COC Evaluations 2021

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Human Biomonitoring for EU and Development of Human Biomonitoring Guidance Values in the HBM4EU project

3.1 A presentation was given by Dr Sepai, Public Health England (PHE), at the COC meeting on 11th March 2021 and the COT meeting on March 23rd, 2021, with a supporting paper 'Development of Human Biomonitoring Guidance Values in the HBM4EU biomonitoring project'.

3.2 Human biomonitoring (HBM) programmes can provide essential information for identifying population exposures to chemicals of concern that can be assessed with regards to potential health risks against derived guidance values (GVs) in specific population subgroups or areas. These can be important complements to the conventional sources of information for regulatory chemical risk assessments and for supporting public and occupational health protection policies.

3.3 There is currently a diversity in the derivation of health-based guidance values for both the general population and for occupational exposures. Dr Sepai outlined the methodology for the derivation of human biomonitoring guidance values (HBM-GVs) by the European Human Biomonitoring Initiative, referred to as HBM4EU. This is a project involving 30 countries, the European Environment Agency and the European Commission, co-funded under Horizon 2020. The UK has been involved in the project with PHE leading the UK input. The initiative is designed to develop a harmonised and systematic strategy for the derivation of HBM-GVs.

3.4 Importantly, the HBM4EU strategy is based on current practices for deriving health-based assessment values based on internal exposure, which will supplement those already derived relating to external exposure measurements. The key schemes on which the HBM-GV derivation methodology is based are those already existing from the German Human Biomonitoring Commission, Summit Toxicology and the French Agency for Food, Environmental and

Occupational Health & Safety. Members of the COC and COT were asked to consider whether the derived HBM-GVs could be used for risk assessment purposes and if the HBM-GVs would be accepted by the UK.

3.5 It was agreed, in principle, by members of both Committees that the framework was a robust and scientifically valid way to determine HBM-GVs but offered suggestions to make some components of the process more explicitly stated, including the impact of data availability (for example, toxicokinetic data) on the estimated level of confidence associated with each HBM-GV. It was accepted that the estimated level of confidence would vary on a case-by-case basis, depending on available data, which should be reflected in the use of the HBM-GV in different tiers for risk assessment purposes. As the values are able to be applied to any population, the absence of UK-specific population data was not considered an issue for derivation, with the caveat that the critical endpoint on which the HBM-GV was derived is appropriate for the UK population. However, members considered that UK-specific data would be required before the HBM-GVs could be used for risk assessment purposes in the UK.

3.6 The COT commented that the HBM-GV's would need to be validated from a toxicological perspective (see paragraph 1.78). It was also suggested that refinements in exposure assessment could be achieved through the collection of environmental data (in collaboration with the Environment Agency or Defra) and through the inclusion of all routes of exposure, including dermal. Members agreed that going forward, the use of HBM-GVs in risk assessment could be particularly helpful to the FSA and that the Committee was happy to look at future case studies and offer their perspective. If endorsement of individual values was needed, the Committee would have to perform a detailed evaluation to offer their opinion.

Modification of Cancer Risk

3.7 COC had expressed its aspiration in the preceding years to move away from traditional risk assessment approaches for potential carcinogens, to a more holistic approach encompassing consideration of the modifying effects of chemicals on all stages of cancer development. This has been reinforced by increasing concern over the reliability and applicability of the rodent two-year bioassay in predicting chemical carcinogenicity relevant to humans. In addition, consideration had also been made of combining two guidance statements covering hazard identification and characterisation (G03), and alternatives to the two-year bioassay (G07) to a combined document on considering modification of

cancer risk using a weight of evidence-based approach.

3.8 The COC discussed this further in 2021, in the main Committee and as a sub-group discussion. It was agreed that there was currently insufficient information available on all aspects of cancer development and the potential modification of these events by chemicals to facilitate its use by risk assessors. Therefore, distinct COC guidance could not be developed at this point, but two guidance statements G03 and G07 should be updated (see 3.26 below). A paper capturing these thoughts was published in Toxicology Research by two members, (Harrison & Doe (2021) The modification of cancer risk by chemicals. Toxicology Research, 10(4), 800-809). This covered many of the aspects discussed by the Committee and it was agreed the topic would not be progressed to a separate published COC document.

FSA Science Council Draft Principles and Guidelines on Third Party Evidence

3.9 The COC was presented the draft set of principles and guidelines on third party and uncommissioned evidence that had been prepared by the FSA Science Council to support consideration of such evidence and provide transparency on the ways in which evidence submitted in a non-standard way would be assessed.

3.10 The COC made some suggestions for clarity in terms of the audience for the principles and guidelines and to be clear on the meaning of the wording on data cleaning.

3.11 The document has subsequently been finalised by the FSA Science Council. See Rapid Evidence Review on the Critical Appraisal of Third-Party Evidence (food.gov.uk) for further details.

Terms of reference for the Office for Product Safety and Standards (OPSS) Scientific Advisory Group on Chemical Safety of Non-Food and Non-Medicinal Consumer Products (SAG-CS)

3.12 The terms of reference for the Office for Product Safety and Standards (OPSS) Scientific Advisory Group on Chemical Safety of Non-Food and Non-Medicinal Consumer Products (SAG-CS) was presented to the COC for awareness

of this group. The COC fed back the suggestion of having lay representation on the group in the future.

Presentation by Dr Steve Dean “In vitro high content screening using patient-derived cell models”

3.13 The presentation by Dr Steve Dean, Imagen, described a personalised treatment for cancer that evaluates potential drug therapies using patient derived cell models. The PredictRx assay utilises a biopsy from patients to derive cells that are screened against 60 drugs to determine sensitivity of the tumour cells. They report a good prediction of clinical response with an 89% positive predictive value and 99% negative predictive value for those currently tested. Due to the low number and heterogeneous nature of the tumours, between 3 and 5 needle biopsies are usually taken which are pooled. The results therefore represent an average of the responses of the different tumour cells.

3.14 Since 2019, with informed consent, the patient-derived cells have been stored in a biobank and a searchable database has been established. The biobank has a range of solid tumour types and is being expanded to include haematological tumours. As with primary cell lines, patient-derived cell models generally have a limited life span, and to ensure that the cell models do not diverge from the original, a limited number of passages are allowed. The biobank and database are a key resource for the evaluation of new drug candidates at all stages of development, including the potential to enhance Phase I II and III clinical trials.

3.15 The biobank and database are also seen as a potentially interesting resource for cancer research to help gain an understanding of carcinogenicity and mutagenicity. Advantages include high throughput analysis of a range of endpoints including cytotoxicity and apoptosis, cell cycle, DNA damage & repair, morphological and phenotypic changes, cell stress and inflammation, cell signalling and transcription factors and drug internalisation. Importantly, the cell models are reliable pre-clinical models with a traceable origin and are accompanied by patient histories.

3.16 Following the presentation, the COC noted that this was potentially a good example of how *in vitro* methodology may allow risk assessors to steer away from the use of traditional *in vivo* study data and allow better understanding of

mechanisms in humans. The stability of the cell models was questioned as this was seen as crucial to ensure that the models continued to represent the patient. As this could be different for each model, whilst this is being evaluated, the models are currently limited to 15-20 passages. It was recognised that validation will be key to getting clinical acceptance as a diagnostic tool and acceptance of findings within regulatory submissions.

3.17 The translatability of the approach, particularly the data, to establish mechanistic rather than response data was also raised. This had been attempted successfully for a metabolic syndrome and was believed to be applicable more widely to non-cancer endpoints. Artificial Intelligence platforms may play a key role in interpreting mechanistic data. Benefits of the use of the approach to assess risk included the high throughput nature, availability of detailed genotypic and phenotypic parameters and a response pathway analysis.