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**Committee for Risk Assessment (RAC)**

ANNEX 2

**Response to comments document (RCOM)**

on the Proposal by the European Chemical Agency(ECHA)

in support of occupational exposure limit values for acrylonitrile in the workplace

**Acrylonitrile**

**EC number: 203-466-5**

**CAS number: 107-13-1**

ECHA/RAC/ O-0000001412-86-188/F

**9 March 2018**

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| **Ref.** | **Date/Name/Org.** | **Type of comment** |
| 6 | **Date/time:**  2017/11/03 11:07  **Type:**  Individual  **Country:** United Kingdom | **Comment**  I used to work for a Vacuum thermoforming company that processed ABS. It regularly had issues with their way of heating up large sheets of ABS to be formed into Caravan fronts and backs. This was because the ABS was heated up and would sag near to the heaters there were sensors that would blow air to keep the material from coming into contact with the heaters. However on regular occasions in the 12 years that I worked for this Company the material would come into contact with the heaters and melt onto them. The operator would then have to remove this material with the heaters on and then scrape this off. This was a regular occurence with no personal protective equipment being used or enforced. The temperatures of this would be at approximately 300 degrees and the acrid pungent smells was awful. This did not only effect one operator but all who would work in that department. Please give some feedback have your monitoring tests included a real case scenario of air monitoring using equipment when such events occur? Please feel free to contact me if you feel fit. Thanks G. Templeton |
| **Dossier Submitter response**  Thank you for your comment.  ECHA has not carried out monitoring tests. The ECHA proposal provides a general description of the occupational exposure reported in the EU Risk Assessment and several other reports or studies. This description intends to give a general idea about the exposure levels encountered during manufacturing and use of acrylonitrile. |
| **RAC Rapporteurs comments**  Thank you for your comment. We note the reply provided by the Dossier Submitter and have nothing further to add. |
| **Ref.** | **Date/Name/Org.** | **Type of comment** |
| 7 | **Date/time:**  2017/11/05 09:56  **Type:**  Individual  **Country:** Netherlands  **Non-confidential attachment:**  Review ECHA acrylonitrile proposal. G. M. H. Swaen.pdf | **Comment**  chapter 7.7 carcinogenicity  chapter 8 cancer risk assessment |
| **Dossier Submitter response**  Thank you for your comments.  The specific comments 1-7 seem to be related to a summary paragraph. This paragraph has been re-worded in the Background Document and it has been clarified that the deficiencies do not invalidate the 4 large good quality cohort studies (Symons et al. 2008; Benn & Osborne 1998; Blair et al. 1998/Marsh and Zimmerman 2015; Swaen et al. 2004).  As regards comment 8, the concern related to post hoc sample calculations has been taken into account with a recommendation to give preference to confidence intervals of the effect estimates generated.  As regards the comment on ECHA guidance R.8 and how to combine human and animal data, ECHA acknowledges that in this particular case the human data is unusually extensive, and therefore, the dose-response derived from animal data could be considered as an upper limit of dose-response to characterise the human excess risk, if any, as further described in the revised ECHA background document.  The cumulative ppm-year calculations from the Appendix A of the comment for the 4 large cohort studies were added to the Background Document as a further illustration of the robustness of the human data set.  The conclusions of Haber and Patterson (2005) and Hagmar (2001) were added. |
| **RAC Rapporteurs comments**  Thank you for your comments. We agree there is rather extensive epidemiology data available on populations occupationally exposed to acrylonitrile. We also agree that the weight of evidence from good quality epidemiology data on current and past workplace exposures levels (with an average of 0.5 ppm, as conservatively estimated in Appendix A to your comments) suggests that acrylonitrile is either not a human carcinogen or that it produces only small increases in cancer risk. Yet, it is also noted that negative epidemiology data do not allow to reach absolute conclusions that a substance is not a human carcinogen: it is extremely difficult to verify or falsify low risk increases for rare diseases (such as brain tumours) in occupational cohort studies. |
| **Ref.** | **Date/Name/Org.** | **Type of comment** |
| 9 | **Date/time:**  2017/11/06 16:23  **Type:**  MemberState  **Organisation Name confidential?**  False  **Country:** Belgium  **Non-confidential attachment:**  OEL - acrylonitrile\_Public\_Consultation\_BE\_Comment.docx | **Comment**  *(see attachment)* |
| **Dossier Submitter response**  Thank you for your comments.  The Background Document has been amended to reflect that the interpretation of Kedderis & Batra (1991, 1993), that in humans microsomal involvement could be considered as an additional detoxification pathway for CEO which appeared not active in rodents, needs to be considered with caution.  As regards the proposition that the negative epidemiological studies could be due to the unexposed comparison groups having had acrylonitrile exposure from tobacco smoke in ambient air, ECHA notes that there is no reason to assume a difference in such exposure between those exposed and unexposed to acrylonitrile at work. Furthermore there is evidence that exposure to acrylonitrile from external tobacco smoke is of the order of a few μg/m3 (see chapter 5.4.2 of the Background Document) while the occupational exposures in the epidemiological studies were of the order of mg/m3 and above.  ECHA considers that the weight of evidence for the available evidence on carcinogenicity supports to derive an OEL. The justification is presented in section 8 of the Background Document. |
| **RAC Rapporteurs comments**  Thank you for your comments. We note the reply provided by the Dossier Submitter and agree with the Dossier Submitter that the weight of evidence supports the derivation of an OEL. |
| **Ref.** | **Date/Name/Org.** | **Type of comment** |
| 23 | **Date/time:**  2017/11/08 09:58  **Type:**  BehalfOfAnOrganisation  **Organisation name:**  Unite the Union  **Organisation Name confidential?**  False  **Country:** United Kingdom | **Comment**  Unite the Union strongly supports this reduction to seek maximum protection for workers. However, we still have doubts about whether this will protect sufficiently against cancer effects. |
| **Dossier Submitter response**  Thank you for your comment. |
| **RAC Rapporteurs comments**  Thank you for your comment. |
| **Ref.** | **Date/Name/Org.** | **Type of comment** |
| 24 | **Date/time:**  2017/11/08 10:58  **Type:**  BehalfOfAnOrganisation  **Organisation name:**  Austrian Workers' Compensation Board (AUVA)  **Organisation Name confidential?**  False  **Country:** Austria | **Comment**  The proposal for occupational exposure limit values for arcylonitrile is refused.  The aim of the proposal is to support the derivation of an OEL in accordance with Directive 2004/37/EC (CMD).  GENERAL COMMENTS:  At present, no threshold can be defined for arcylonitrile with the current scientific knowledge that excludes health risks (recital 11 of CMD). In particular, regarding exposure to carcinogens, the precautionary principle should be applied in the protection of workers’ health (recital 14 of CMD). The employer has to ensure that the level of exposure of workers is reduced to a low level as is technically possible (CMD, Article 5(3)). [In respect to technical possibility, the framework directive 89/391/EEC explicitly emphasizes that the improvement of workers’ safety and health at work is NOT to be subordinated to purely economic considerations (13th recital of that Directive)].  To support and to guide this minimization obligation, an OEL representing a VERY low cancer risk has to be established.  In the related field of potentially dangerous products and consumer-use chemicals the European Commission already has established a benchmark for assigning the terms “serious risk”, “high risk”, “medium risk” and finally “low risk” (Commission Decision 2010/15/EU of 16.12.2009, OJ No L 22, 26.1.2010). Cancer from contact with substances is classified as a hazard of the (highest) Severity Group 4. This Commission Decision provides (in its table 4) the combination of the severity of harm and its probability: Only if the probability of cancer causation is LESS THAN 1:1,000,000 (related to the exposure duration) the risk is judged to be “low risk”!  This clearly shows that strict criteria have to be met, and cancer risks have to be in the order of 1:1,000,000 and preferable lower to be acceptable.  In significant European member states a risk-based approach is implemented (DE, NL) for controlling the exposure to carcinogens at the workplace. The acceptable cancer risk in these concepts is 1:1,000,000 per work year, resulting in an “acceptable” cancer risk of 4:100,000 per work lifetime.  A work lifetime cancer risk of 4:100,000 is a reasonable and necessary concretion of the minimization principle (and of recital 4 of CMD), being the main objective of the CMD.  Besides that, also REACH demands that a low risk must be ensured when using a carcinogenic substance. Guidance documents published by ECHA (e.g. Chapter R.8) suggest an excess lifetime cancer risk of the same order of magnitude as outlined above.  Therefore, an OEL associated with a work lifetime cancer risk NOT HIGHER THAN 4:100,000 has to be required.  SPECIFIC COMMENTS:  Arcylonitrile is to be considered a NON-threshold carcinogen; this is emphasised by the actual proposal as well by AGS (2010).  The proposed OEL only (and indirectly) takes into account thresholded assessments, which however are questionable. AGS (2010) refuses the use of a non-linear exposure-risk relationship because an even weak genotoxicity may contribute considerably to the cancer risk. This also is necessary to follow the precautionary principle set out in recital 14 of the CMD.  The proposed OEL (0.1 mg/m³ or 0.045 ppm) would be associated with an estimated work lifetime cancer risk of approximately 2:10,000 (instead of 4:100,000). This excess risk cannot be accepted deliberately.  No reasoning nor any substantial explanation is given for the proposed OEL of 0.1 mg/m³.  Exposure levels of acrylonitrile preventing non-cancer health impairments have to be established possibly as low as 0.007 mg/m³.  An OEL corresponding to a work lifetime cancer risk of 4:100,000 (or to protect from non-cancer effects, if this value would be lower) has to be required.  BIOMONITORING:  A biological limit or guidance value should NOT be established because biomonitoring is not feasible at low exposures. Even at an inhalable exposure level of 0.1 mg acrylonitrile/m³ the expected concentration of cyanoethylvaline (CEV) is ~5 µg/L blood. For an exposure level of 0.028 mg/m³ (being the concentration associated with 4:100,000 risk according to AGS) roughly 1.5 µg CEV/L blood could be estimated.  It should be noted that measured data only are available for air concentrations of 1; 0.5; and 0.3 mg/m³, and show a considerable variation (DFG: BAT value documentation for acrylonitrile, 9th supplement, 2000).  Above all, the background blood level of CEV in the general population without occupational exposure to acrylonitrile is relatively high and depends strongly on smoking status. CEV blood concentration is 1.4--3.3 µg/L (median) and 3.7--8.3 µg/L (percentile 95) in smokers, and up to 15 µg/L in heavy smokers. Passive smoking is likely, and rare smoking is proofed to enhance CEV blood concentration. In non-smokers, CEV levels are low. A CEV reference concentration of 0.3 µg/L for the non-smoking individuals of the general population was defined in Germany. (DFG: BAT value documentation for acrylonitrile, 17th supplement, 2010).  Furthermore, taking blood samples from workers must be avoided for ethical reasons (respecting e.g. the fundamental right to physical integrity), in particular, when workplace measurements are possible and routine methods for those are available.  In summary, no interpretable information is possible to be obtained from CEV biomonitoring.  REMARKS:  A consistent level of protection from the risks related to carcinogens or mutagens has to be established for the EU as a whole (recital 4 of CMD). It should be noted that “risk” means the likelihood (probability) that the potential for harm will be attained under the conditions of use and/or exposure (Directive 98/24/EC, Article 2; to be applied according to Article 1(3) of that Directive).  Adopting an opinion on an OEL for acrylonitrile in accordance with the CMD (as declared in the mandate) necessarily has to take into account political and socioeconomic issues. Neither the ECHA nor the RAC is competent to argue on the time scale of implementation, on transitional measures (if necessary) or on other matters referring the regulatory enforcement of OELs. The partial questionable handling of scientific findings and ignoring the risk-based approach creates the impression that also (undeclared) non-scientific interests are incorporated into the proposal. |
| **Dossier Submitter response**  Thank you for your comments.  GENERAL COMMENTS & SPECIFIC COMMENTS: It is not the remit of ECHA or RAC to comment on or to determine the acceptability of cancer risks. From the total weight of evidence from both animal and human data a mode of action-based threshold[[1]](#footnote-1) can be assumed for the carcinogenic effects of acrylonitrile. At acrylonitrile exposures below the resulting proposal for a limit value, no significant residual cancer risk is expected for workers. The justification is presented in the Background Document.  BIOMONITORING: The analytical methodology for measurement of CEV in blood is sensitive, with a limit of detection corresponding to 0.0024-0.024 μg CEV/L blood. A CEV level of 60 μg CEV/L blood can be considered to be an appropriate biological limit value (BLV). CEV levels are indeed influenced by other sources of acrylonitrile (e.g. smoking). The contribution to the CEV blood levels of 4 (0.8 to 9.2) μg CEV/L blood (Fennell et al., 2000) due to smoking can be accounted for when interpreting the measurements. Background levels in non-smokers are <10 pmol/g globin (<0.24 μg CEV/L blood).It should be noted that the mandate of RAC is to evaluate the scientific relevance of occupational limit values for acrylonitrile, and to assess the most recent and relevant scientific information. The RAC-opinion on acrylonitrile is used by the Commission to set limit values for the protection of workers from exposure to chemical risks, as per Directive 2004/37/EC. The Commission takes socio-economic and technical feasibility factors into account in their legislative procedure for developing EU OELs.  REMARKS: Independence is extremely important to ECHA. ECHA’s work is based on science and it is of the utmost importance to guarantee the independence of the ECHA’s staff and Committee members nominated by the Members States. All ECHA staff has completed a detailed declaration of interest before starting to work, these declarations are updated and examined at least annually. Similarly the experts in the scientific Committees are screened against targeted eligibility criteria. Their published Declarations of Absence of Conflict of interest are examined and updated annually. In addition to these regular Declarations of Interest, every Committee meeting starts with an oral declaration on any specific interests related to the agenda items to be discussed. |
| **RAC Rapporteurs comments**  Thank you for your comments. We agree with the reply provided by the Dossier Submitter and have nothing further to add. |

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| **Ref.** | **Date/Name/Org.** | **Type of comment** |
| 25 | **Date/time:**  2017/11/09 11:46  **Type:**  BehalfOfAnOrganisation  **Organisation name:**  Ministry of labour and Social Affairs  **Organisation Name confidential?**  False  **Country:** Italy | **Comment**  Acrylonitrile  It is important to underline that in Italy there is not an OEL binding. For this reason the value in the table 4 (by Germany BAUA 2014) is wrong. Probably this value is taken by ACGIH USA but it is not Italian OEL. Nevertheless we agree with OEL proposed. |
| **Dossier Submitter response**  Thank you for your comments. ECHA has corrected the information in the Background Document. |
| **RAC Rapporteurs comments**  Thank you for your comments. |
| **Ref.** | **Date/Name/Org.** | **Type of comment** |
| 26 | **Date/time:**  2017/11/09 15:07  **Type:**  BehalfOfAnOrganisation  **Organisation name:**  the Polish Interdepartmental Commission for Maximum Admissible Concentrations and Intensities for Agents Harmful to Health in the Working Environment  **Organisation Name confidential?**  False  **Country:** Poland  **Non-confidential attachment:**  Acrylonitrile-benzene-nickel-comments from Polish MAC Commmission.docx | **Comment** |
| **Dossier Submitter response**  Thank you for your comments.  Point 1 is noted and is indeed in line with the epidemiology described in the Background Document.  Regarding point 2, ECHA would like to clarify that the mandate of RAC is to evaluate the scientific relevance of occupational limit values for acrylonitrile, and to assess the most recent and relevant scientific information. The RAC-opinion on acrylonitrile is used by the Commission to set limit values for the protection of workers from exposure to chemical risks, as per Directive 2004/37/EC. The Commission takes socio-economic and technical feasibility factors into account in their legislative procedure for developing EU OELs.  Regarding point 3, ECHA appreciates your concern about the length of the public consultation, however, the deadline to deliver the opinion of RAC to the European Commission (26 March 2018) unfortunately did not allow for a longer public consultation. |
| **RAC Rapporteurs comments**  Thank you for your comments. We note the reply provided by the Dossier Submitter and have nothing further to add. |
| **Ref.** | **Date/Name/Org.** | **Type of comment** |
| 27 | **Date/time:**  2017/11/09 15:19  **Type:**  BehalfOfAnOrganisation  **Organisation name:**  ANSES  **Organisation Name confidential?**  False  **Country:** France  **Non-confidential attachment:**  Comments on acrylonitrile\_OEL RAC\_vf.docx | **Comment**  Please, see attachment |
| **Dossier Submitter response**  Thank you for your comments.  ECHA appreciates your concern about the length of the public consultation, however, the deadline to deliver the opinion of RAC to the European Commission (26 March 2018) unfortunately did not allow for a longer public consultation.  Regarding the process, ECHA considers it sensible to have a consultation on a proposal. The aim is to ensure completeness and scientific rigour through public scrutiny. Similarly, in other ECHA processes, the public consultation is on a proposal or application and not on the opinion of RAC as such. However, we note your comment and will consider it when revising the interim procedure that was established for this area of work (<https://echa.europa.eu/documents/10162/13579/interim_wponevaluation_oel_agreed_rac_42_en.pdf/021bc290-e26c-532f-eb3f-52527700e375>).  Regarding the developmental toxicity, ECHA considers their conclusion to be in line with the weight of evidence and with the conclusions previously drawn in the EU risk assessment report on the same data. There were no clear treatment related teratogenic effects in the inhalation studies despite maternal and foetal toxicity.  Upon further consideration, ECHA is of the view that the weight of evidence for the available evidence on carcinogenicity supports to derive an OEL. At acrylonitrile exposures below the resulting proposal for a limit value, no significant residual cancer risk is expected for workers. The reasons are presented in the Background Document. However, as the possibility of an occupational cancer risk cannot totally be excluded, an illustrative dose-response relationship for carcinogenicity is derived by linear extrapolation to estimate the upper boundary of excess risk (if any) at this OEL. A linear dose-response relationship based on the BMDL05 has been included in the Background Document and the conservative nature of the T25 is stressed.  A STEL has been included in the Background Document.  It is not clear from your comment which additional elements would need to be considered to warrant a skin notation. In any case, the proposal is in line with the opinion of SCOEL from 2003.  An assessment for a noise notation has been included in the Background Document. The evidence for ototoxicity is weak and does not warrant a noise notation for acrylonitrile.  Thank you for the references regarding the mode of action, they have been included in the Background Document. |
| **RAC Rapporteurs comments**  Thank you for your comments. We note the reply provided by the Dossier Submitter and have not much to add, aside from the fact that we agree with the Dossier Submitter that the weight of evidence supports the derivation of an OEL for the cancer endpoint. We also support the inclusion of a STEL and BLV. |
| **Ref.** | **Date/Name/Org.** | **Type of comment** |
| 28 | **Date/time:**  2017/11/09 18:42  **Type:**  BehalfOfAnOrganisation  **Organisation name:**  Acrylonitrile EU REACH Consortium  **Organisation Name confidential?**  False  **Country:** United Kingdom  **Non-confidential attachment:**  Industry Response to Acrylonitrile OEL Proposal by ECHA v3.0.docx | **Comment**  P78 ECHA concludes the current OELS are not considered protective against carcinogenicity;Industry does not agree there is a lack of protection of workers for cancer effects at the present range of OEL’s in operation in the EU and in the US. This is borne-out by the lack of cancer risks in the extraordinary extensive epidemiology for exposed workers.  P78 regarding ECHA's OEL proposal; there is inappropriate use of the observed irritation effects in the F1 generation in the Nemec et al (2008) two-generation rat study. The industry also proposes a realistic and highly protective operator exposure value for European industrial users of the monomer and its polymers based on the F0 generation NOAEL and observed occupationally exposed humans; 0.5 ppm (1.1 mg/m3.  P 6 Occurrence; we provide an update on natural sources of acrylonitrile, which are increasingly important to consider, especially as any OEL value decreases below 1ppm and potential biological markers of exposure are considered.  P50 Latest Reports of epidemiology; The US Industry Group will provide an update on the continuing update of the large scale US National Cancer Institute update for ca 25,000 occupationally exposed individuals to acrylonitrile.  P17 Section 7.1.2 We provide an update and additional further details of metabolic pathways for acrylonitrile showing differences in metabolic potential between species and tissue types.  P 35 Genotoxicity; a critical review of the in-vivo gene toxicity data is provided with an emphasis on the quality of the negative studies and the K scores in table 12. We also provide a comment on the lack of instructive information from the Drosophila studies. It is also noted that there is a link to oxidative stress in some of the in-vivo outcomes.  P 47 Gene toxicity summary; industry provide details of the tumour dose response and compared to markers for oxidative stress response. This shows a strong correlation between rodent brain lesions and markers of oxidative stress. Details of the ameliorative impact of dietary anti-oxidants are also demonstrated in rats. It is also noted that in vitro, human astrocytes did not respond similarly to rat astrocytes.  P 55; 7.7.2 Animal data; rat brain tumours; The industry provides further details of the recent immunohistochemical assessment of the rodent brain lesions, from the key carcinogenicity bioassay. These are reclassified as microglioma, rather than astrocytomas, which are proposed to be a rodent specific lesion. It is noted that given a lack of similar tumours in mice, there is also limited likelihood of relevance in man. In addition a review and update of the available evidence for a lack of DNA binding in the rodent target tissues is provided, with the relevance of a new study highlighted (Williams et al. 2017).  p 14 Biomonitoring; The haemoglobin adduct N-(2-cyanoethyl)valine (CEV) is suggested to be the most useful biomarker of exposure. However, it should be noted that this is not a useful marker of peak or short term exposures and is influenced by other sources of acrylonitrile, i.e. smoking and other sources of burning of complex organic matter. CEV-Hb adducts are mainly useful as a qualitative assessment of exposure rather than a quantitative method of determining occupational exposure level compliance. |
| **Dossier Submitter response**  Thank you for your comments. A response by section is provided below.  *Industry proposed alternative EU-wide OEL*: It is noted that the acrylonitrile industry supports an OEL of 0.5 ppm (1.1 mg/m3). The Background Document has revised the protective level for irritancy considering your arguments and derives a level of 0.67 ppm (1.5 mg/m3) based on Quast et al. (1980a). Regarding the cancer endpoint, an OEL of 0.45 ppm (1 mg/m3) is recommended in the opinion of RAC, based on a mode of action-based threshold[[2]](#footnote-2). This level is in line with your proposal.  *Acrylonitrile STEL*: Thank you for your proposal for a STEL of 4.6 ppm. A pragmatic STEL of 1.8 ppm is recommended in the opinion of RAC, which is 4 times the OEL of 0.45 ppm. The study by Jakubowski et al. (1987) is considered as supportive evidence.  *Sources of Acrylonitrile in the Environment*: The Background Document has been amended to acknowledge the non-industrial sources of acrylonitrile.  *Epidemiology*: Thank you for informing us about the anticipated publication of a follow-up study of the US-NCI cohort.  *Acrylonitrile Metabolism*: Thank you for sharing the exerpt from the draft paper “Acrylonitrile’s genotoxicity; the complex profile of a rodent carcinogen”. The information in the exerpt seems largely in line with the information that was contained in the ECHA proposal that was subject to the consulation. The Background Document has been amended as relevant.  *Acrylonitrile: review of evidence for genotoxicity in vivo* and *Comparison of tumour response and oxidative stress indicator dose rates*: Thank you for the review of the available data. The Background Document has been amended as relevant.  *Tumour type*: The Background Document has been amended to acknowledge the reclassification of the brain tumours by Kolenda-Roberts et al. (2013).  *Summary of key DNA Binding Information for Acrylonitrile (AN)*: Thank you for the review of the available data. The Background Document has been amended as relevant.  *Biomarkers of Acrylonitrile (AN) Exposure*: The Background Document noted that CEV in blood erythrocytes is a marker for long term exposures and is influenced by other sources of acrylonitrile (e.g. smoking). The effect from smoking can be accounted for when evaluating measured CEV concentration in blood (around 4 μg CEV/L blood from smoking or 8.5 fmol/mg globin/cigarette/day (Fennell et al., 2000)). |
| **RAC Rapporteurs comments**  Thank you for your comments. We note the reply provided by the Dossier Submitter and have not much to add, aside from the fact that we agree with the change in point of departure/protective level for nasal irritancy. We further agree that the evidence is suggestive of indirect DNA damage (from oxidative stress) being the main mechanism in rat brain tumour formation. This (thresholded) mechanism supports a non-linear dose-response curve, and the derivation of an OEL. Finally, we support the setting of a STEL at 4 times the OEL. |
| **Ref.** | **Date/Name/Org.** | **Type of comment** |
| 29 | **Date/time:**  2017/11/10 11:40  **Type:**  BehalfOfAnOrganisation  **Organisation name:**  European Tyre and Rubber Manufacturers’ Association  **Organisation Name confidential?**  False  **Country:** Belgium  **Non-confidential attachment:**  20171110\_ETRMA-Acrylonitrile\_OEL\_V2.pdf | **Comment**  - |
| **Dossier Submitter response**  Thank you for your comments.  ECHA and RAC have considered the mode of action for carcinogenicity in detail. From the total weight of evidence from both animal and human data a mode of action-based threshold[[3]](#footnote-3) can be assumed for the carcinogenic effects of acrylonitrile. An OEL of 0.45 ppm (1 mg/m3) is recommended in the opinion of RAC. At acrylonitrile exposures below the proposal for a limit value, no significant residual cancer risk is expected for workers. The reasons are presented in the Background Document. |
| **RAC Rapporteurs comments**  Thank you for your comments. We agree with the reply provided by the Dossier Submitter and have nothing further to add. |
| **Ref.** | **Date/Name/Org.** | **Type of comment** |
| 30 | **Date/time:**  2017/11/10 19:18  **Type:**  BehalfOfAnOrganisation  **Organisation name:**  AN Group  **Organisation Name confidential?**  False  **Country:** United States  **Non-confidential attachment:**  Summit Comments on ECHA Report 111017.pdf | **Comment** |
| **Dossier Submitter response**  Thank you for your comments. A response point by point is provided below.   1. The Background Document has been corrected to avoid confusion regarding the lifetime continuous exposure versus occupational exposure. The numerical values corresponding to occupational exposure have been used as the basis in deriving an OEL for acrylonitrile. 2. The point of departure for nasal irritancy has been reconsidered. Indeed, given that the LOAEC of 5 ppm in F1 males was not statistically significant and that there may be age related sensitivities of the nasal epithelium, the NOAEC of 15 ppm for the parental generation may be more appropriately chosen as a point of departure, resulting in a level of 1.1 ppm from Nemec et al. (2008). However, a level of 0.67 ppm from Quast et al. (1980), a good quality chronic study, is taken forward in the Background Document. 3. Thank you for highlighting these missing studies regarding oxidative stress. They have been included in the Background Document. 4. Thank you for highlighting the inaccurate statement and suggestions. The Background Document has been amended accordingly. 5. An (illustrative) linear dose-response relationship has been included in the Background Document, based on the BMDL05 from the pooled data set for rat brain tumours, and the conservative nature of the T25 as a point of departure is stressed. 6. A summary of Strother & Kirman (2011) has been included in the Background Document. 7. Thank you for your recommendations regarding biomonitoring. The Background Document has been amended where considered relevant. |
| **RAC Rapporteurs comments**  Thank you for your comments. We note the reply provided by the Dossier Submitter and have not much to add, aside from the fact that we agree with the change in point of departure for nasal irritancy. We further support your dose-response analysis based on the pooled rat data set, and have taken the BMDL05 (external, occupational) as point of departure for the OEL. |
| **Ref.** | **Date/Name/Org.** | **Type of comment** |
| 31 | **Date/time:**  2017/11/10 20:08  **Type:**  BehalfOfAnOrganisation  **Organisation name:**  Acrylonitrile Group/Global Acrylonitrile Product Stewardship  **Organisation Name confidential?**  False  **Country:** United States  **Non-confidential attachment:**  comments to ECHA on AN OEL.pdf | **Comment**  Re: Comments on the Draft Report “Proposal by the European Chemical Agency (ECHA) in support of occupational exposure limit values for acrylonitrile in the workplace”  Dear: Dr. Bowmer:  On behalf of The Acrylonitrile Group (AN Group) and the Global Acrylonitrile Product Stewardship (GAPS) program, I am pleased to submit information relevant to the Committee for Risk Assessment (RAC) review of the draft report “Proposal by the European Chemical Agency (ECHA) in support of occupational exposure limit values for acrylonitrile in the workplace.”  The AN Group, is a not-for-profit organization based in Washington, DC, representing the major manufacturers and users of AN in North America. The AN Group is a member of GAPS, which represents various regional acrylonitrile (AN) manufacturer associations. The AN Group/GAPS have been coordinating their review of the ECHA draft report with their counterparts in the EU (EU REACH Consortium and the CEFIC European Acrylonitrile Producers) and therefore will largely limit these comments to information regarding the United States National Cancer Institute’s (NCI) cohort study on the health impacts from occupational exposure to AN.  National Cancer Institute Occupational Cohort Epidemiology Study Update  As ECHA/RAC recognize, there are numerous worker studies available relevant to assessing the risk from exposure to AN. Of particular note is the very large NCI occupational cohort study, which includes over 25,000 workers; this is one of the largest occupational epidemiology studies ever conducted. This cohort provides a very robust dataset from which to assess the health implications of AN occupational exposure, and is particularly useful in assessing the contradiction between the rodent and human response to AN exposure.  The ECHA draft contains an accurate summary of the results of the NCI cohort study as reported in Blair et al. 1998. That study evaluated workers employed in US AN monomer and polymer plants from the early 1950s through 1983. Blair et al analyzed the vital status of the workers through 1989, at which point in time there was slightly less than 10% mortality.  As ECHA notes in the draft, the SMRs for all forms of cancer collectively, as well as most individual tumor types were less than the unexposed workers. Even in the few instances where the SMR’s were above 1.0, there was no increased risk with increased exposure thus suggesting a lack of an association. Nonetheless, some questions have been raised about the adequacy of the data for drawing firm conclusions about health risk associated with occupational exposure to AN.  The primary purpose of this submission is to inform ECHA/RAC that the NCI cohort study is being updated and will soon be available. The update will add 21 years of additional follow-up as the vital statistics extend through December 31, 2011. Given the age of the workers in the cohort, it is likely that vital status/cause of death information will be available for over 40% of the workers thus significantly increasing the ability to discern whether there is a risk from exposure to AN. The significance of these added years of follow-up cannot be overstated; once available, the data will represent the most significant and comprehensive occupational mortality dataset on the effects from AN exposure.  I notified the NCI of ECHA’s ongoing activities to analyze the available health effects information on AN applicable to setting an OEL. Based on very recent discussions with NCI staff, it is not possible at this time to provide a specific timeframe when the data and NCI analysis will be available, although the expectation is the update will be completed relatively soon. As such, ANG/GAPS advocate that the ECHA/RAC report acknowledge the conduct and importance of the ongoing NCI cohort update, and that when available, those data should be considered in assessing the scientific information for setting an OEL for AN. Moreover, given that the results will likely be available in less than one year, ECHA may want to defer final consideration of an AN OEL until the results are available.  The ANG commits to keep ECHA apprised on the progress of the study. |
| **Dossier Submitter response**  Thank you for informing us about the anticipated publication of a follow-up study of the US-NCI cohort. The Background Document makes a mention of the upcoming update of the US-NCI cohort. The deadline to deliver the opinion of RAC to the EU Commission is 26 March 2018 and unfortunately does not allow to await the results of the study. |
| **RAC Rapporteurs comments**  Thank you for your information. We note the reply provided by the Dossier Submitter and have nothing further to add. |

1. Regarding the term “mode of action-based threshold” see Joint Task Force ECHA Committee for Risk Assessment (RAC) and Scientific Committee on Occupational Exposure Limits (SCOEL) on Scientific aspects and methodologies related to the exposure of chemicals at the workplace. Task 2. 6 December 2017. https://echa.europa.eu/documents/10162/13579/jtf\_opinion\_task\_2\_en.pdf/db8a9a3a-4aa7-601b-bb53-81a5eef93145 [↑](#footnote-ref-1)
2. Regarding the term “mode of action-based threshold” see Joint Task Force ECHA Committee for Risk Assessment (RAC) and Scientific Committee on Occupational Exposure Limits (SCOEL) on scientific aspects and methodologies related to the exposure of chemicals at the workplace. Task 2. 6 December 2017. <https://echa.europa.eu/documents/10162/13579/jtf_opinion_task_2_en.pdf/db8a9a3a-4aa7-601b-bb53-81a5eef93145> [↑](#footnote-ref-2)
3. Regarding the term “mode of action-based threshold” see Joint Task Force ECHA Committee for Risk Assessment (RAC) and Scientific Committee on Occupational Exposure Limits (SCOEL) on scientific aspects and methodologies related to the exposure of chemicals at the workplace. Task 2. 6 December 2017. <https://echa.europa.eu/documents/10162/13579/jtf_opinion_task_2_en.pdf/db8a9a3a-4aa7-601b-bb53-81a5eef93145> [↑](#footnote-ref-3)