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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 benzene in the workplace

**Benzene**

**EC number: 200-753-7**

**CAS number: 71-43-2**

ECHA/RAC/A77-0-0000001412-86-187/F

**9 March 2018**

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| **Ref.** | **Date/Name/Org.** | **Type of comment** |
| 4 | **Date/Time:**  2017/10/24 16:06  **Type:**  BehalfOfAnOrganisation  **Organization name:**  [Confidential] | **Comment**  Routine personal exposure monitoring of workers at the petrochemical complex indicate that it would not be possible to comply with the proposed exposure limit changes without significant investment and changes in methods of working. Sampling data is available on request. |
| **Dossier Submitter response**  Thank you for the comment.  ECHA takes note that lowering the OEL for benzene might require significant investment and changes in methods of working.  ECHA takes note that sampling data is available on request. |
| **RAC Rapporteurs comments**  Thank you for your comment. |
| **Ref.** | **Date/Name/Org.** | **Type of comment** |
| 12 | **Date/Time:**  2017/11/07 10:30  **Type:**  BehalfOfAnOrganisation  **Organization name:**  European Tyre and Rubber Manufacturers’ Association  **Country:** Belgium  **Non-confidential attachment:**  20171107\_ETRMA-BenzeneOEL\_Clean.pdf | **Comment**  p 117The conclusion on occupational exposure limits (OEL) for benzene |
| **Dossier Submitter response**  Thank you for the comment.  ECHA takes note that an OEL of 0.1 ppm for benzene is achievable by rubber producers at the workplace. |
| **RAC Rapporteurs comments**  Thank you for your comment. |
| **Ref.** | **Date/Name/Org.** | **Type of comment** |
| 13 | **Date/Time:**  2017/11/07 11:13  **Type:**  BehalfOfAnOrganisation  **Organization name:**  British Occupational Hygiene Society  **Country:** United Kingdom  **Non-confidential attachment:**  ECHA Proposal OEL for Benzene 2017 BOHS Comments V1.docx | **Comment**  See attached document for comments... |
| **Dossier Submitter response**  Thank you for the comment.  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.  ECHA takes note that   * BOHS supports the reduction of OEL but not by factor 10 * A lowered TWA might require change of monitoring techniques * There might be an impact on a lowered TWA with regard to manpower   ECHA has taken the following scientific comments into consideration:   * Exposure data on oil and gas and marine sector sea have been added including HSE exposure data (1999). * The scientific reasons for an STEL were re-considered and no STEL is recommended any longer. * Biomonitoring of benzene in urine has been performed in several studies. In 2017 the German Research Foundation (DFG) published a correlation between benzene in urine and benzene in air which was taken over. * The toxicological data have been re-evaluated with respect to traceability issues and amended accordingly |
| **RAC Rapporteurs comments**  Thank you for your comment. |
| **Ref.** | **Date/Name/Org.** | **Type of comment** |
| 14 | **Date/Time:**  2017/11/07 11:13  **Type:**  BehalfOfAnOrganisation  **Organization name:**  Austrian Workers' Compensation Board (AUVA)  **Country:** Austria | **Comment**  The proposal for occupational exposure limit values for benzene 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 benzene with the current scientific knowledge that excludes health risks (recital 11 of this Directive). 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 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 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:  In contrast to this demand, the proposed OEL for benzene (0.1 ppm) is associated with an approximate risk of cancer of 7:10,000.  The recommended 8-hour TWA of 0.1 ppm (0.33 mg/m³) for repeated benzene exposure is mainly based on the studies by Lan et al (2004) und Uzma et al (2010). The study of Lan et al (2004) is related to haematological effects and has been questioned by AGS (2012) as to the correct numbers of employees (109 vs 30) in the class of lowest exposure and the actual exposure to benzene. The findings by Uzma et al (2010) apply to immunological effects caused by benzene. Even DECOS/The Netherlands conceded an underrepresentation of evidence as to the benzene-induced haematotoxicity and neoplastic disease. Even less evidence exists between immunological effects and cancer due to benzene exposure.  For regulatory purposes, it is not appropriate to set an exposure limit only for the prevention of haematological effects, rather than adequately addressing the cancer risk. Unfortunately, the objective to properly minimize the cancer risk through benzene exposure has not been taken into account. The carcinogenicity of benzene is based on sufficient evidence in humans, sufficient evidence from animal experiments and strong mechanistic evidence.  Therefore, an excess risk (related to the ECHA proposal of 0.1 ppm) cannot be accepted deliberately. Hence the procedure used by AGS/Germany (0.006 ppm or 0.02 mg/m³ according to a cancer risk of 4:100,000 for work lifetime exposure) is recommended.  No sound scientific evidence exists for the assumption of a non-linear dose-response relationship for the reasons extensively explained in AGS (2012, p. 43 ff). No new data became available since that document.  REMARKS:  A consistent level of protection from the risks related to carcinogens or mutagens has to be established for the entire EU (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 Directive 98/24/EC).  Adopting an opinion on an OEL for benzene 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 omitting the risk-based approach creates the impression that also (undeclared) non-scientific elements are incorporated into the proposal. |
| **Dossier Submitter response**  Thank you for the comment.  It is outside the remit of ECHA or RAC to comment on, or to determine, the acceptability of cancer risks.  Benzene is often categorised as a genotoxic carcinogen for which fully protective, health based limit values have not been derived based on the scientific evidence. However, RAC is of the opinion that a mode-of-action (MoA-) based threshold[[1]](#footnote-1) can be established based on chromosomal aberrations/damage effects (aneugenicity and clastogenicity) in workers. The proposed limit will avoid exposures that induce chromosomal damage in workers, is considered to have no significant residual risk and will also avoid other adverse effects. The justification is presented in the in the ECHA Background Document.  It should be noted that the mandate of RAC is to evaluate the scientific relevance of occupational limit values for benzene, and to assess the most recent and relevant scientific information. The RAC-opinion on benzene 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.  ECHA has taken the following scientific comment into consideration:   * The study by Lan et al (2004) has been re-evaluated based on the biomonitoring data of the study. |
| **RAC Rapporteurs comments**  Thank you for your comment. |
| **Ref.** | **Date/Name/Org.** | **Type of comment** |
| 17 | **Date/Time:**  2017/11/07 13:15  **Type:**  BehalfOfAnOrganisation  **Organization name:**  European Trade Union Confederation  **Country:** Belgium | **Comment**  General comments  The European Trade Union Confederation (ETUC) welcomes the fact that the OEL for benzene is being discussed in the framework of the 4th amendment to Directive 2004/37/EC. ETUC calls on the EU to update the Carcinogens and Mutagens Directive (CMD) and adopt binding OELs for at least 50 priority carcinogens by 2020. Our research institute (ETUI) has recently published a list of carcinogens that are relevant for workers ‘exposure via inhalation at a considerable number of workplaces in Europe and thus, for which a binding OEL under the CMD should be suggested in priority.  https://www.etui.org/Publications2/Reports/Carcinogens-that-should-be-subject-to-binding-limits-on-workers-exposure  Benzene is included in the trade union list and there is certainly a need to revise the existing OEL set at 1 ppm for that carcinogen in the Annex III of the CMD which is 20 years old.  The adoption of a binding OEL in the CMD is a long and complex procedure where the scientific advice on the OEL (to be later discussed within the tripartite Advisory Committee on Health and Safety) plays a key role. ETUC therefore regrets that the public consultation organized by ECHA on its proposal for an OEL is extremely short. One month is not enough to provide meaningful input and ensure possible relevant contributions from stakeholders are taken into account. When SCOEL is in charge the public consultation is minimum 3 months. Moreover, for all REACH processes, the public consultations organized by ECHA are longer (between 45 days and 6 months).  Specific comments  ETUC appreciates the comprehensive and updated information collected by ECHA on benzene. However, we are concerned that ECHA seems proposing an 8h TWA OEL (set at 0.1 ppm) for the non-carcinogenic adverse effects of benzene (heamatotoxicity & immunotoxicity) and the leading genotoxic effects because thresholds are likely to exist for those effects.  On the other hand, it is clearly stated that benzene is genotoxic, that its modes of action are complex, not fully understood and that an 8h TWA OEL cannot be derived for carcinogenic effects because there are uncertainties on whether all modes of action have a threshold (i.e. some might be non-threshold).  The conclusions of ECHA should be clearer. Either the existence of a threshold for carcinogenic effects can be supported or not. If a threshold cannot be scientifically supported, then no OEL should be recommended and ECHA should provide an exposure risk relationship. This is the way SCOEL is presenting its conclusions.  In a next step, based on these scientific information, it is the role of the tripartite Advisory Committee on Safety and Health to advice the Commission on the OEL to be adopted.  ETUC therefore recommends the conclusions of ECHA’s proposal in support of an OEL for benzene are reworked to align them with the SCOEL methodology. A one-page summary at the beginning of the report with the principal conclusions (threshold / non-threshold and proposed OEL or Exposure Risk Relationship) would also be appreciated. |
| **Dossier Submitter response**  Thank you for the comment  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.  ECHA takes note that   * ETUC is concerned that ECHA seems proposing an 8h TWA OEL (set at 0.1 ppm) for the non-carcinogenic adverse effects of benzene (heamatotoxicity & immunotoxicity), whereas an 8h TWA OEL cannot be derived for carcinogenic effects * ETUC considers that if no threshold for carcinogenic effects can be derived, no OEL should be recommended by ECHA but only by the tripartite Advisory Committee on Safety and Health |
| **RAC Rapporteurs comments**  Thank you for your comment. |
| **Ref.** | **Date/Name/Org.** | **Type of comment** |
| 18 | **Date/Time:**  2017/11/07 14:16  **Type:**  BehalfOfAnOrganisation  **Organization name:**  Concawe  **Country:** Belgium  **Non-confidential attachment:**  Concawe letter to RAC concerning Benzene OEL.pdf | **Comment**  Concawe, the scientific division of the European Petroleum Refiners Association, would like to express its concerns on the ECHA/RAC proposal to lower the occupational exposure limit (OEL) for Benzene by 10-fold, to 0.1 ppm. Concawe has not directly provided comments on the report via the public consultation process, but Concawe's industrial hygiene and toxicology experts have been actively involved in the development and submission of scientific feedback provided by the Lower Olefins and Aromatics (LOA) consortium. Concawe endorses the value suggested by LOA (0.4-0.7 ppm) as a scientifically sound alternative OEL to protect worker safety based on the most current scientific evidence.  Concawe's formal feedback is provided in the attached letter (pdf document). |
| **Dossier Submitter response**  Thank you for the comment  ECHA takes note that   * Concawe expresses its concern to lower the OEL by factor 10. * Concawe supports the LOAE proposal for an OEL of 0.4 to 0.7 ppm |
| **RAC Rapporteurs comments**  Thank you for your comment. |
| **Ref.** | **Date/Name/Org.** | **Type of comment** |
| 19 | **Date/Time:**  2017/11/07 15:39  **Type:**  BehalfOfAnOrganisation  **Organization name:**  Oil and Gas UK  **Country:** United Kingdom  **Non-confidential attachment:**  Consultation response.pdf | **Comment**  Please see attached response to the proposed exposure limits on pp 117-119 |
| **Dossier Submitter response**  Thank you for the comment  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.  ECHA takes note that   * OIL&GASUK considers that OEL should be based on a variety of cohorts and working environments * OIL&GASUK considers that STEL should be based on specific scientific investigations rather than generic safety factor   ECHA notes that no scientific justification and evidence has been provided by OIL&GASUK. However, based on comment from other 3rd parties, ECHA has re-evaluated both aspects. |
| **RAC Rapporteurs comments**  Thank you for your comment. |
| **Ref.** | **Date/Name/Org.** | **Type of comment** |
| 21 | **Date/Time:**  2017/11/07 18:26  **Type:**  BehalfOfAnOrganisation  **Organization name:**  Lower Olefins and Aromatics Reach Consortium vzw  **Country:** Belgium  **Non-confidential attachment:**  2017\_11\_07 LOA comments on Benzene RAC proposal.zip | **Comment**  These comments on the Benzene OEL Proposal are from LOA, the Lower Olefins and Aromatics REACH Consortium. LOA acts on behalf of Member Companies and other Registrants to support benzene in REACH. Benzene is a key substance in the Aromatics sector which employs about 20,000 in the EU. LOA also supports the steam cracking sector which produces olefins and pyrolysis gasoline from which aromatics are extracted. Experts from these sectors and the Refining sector have contributed to these comments.  Due to the web form size limitation, full comments are attached and here only a summary is provided. On the ECHA benzene OEL proposal, LOA makes the following key points:  Benzene Uses  \* The LOA registration dossier for benzene only supports the use of benzene as an intermediate (under strictly controlled conditions) and indicates that all other uses are uses advised against. ECHA’s web page indicates that there are many uses registered, most of which would contradict Annex XVII. LOA will conduct a use survey and work with ECHA to clarify this confusing situation.  \* ECHA text implies benzene is added to gasoline. This is not the case. Benzene containing streams can be blended to give gasoline, but not benzene itself.  Worker Exposure  \* Value of health surveillance data: There is no justification to rate the results from epidemiology studies higher than those obtained from long-term health surveillance. In health surveillance benzene exposure estimates are based on sampling strategies targeted at representative jobs and workplace combinations.  \* Exposure levels: There is no reference made to the fact that most of the exposure level concentrations reported do not consider the use of respiratory protection. For that reason, these exposure levels should be reported as potential exposures.  \* Hydrocarbon solvents: potential exposures related to trace levels of benzene in hydrocarbon solvents. Such a product would not be taken up in the market in view of the availability of the non-carcinogenic alternative.  \* Missing references and data and some editorial comments: e.g. Spanish service stations, exposure via dietary sources and loading vrs unloading operations at service station.  \* Dermal exposure: There is uncertainty about the contribution of skin uptake. However, it should not be considered negligible.  Human biomonitoring  LOA concurs with the opinion of ECHA regarding the choice of the benzene biomarkers of exposure and the usefulness of BLVs in general. LOA doubts the values derived are correct at <1 ppm concentrations, nor have they been justified, and applying the proposed BLV values in non-occupational add-on exposure (smokers) will be problematic.  Monitoring methods (Analytical)  \* Section fails to mention the use of passive samplers (far more acceptable to workers being monitored than pump and tube) but which may face sensitivity issues at the levels proposed.  \* If samples are to be collected for a shorter period of time, the detection limit would increase, yielding uncertainty around the measure.  \* An overall review of exposure monitoring methodologies is necessary since most of the ones currently used cannot be used with the proposed OELs.  Toxicokinetics/Modelling  Multiple re-analyses of air benzene to urine biomarker correlations suggest benzene metabolism is linear or nearly linear in the <1 ppm range. LOA believes there is no strong basis to justify non-linearity for metabolism.  Haematology  \* Concerns are raised about statistical analyses and uncertainties in exposure assessment.  \* A true weight of evidence assessment of the haematological data in workers has not been carried out by ECHA. Inappropriate weighting is assigned to the work of Lan et al, despite at least partial acknowledgement of the study’s limitations. It is not clear why in the Lan et al study the exposure assessment/groupings were done on individual exposure results, despite a thorough categorization being made by Vermeulen et al. The conclusions drawn by Lan et al that haematotoxicity occurred at benzene air levels of ?1 ppm is questionable. We doubt that the population studied by Lan et al was a truly low exposed group based also on the measured urinary benzene levels.  Immunology  \* Given the uncertainties of several studies (Lan et al 2004, Huang et al 2014, Uzma et al 2010, Moro et al 2015) both in terms of the findings and the definition of the associated exposure to benzene it would seem appropriate to fall back on haematological data to define a DNEL.  \* Overall the studies cited do not appear to support a clear immunomodulatory effect at benzene exposures of <1 ppm.  Genetic Toxicology  \* LOA would concur with the position taken that the key effects are cytogenicity and aneuploidy in high exposure workers, and that studies of DNA damage (e.g. Comet) data can be misleading.  \* Due to uncertainties in the data (Marcon et al 1999, Kim et al 2010, Rekhadevi et al 2010 & 2011) LOA does not consider that the evidence demonstrates cytogenetic and aneugenic activity below 1 ppm. LOA considers that the ECHA contention that aneugenicity is a more sensitive endpoint than haematoxicity is not soundly based.  Carcinogenicity (Epidemiology)  • ECHA should base any carcinogenic assessment on endpoints that are clearly linked to benzene, viz. AML/ANLL and/or MDS.  • ECHA should recognize that several studies suggest an empirical threshold for AML/ANLL, and model risk using sub linear dose response curves to account for this.  • ECHA ignore persuasive data from one of the highest quality studies of Pliofilm workers that suggests that:  – ANLL is the only subtype related to benzene  – Excess risk is only present in a 10 year, or possibly a 20-year window after exposure  – A sub-linear or empirical threshold is suggested by the Pliofilm study  • ECHA fail to recognize important limitations of the meta-analyses.  • ECHA overstate the potential or possible relationship between benzene and ALL, CLL, CML, NHL and MM.  • ECHA fail to recognize the variance in exposure assessment techniques used in the studies that quantify benzene exposure, thereby mixing lower with higher quality studies.  Carcinogenicity (MoA)  \* As shown by both DECOS and LOA analysis, a threshold model is supportable for benzene. LOA’s paper “Benzene: Importance of Dose Metrics in Assessing Stochastic versus Threshold Mechanisms” is attached.  \* SCOEL carcinogen group C assignment of benzene is more consistent with its nature as a weak genotoxin with important secondary mechanisms.  Carcinogenicity (Risk Extrapolation)  \* ECHA fail to critically analyse the strengths and weaknesses of published assessments, citing comparatively recent publication as justification. This is an inappropriate rationale for model selection.  \* The selected AGS model uses a model averaging that may systematically misestimate risks due to insufficiently rigorous weighting of different studies.  \* ECHA fail to address the potential influence of exposure misclassification due to study design decisions and unaccounted sources in epidemiology studies resulting in overestimates of benzene health risks.  \* ECHA fail to discuss the impact of using risk estimates from the Pliofilm worker cohort calculated using exposures assessments for which key assumptions regarding historic exposure have been shown to be incorrect, and result in overestimates of benzene leukemia risk.  \* ECHA fail to critically evaluate the ATSDR BMD analysis, particularly the decision to select a response for the value it calculated instead of being based on a non-adverse effect size or an accepted default.  \* ECHA fail to critically analyse the use of reported air benzene concentrations as the sole exposure measure when reported urinary benzene biomonitoring data suggests additional sources of exposure.  OEL setting  \* Occupational Exposure Limit (OEL) setting: exposures are well known to vary from day to day as a result of fluctuations in the underlying exposure factors, such as ambient air velocity and temperature, work load, process throughput, etc. Therefore, if an OEL is set to protect from long-term exposure and the accompanying measurement strategy is specified as aiming at daily OEL compliance, the OEL can be set at a level 2-4 times higher than the maximum long-term exposure level considered to be still health-protective.  \* The STEL of 0.2 ppm should be removed from the ECHA proposal because no health protection objective related to health effects resulting from short-term exposures is made. Simple use of a factor in deriving a STEL has no scientific basis (SCOEL).  \* No justification to publish a biological guidance value – there is a biological limit value.  The Reader’s attention is drawn to 3 attached documents. LOA’s detailed comments are attached together with an LOA paper about benzene dose metrics and a threshold Mode of Action and a paper deriving DNELs for benzene based on haematology data. The latter points to an OEL in the range 0.4-0.7 ppm. LOA is open to questions and discussion to help ECHA progress their OEL proposal.  6 Attachments |
| **Dossier Submitter response**  Thank you for the comment  ECHA has taken the following comments into consideration:   * Benzene uses: ECHA notes that in dossiers submitted to ECHA uses are listed that might contradict Annex XVII. However, it is the registrant’s responsibility to correct the uses in the dossiers. * Benzene uses: ECHA clarified that “benzene in gasoline has a role as an anti knocking agent” to avoid impression that benzene is added to gasoline. * Use of historical monitoring data: It is clarified in the text that Table 7 includes some older exposure data if recent data from Europe is not available. * Value of health surveillance data: ECHA considers that studies in which exposure was assessed by personal monitoring could provide more reliable information on dose-response relationships than studies, in which exposure was estimated or measured stationary. * Exposure levels: It is common practice to report concentrations of substances measured in the breathing zone of the workers or from the stationary locations that represent the workers’ exposure. When the internal exposure of workers is assessed, the use of PPE is taken into account or e.g. biomonitoring is used in assessment. * Hydrocarbon solvents: a note was added that benzene concentration as a constituent of other substances, or in a mixture placed on the market should be less than 0.1% by weight. * Missing reference and editorial comments: The reference to “fuel tank drivers” has been removed in the conclusion of service station, while the correct one would be “petrol pump attendant” according the article. In the article, the task is described as a fuel loading operation (Campo et al 2016). The data from Campo et al 2016 for service station is included to the Table 7. A reference on benzene measurements for Spanish service stations has been added. * Dermal exposure: A senstence indicating that absorption due to vapour was negligible was deleted. Instead it is highlighted that in incertain situations, the dermal route can be an important contributor to total benzene exposure. * Human biomionitoring: ECHA acknowledges that LOA concurs with ECHAs opinion regarding the choice of biomarkers of exposure and the usefulness of BLVs in general. The biomonitoring values corresponding to benzene concentrations below 1 ppm in air are indeed justified. The study results are summarized in tables in the appendix and cross-references in the text have been added. Furthermore, the correlation for the miononitoring parameters are justified by DFG. Unfortunately, the background document will only be published beginning of next year. However, the documentation was available for drafting and the DFG document can be requested from the Secretariate of the German MAK Commission (Dr. Heidrun Greim, Technische Universität München, Hohenbachernstrasse 15-17, D-85350 Freising - Weihenstephan). ECHA further notes that smoking is specifically considered for the biomonitoring parameters. * Monitoring methods: exposure monitoring methods have been reviewed and amended; specifically passive sampling methods have been amended. * Toxicokinetics/Modelling: the document already includes critical comments on the hypothesis of non-linearity of metabolism. * Haematology/   + The comments made on the study by Lan et al (2004) have been taken into consideration and the text has been revised, especially with respect to potential contribution of dermal absorption as indicated by the biomonitoring data.   + Weight of evidence: ECHA has taken into consideration the comments received and is concluding on the haematological data using weight of evidence considerations. * Immunology: The text has been revised taking into consideration the shortcomings of the cited studies (e.g., control groups) and hence, their insufficient suitability to derive NOAELs or LOAELs. * Genetic Toxicology: The conclusion on the studies by Marcon et al (1999) and Rekhadevi et al. (2010, 2011) with respect to effects observed below 1 ppm were revised. * Genetic Toxicology/haematology: ECHA notes that the results of the study by Zhang et al. (2016) indicate that increased incidences of micronucleus formation occur at lower exposure concentrations compared to reduced white blood cell count. ECHA acknowledges that the study might not be sufficient robust to conclude that genotoxicity would be a more sensitive endpoint than haematotoxicity because only limited parameters have been investigated. * Carcinogenicity (Epidemiology)   + The description and conclusions of increased risks of AML/ANLL and/or MDS versus other types of leukaemia were revised. It is also further explained why there is reason to consider all leukaemia rather than only AML/ANLL or MDS. However when describing the AGS approach also this uncertainty is further described.   + Descriptions of the epimiological studies as regards if they suggest “an empirical threshold for AML/ANLL” were revised, including the Pilofilm cohort specifically citing the conclusion of the latest report by Rhomberg et al 2016 “*the dose-response relationship at lower benzene exposures remains difficult to resolve with this dataset, owing to a lack of cases in lower exposure categories, Still, the absence of cases in lower exposure categories suggests that benzene may have a threshold effect on induction of certain types of leukaemia*”. Both linear and sub linear dose response curves are described along with the inherent uncertainties. Nevertheless as pointed out above, such analyses are hampered by the small number of observed cases in low exposure categories resulting in quite wide confidence intervals for the risk estimates.   + The quality ranking by Vlaanderen et al 2008 of the AML epidemiologic studies was added as suggested by LOA Reach Consortium, including the information that the Pliofilm cohort study ranked on 4th place of the 5 studies that passed the ranking. In that regards it is noted that this quality assessment does not allow to confirm Pliofilm cohort being the “highest quality” and thus justifying it to be given priority over the other studies published.   + The description of the epidemiologic studies and their conclusions as regards the relevant time window were revised, including the Pliofilm study. It is acknowledged that exposures e.g. more than 20 years ago contain both recent and distant exposures and it is indeed difficult to conclude which were more relevant as the changes in intensity by time are often not further described.   + The specific problems mentioned for the meta-analyses are now described.   + The variance in exposure assessment techniques used in the cancer epidemiology studies that quantify benzene exposure were further described, including the assessment of the four exposure estimates that have been published for the Pliofilm cohort.   + The specific uncertainties pointed out for of the AGS (2012) average ED10 approach were further described along with their possible impact. As regards whether incidence or mortality data should be used, ECHA considers this more a question of socio-economic assessment, where indeed a fatal and a non-fatal case can be valued differently. However all incident cases should be considered when aiming to prevent occupational ill-health, as also described in the ECHA/RAC-SCOEL Joint Task Force Report referenced in the ECHA Background Document Chapter 8.2.2.Obviously preventing incident cases prevents also the fatal cases. ECHA notes also the alternative excess risk calculations provided by LOA based on the Pliofilm cohort and reflects them in chapter 8.2.2 of the ECHA background document.   + As regards the more specific comments on individual studies described in the ECHA proposal, revisions were made to better reflect the uncertainty/deficiency that was indicated. * Carcinogenicity /MoA: ECHA acknowledges that benzene has modes of action for which a threshold is likely. However, the metabolism of benzene is complex and it is not clear if for all modes of action a threshold would exist. * Carcinogenicity/SCOEL carcinogen group: the assignment to a SCOEL carcinogen group has been removed. * Carcinogenicity/Risk extrapolation:   + ECHA has reviewed published assessments and has provided a justification for the selected model.   + See also replied for Carcinogenicity (Epidemiology) above. * OEL setting/methodology: OEL setting follows the SCOEL methodology * OEL setting/STEL: the STEL has been revised and no STEL will be recommended any longer. * Biological guidance value/biological limit value: even if biological limit values are proposed, biological guidance value are useful in providing further information on background exposure. * LOA approaches for an OEL have been reviewed. However, considering all available studies, the proposed approaches are not considered as justified. |
| **RAC Rapporteurs comments**  Thank you for your comments. |
| **Ref.** | **Date/Name/Org.** | **Type of comment** |
| 22 | **Date/Time:**  2017/11/07 19:01  **Type:**  BehalfOfAnOrganisation  **Organization name:**  Energy Institute  **Country:** United Kingdom | **Comment**  Other related comments/General Statements:  1. Insufficient review time for major impact on O&G Industry to give scientific review and response, as benzene is a varying constituent of crude oil and gas condensate and thus can be found throughout upstream process, rather than a benzene specific use.  2. Scientific foundation for such a significant change, needs review further and technical justification.  3. The proposal appears to be based on a single study of 109 persons, not a meta study across multiple studies with a variety of cohorts and working environments.  4. The studies, some from the far east and china, although presented as technical papers may not have the same validation as UK / European / US research and, by referencing China shoe workers for example as a base for reducing the limit is, in my opinion not completely substantiated by the evidence from elsewhere.  Monitoring Exposure:  1. By the reduction of exposure limits by a factor of 10 the upstream O&G sector lose the ability to deploy passive techniques to remote locations for exposure risk assessments, which is inherent part of how benzene exposure risks are managed currently.  2. The information in Section 8 outlining a summary of exposures omitted upstream oil & gas out completely and the marine sectors mentioned are in dock, not at sea. As a result, the conclusions on the levels of exposure are well below the averages in these sectors and well below the HSE’s own findings, not cited from a study of nearly 300 individuals in the UK upstream industry conducted in 1999  3. The inclusion of direct benzene measurements as a biomarker in urine is mentioned without due consideration of the clear biodegradation that occurs with individuals and, carries credibility issues  - s-PMA limit of detection at level issue at BLV if applied.  4. STEL of 0.2ppm is impractical with current passive techniques and in the summary, is stated in Section 8 in one paragraph without any summary information to support it.  5. The methods suggested for air monitoring and stated as the one that should be used is active pump & tube techniques. HSE methods for this and passive devices not openly mentioned or discussed. |
| **Dossier Submitter response**  Thank you for the 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.  ECHA takes note that The Energy Institute considers that   * A lowered TWA might require change of monitoring techniques   ECHA has taken the following scientific comments into consideration:   * The foundation for the OEL has been reviewed and is finally based on a weight of consideration of all reviewed studies that investigated clastogenic and/or aneugenic effects in workers. * Therefore, the starting point for deriving the OEL is no longer based on haematological effects, as evident from RAC opinion and ECHA Background Document. * Exposure data on oil and gas and marine sector sea have been added including HSE exposure data (1999). * Biomonitoring of benzene in urine has been performed in several studies. In 2017 the German Research Foundation (DFG) published a correlation between benzene in urine and benzene in air which was taken over. * Passive sampling methods have been added |
| **RAC Rapporteurs comments**  Thank you for your comments. |

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| **Ref.** | **Date/Name/Org.** | **Type of comment** |
| M1 | **Date/Time:**  Monday, November 06, 2017 4:07 PM  **Type:**  Member State  **Organization name:**  Ministero del Lavoro e delle Politiche sociali  **Country:**  Italy | **Comment** |
| **Dossier Submitter response**  Thank you for the comment  ECHA takes note that the Italian MSCA is supportive with the proposed OEL for haematotoxic effects. However, as explained under reply to comment nr. 22 the starting point for deriving the OEL is no longer based on haematotoxic effects. |
| **RAC Rapporteurs comments**  Thank you for your comment. |

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)