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Pepper is a non profit association co founded by the French Government and Industry and rejoined by The Netherlands. Its goal is to organize and fund validation of methods on Endocrine Disruptors. Even if this is not a rule of principle, in practice, these methods are NAMs

Comments on ICCVAM 2023 report on Validation Quantification and Regulatory Acceptance of New Approach Methodologies.

Dear Authors

We thank you for this report and for the opportunity to comment.

To us, the report appears a very valuable step forward for many reasons ; because validation is not separated from the ultimate goal that is regulatory acceptance, and because there is a comprehensive descriptions of the issues.

Flexible & fit-for- purpose validation concepts are definitely a relevant approach when one looks at the variety of the purposes. However, it may be more difficult to keep those lines once a substance is within a regulatory process, because the process can be controversial, including many stakeholders who might not respect the barriers between the contexts of use when fueling the controversy, including in legal matters.
Robustness of those barriers between the COUs can be an element of acceptability, and may be suggestions would be useful in order to avoid that the confusion in the “contexts of use” do come back through the back door.
The fact to base the validation/qualification of a NAM on its “context of use” may lead to a lot of supplementary work in case this COU changes, or is to be extended. The report mentions that a new set of reference chemicals may need to be selected, or that a second peer-review may be necessary. It may be interesting to develop more this point of supplementary work.

The stress put on reference data is an essential point in the report, and developments and suggestions on use of human and animal data are very useful.
When referring to” Existing Laboratory Animal Methods”, it is not clear whether validated methods only or any scientifically sound methods are to be considered. Actually the word that is used is “traditional”. The classical approach of validation suggest the first hypothesis, but one may think that the working group promotes a broader approach, which makes sense when a NAM targets an effect which can be observed in “non traditional” animal method. Is it possible to clarify this point, or to make a development ?
The use of other *in vitro* data is referred to through references (e.g. Judson et al., 2019) : Is it possible to insert advices on the limits of such uses, may be in connection with the COU.
the report suggests that the solution may be only imperfectly satisfactory. Is it possible to give advices to deal with such cases?

In connection with the “historical bias in literature”, the consequences can be more severe that what is mentioned. Not only it is difficult to find “negative” substances, but also there might be undue

“positive”, because it may happen that an experiment with a borderline positive effect is published, while other experiments with no effects are not published.

The technical characterization section provides the necessary elements in an exhaustive manner. The paragraph on communication and training might usefully refer to it. Indeed the developers should be made well aware of those issues at a very early stage of development. It can also be advocated that technical characterization criteria should be present in the research calls.

The report mentions in some places the involvement of other labs (on top of the developer). However, it is not specified what the work of these other labs may be, what level of involvement may be required. Is it intended to be different dependent of the COU? Some more explanation on this aspect would be interesting.

Sincerely Yours.
Philippe HUBERT