2017	Closed
titanium dioxide	2 May 2017 (extended to 4 May)	Closed
fludioxonil (ISO)	24 April 2017	Closed
4,4'-sulfonylbisphenol, polymer with ammonium chloride (NH4Cl), pentachlorophosphorane and phenol	17 April 2017	Closed
benzo[rst]pentaphene	27 April 2017	Closed
dibenzo[b,def]chrysene; dibenzo[a,h]pyrene	27 April 2017	Closed
diisohexyl phthalate	27 April 2017	Closed
phenyl bis(2,4,6-trimethylbenzoyl)-phosphine oxide	28 April 2017	Closed
pentapotassium 2,2',2'',2''',2''''-(ethane-1,2-diylnitrilo)pentaacetate (DTPA-K5)		
N-carboxymethyliminobis(ethylenenitrilo)tetra(acetic acid) (DTPA-H5)	5 May 2017	Closed
Pentasodium (carboxylatomethyl)iminobis(ethylenenitrilo)tetraacetate (DTPA-Na5)		
Application for Authorisation		
PD_Haas Consultation on draft opinion	11 May 2017	Closed
SD_Haas	11 May 2017	closed

Subject / document	Deadline	Status / follow-up
Consultation on draft opinion		
SC_Aviall Consultation on draft opinions	11 May 2017	Closed
MOCA_Reachlaw Consultation on draft opinion	11 May 2017	Closed
CT_Hansgrohe Consultation on draft opinions	11 May 2017	Closed
CT_Haas Consultation on draft opinion	12 May 2017	Closed
CT_ZFL Consultation on draft opinions	12 May 2017	Closed
SD_ZFL Consultation on draft opinion	12 May 2017	Closed
Diglyme_Acton Consultation on draft opinion	12 May 2017	Closed
EDC_Bayer Consultation on draft opinion	16 May 2017	Closed
SD_Colle Consultation on draft opinion	16 May 2017	Closed
Diglyme_ISOCHEM Consultation on final opinion	19 May 2017	Closed
PC_SC_Saes Consultation on application	28 June 2017	Open
Restrictions		
Consultation on the conformity check outcome of lead in shots	23 May 2017	Closed
Consultations on first draft opinion on lead in pvc and on Diisocyanates	23 May 2017	Closed

2.3 Other written consultations of RAC (status by 22 May 2017)

Subject / document	Deadline	Status / follow-up
Consultation the draft minutes of RAC-40	19 April 2017	Closed

2.4 Calls for expression of interest

Calls for expression of interest	Date	Outcome
Harmonised classification and labelling – no calls		
Applications for Authorisation – no calls		
Restrictions		

Call for expression of interest for rapporteurship	13 April – 5 May 2017
2 restriction dossiers (the pools of (co-)rapporteurs to be agreed at RAC-41. More volunteers are invited to come forward.)	

2.5 Written procedures for the appointment of (co-)rapporteurs

Appointment of (Co-)rapporteur(s)	Substance	Deadline	Outcome
Harmonised classification and labelling			
Written procedure for the appointment of (co-)rapporteurs	▪ Lead metal	7 April 2017	Closed No comments were received from RAC members on the recommendation of the Chairman; the RAC (co-)Rapporteur was appointed with tacit agreement.
Applications for Authorisation– no written procedures			
Restrictions – no written procedures			

2.6 Follow-up on the opinions on applications for authorisation agreed by RAC and SEAC

Opinion(s)	Sent on
Opinions sent to the European Commission, the Member States and applicants	
PD_Gentrochema (2 opinions) SD_Gentrochema (3 opinions)	17 March 2017
Diglyme_Maflon (1 opinion)	23 March 2017
CT_Gerhardi (1 opinion) MDA_Polynt (2 opinions)	27 March 2017
AsA_Circuit (1 opinion) CT_Circuit (1 opinion)	31 March 2017
Diglyme_Bracco (1 opinion)	6 April 2017
EDC_Eurenco (1 opinion)	11 May 2017
SD_Ormezzano (2 opinions)	15 May 2017

ANNEX V

Statement provided by the Dossier Submitter of the TiO_2 CLH proposal

Présentation RAC – 8 juin

First on epidemiological data, despite the availability of 5 cohort studies, some of them share a large part of their population leading in fact to only 3 separate populations. We acknowledge that the authors did not report a consistent dose-response association; however the dose-response assessment is not considered valid due to the several methodological deficiencies listed in the background document (sent by France) and discussed briefly last week. However, association is observed between TiO2 exposure and an increase in mortality by lung cancer in 2 populations among the 3 different populations assessed. In conclusion for epidemiological data, the data are inadequate to prove no effect in humans!
Regarding animal data, lung tumors are reported consistently in 2 inhalation studies and one instillation study in rats. The evidence of carcinogenesis is thus sufficient in animals. The concentrations tested are judged compatible with existing guidances and guidelines as discussed in the presentation made by France last week. It should be reminded that classification is only related to hazard of a substance. In addition, due to slower clearance in humans, it is adequate to test concentrations higher than expected human exposures to cover workers in dusty conditions. Thus the studies are reliable to conclude on the carcinogenicity of titanium dioxide. Most importantly, the epidemiological data report some positive responses between TiO2 exposure and increased lung cancer mortality which do support the rat findings.
Regarding interspecies differences, there is no mechanistic data available with titanium dioxide allowing a comparison between human and rodent responses after inhalation exposure. In this context, additional information from other poorly soluble particles has been used in the CLH report to understand the hypothesized mode of action of carcinogenicity. Based on a weight of evidence approach, it has been considered that the major mode of action expected for TiO2 lung carcinogenicity is an inflammatory process with secondary genotoxicity. Data on other poorly soluble particles were never used in the CLH report for other considerations. Indeed, data with titanium dioxide are judged sufficient to conclude on carcinogenesis. In addition, titanium dioxide can be considered as poorly soluble particles but does not fulfill the criteria for low toxicity as titanium dioxide has specific properties linked to its surface reactivity and cytotoxicity. Therefore, other modes of action other than a secondary genotoxic can be anticipated due to its particular properties.
We agree that some differences exist between rats and humans due to anatomical / biological differences in respiratory tract. However, these differences are only weak and cannot be used to refute observations made on rats.

Interspecies difference appears to be a major issue for the rapporteur. However, we would like to remind RAC members that:

- the responses to dust inhalation are qualitatively similar between rats and humans. The difference of deposition between alveolar and interstitium is not a major issue. Particles are found in rats and humans in both compartments.
- only <u>one</u> study (Nikula, 2001) carried out on few cases of coal miners has worked on this issue and suggested that deposition is mainly in interstitium in humans. Particles deposition was also found in alveolar compartments in this study. Moreover, it should be noted that this unique study also report 57% of particles in the interstitium of non-exposed workers., This

unique study not performed with TiO2 cannot be used to rule out the relevance of rats for humans because of its limitations & poor quality.

- Anyway, an association between interstitial lung disease and lung cancer is reported in the literature (*Archontogeorgis et al. 2012*). The presence of hot spot in humans is related to the anatomy of the respiratory tract with high deposition of particles at the bifurcations of the terminal airways. Interestingly, the localization of human lung tumours in this region is rather high. This suggests that local overload may occur in humans at concentrations lower than those inducing a generalized overload in the lung.

All these discussions on interspecies differences are only related to the hypothesized mode of action secondary to an overload. However, other modes of action can be anticipated due to the specific properties of titanium dioxide. For example, we can cite:

- First: The surface reactivity of titanium dioxide with bound redox reactions. This has been proven under light but also in dark conditions in various models (model organic compounds, bacteria, invertebrates, human cell lines) *(Fenoglio et al., 2009; Jomini et al., 2012, Dalai et al., 2013, Sanders et al., 2012*). This is also evidenced by the fact that titanium dioxide is often coated for minimizing its surface reactivity (in particular as UV filter) *(Nel et al, 2006*). In summary, free radicals can be generated at the surface of titanium dioxide that can interact with many cellular or intracellular proteins.

- Secondly: Cytotoxicity of titanium dioxide has been reported in various cell lines, such as neuroglia cells [*Liu, 2013*], mouse fibroblast cell [*Jin, 2008*], human hepatocellular carcinoma cell line (SMMC-7721), human liver cell line (HL-7702), rat hepatocarcinoma cell line (CBRH-7919) and rat liver cell line (BRL-3A) [*Sha, 2011*].

- And finally the possible primary direct or indirect genotoxicity of titanium dioxide. Among the data found in the literature, we can note the increasing number of publications reporting a disturbance of enzymes involved in repair machinery. In addition, titanium dioxide has been detected inside the nucleus in various *in vitro* studies suggesting that titanium dioxide could interact with DNA. Regarding the reference to EFSA last week, EFSA has concluded that there is some evidence of genotoxicity *in vitro* and limited evidence of genotoxicity *in vivo*. However, we consider that the *in vivo* studies are not sufficiently robust due to several deficiencies from OECD guidelines. In addition, we should have in mind that EFSA conclusion is only related to titanium dioxide as a food additive for which an oral bioavailability is very limited. Therefore, for inhalation exposure, we consider that a concern of a primary genotoxicity (direct or indirect) still remains because of the presence of positive alerts.

Even if some interspecies differences can be anticipated as often in toxicology, rat remains a relevant model for TiO2 lung carcinogenicity. Thus, by extrapolation, humans have to be considered responsive to titanium dioxide toxicity. If we strictly compare the CLP criteria with the data we have, it is clear that a classification is required for titanium dioxide based on sufficient evidence in animals, inadequate evidence in humans and a mode of action that is considered valid in both species. This project of classification of TiO2 as inhalative carcinogen was initiated at European level based on a german suggestion. The carcinogenicity of titanium dioxide has been agreed by several international organisms. It has been clearly supported by 4 of the 5 member states who commented during public consultation either as Category 1B or 2. The 5th member state requested further discussion regarding the form.

Regarding the scope of the proposal, the exclusion of some forms of titanium dioxide can be misinterpreted by the general population. In particular, for fibers, it could be understood that these forms are not or less toxic if they are excluded from the scope. However, it is clearly not the case, that's why in the CLH report, the classification has been proposed as a minimal classification for complex forms that can be associated to higher toxicity than granular forms. We are foreseeing possibilities to submit further proposal for specific forms in the future. In the meantime it is important to guaranty a minimal level of protection for these forms.

ANNEX VI

Short summary

Rapporteur's preparatory workshop on the Authorisation Applications – RAC 41

29 May 2017
ECHA (Annankatu 18, Helsinki) the auditorium on the top (7th) floor
18:15-20:45

A preparatory workshop on Authorisation may be held on an ad hoc basis in advance of RAC plenary meetings. The need is partly determined by the volume of dossiers tabled for discussion and any specific scientific issues arising in preparing the work of the Committees. The intention is to encourage an exchange of views on common issues in workplace exposure assessment methodology and the effectiveness of RMMs.

The discussion during Rapporteur's preparatory workshop on the Authorisation Applications was based on 2 presentations by RAC co-opted members and one Authorisation case presented by the Rapporteur (see the Agenda below).

The first presentation discussed the relevance of surfaces contamination assessment on the example occupational exposure assessment to antineoplastic drugs. As the results of sampling in selected hospitals in Portugal contamination has been found after surfaces cleaning and before handling of drugs started, inside gloves, on the toilets surfaces, in the storage area, in the administration units, on the drugs packages. It has been discussed that training of the workers i.e. how to use gloves and correct working procedures and correct frequency of changes of gloves are critical to protect workers against exposure via contaminated surfaces. Participants of the workshop agreed that in case of some substances applicants should consider to use more frequently the wipe sampling for the assessment of the occupational exposure.

The second presentation was based on two recently published scientific articles about evaluation of accuracy of selected modelling tools for occupational exposure assessment.

In the third presentation the rapporteur presented complicated case of the application covering 5 DUs and the process of development of the opinion including several efforts of the authorisation team responsible for this case to clarify missing information.

Agenda

1.	18:15–18:20	Welcome	Tim Bowmer
2.	18:20-19:05	OCCUPATIONAL EXPOSURE ASSESSMENT TO ANTINEOPLASTIC DRUGS- Relevance of surfaces contamination assessment	Susana Viegas
3.	19:05-19:50	The accuracy and robustness of exposure models	Rudolf van der Haar

4.	19:50-20:35	Presentation of a DO on a AfA case – Diglyme Acton use 2	Lina Dunauskienė
5.	20:35-20:45	Summary of the workshop	Tim Bowmer