EUROPEAN COMMISSION
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Institute for Health and Consumer Protection
European Centre for the Validation of Alternative Methods (ECVAM)

Ispra, 27/05/2010
IHCP/I.3/jk-ARES(2010)284892

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Dear Marilyn,

Dear Bill,

The development of harmonized test method recommendations is a key element of the ICATM framework and we therefore appreciate to collaborate with you on the development of final recommendations that take the different views among the participating validation bodies into account, with the aim to avoid the situation of a partner VAM issuing a deviating position.

ECVAM agrees with ICCVAM's conclusion that the BCOP should not be recommended for the identification of chemicals not classified as ocular irritants under the EPA (Category IV) and FHSA (Not Labeled) classification systems due to false negative rates of 5-6%.

On the other hand we still strongly disagree with ICCVAM's opinion that the accuracy and reliability of the BCOP test method does not allow its use for identifying chemicals not classified as ocular irritants under the EU DSD (Not Labeled), the UN GHS (No Category), and the EU CLP (No Category) classification systems. The reason for this disagreement is that the BCOP produces reliable results and has shown a rate of 0% false negatives under these classification systems. Obviously this performance is related to the

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Category), and the EU CLP (No Category) classification systems. The reason for this disagreement is that the BCOP produces reliable results and has shown a rate of 0% false

thresholds applied, which have been established as a result of a long and intensive international process.

Please note that we therefore continue to be in full agreement with the conclusions and recommendations of the ICCVAM Ocular Peer Review Panel (PRP) that convened in Bethesda, USA, on 19-21 May 2009, which concluded that the usefulness of the BCOP for the identification of chemicals not classified as ocular irritants depended on the intended purpose (i.e. the classification system) and that, therefore, the BCOP could be recommended for the identification of chemicals not classified as ocular irritants under the EU DSD and UN GHS classification systems (the CLP was not yet adopted), while such recommendation was not possible when considering use of the BCOP for the EPA classification system.

We therefore believe that the most appropriate approach to evaluate the usefulness and limitations of the four organotypic test methods (BCOP, ICE, IRE and HET-CAM) for the different classification systems (EU DSD, UN GHS/EU CLP, EPA, FHSA) would be through a separate and independent analysis of each test method's predictive capacity for each classification system.

ICCVAM expresses concern of ensuring sufficient protection of public health that could result from classifying substances as "Not Labeled" (EU DSD) or as "No Category" (the UN GHS and the EU-CLP). However, as we all know, all classification systems are simplifications of a rather complex scientific reality and they represent compromises that are (internationally) accepted to sufficiently protect public health. .

We remain, in this context, concerned by a statement in the latest draft version of the ICCVAM Test Method Evaluation Report that in our understanding is – so far – not substantiated by scientific evidence: ICCVAM states that "the nature, severity, and duration of these eye injuries [i.e. those induced in rabbit eyes] **suggest the potential to cause human injury**", when referring to the 70% EPA category III chemicals that are not classified under the UN GHS classification system. In view of the limitations of the Draize test due to species differences and other parameters, we would kindly like to ask ICCVAM to substantiate this claim that these chemicals indeed produce injury to the human eye with further data. Should there be no data available substantiating this claim, ECVAM would not be able to support a recommendation containing the conclusions as they now stand.

Please note, that the EU DSD classification system is in place in Europe since 1967 (Directive 67/548/EEC) without any known case of human eye injury caused by chemicals classified as "not labelled" under this classification system. In this context it is also relevant to recognize that the EU DSD system is even less conservative than the new EU CLP system, which is based on UN GHS (cut-off Draize scores for EU DSD R36 classification are higher than for UN GHS/EU CLP Cat 2 classification). We conclude from this that there is no empirical evidence that the EU-DSD system in reality poses any human health problem with regard to eye irritants.

Nevertheless, we recognize that the reduced eye hazard labeling resulting from the use of GHS instead of current U.S. regulatory classification criteria is of concern to the U.S. and we support that this issue be presented and discussed at international level. This could happen, for example, with experts from the UN Sub-Committee of Experts on the GHS and/or OECD. Importantly, such discussions should occur before judging on the appropriate public protection of one or several internationally agreed classification systems and should not be confounded with recommendations of test methods against the current criteria.

In conclusion, ECVAM suggests that the recommendations on BCOP should be along the lines proposed by the ICCVAM Ocular Peer Review Panel (PRP), cited above, clearly spelling out that the performance of the BCOP differs for the different classification systems.

In addition, ECVAM strongly recommends the development of full Performance Standards (Essential Test Method Components, Reference Chemicals and Target Accuracy Values in function of the target classification system) for BCOP, to allow for the faster evaluation and validation of variations/updates of the method (a new opacitometer is, for example, available from BASF and revised protocols are being developed to address problematic chemical classes, etc.).

Let me underline once more our appreciation of this cooperation and of the opportunity to find together and in true partnership suitable formulations. These should bring forward the concern expressed in the current draft but also make it very clear that for certain current classification systems the BCOP can very well serve as a means to identify substances that are not labelled or not classified with regard to eye irritation. In our view the formulation of the ICCVAM Ocular Peer Review Panel pointed in the right direction.

On the other hand, if ICCVAM cannot recommend the BCOP test for identification of not labelled and no category chemicals under EU DSD and UN GHS/EU CLP, ECVAM will have to issue its own recommendation along this line.

/s/

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On behalf of ECVAM

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