

October 19, 2004

Dear Dr. Wagner,

In this letter, BIAC respectfully submits comments and suggestions concerning refocusing the Test Guidelines (TG) Programme. Sound assessments of chemical substances and products containing them depend on sound methods and, as a consequence, BIAC members are key customers of work of the TG Programme.

BIAC believes that there are three core areas where the TG Programme activities provide essential value and these should be considered sacrosanct:

- A. International harmonization of TGs to ensure mutual acceptance of data and optimal use of testing resources.
- B. Consensus decision making in TG development and modification to ensure all viewpoints of working groups, national delegations etc. are appropriately aired, discussed and resolved to the mutual satisfaction of all participants.
- C. TG methods are developed that are scientifically sound, properly evaluated, relevant, reliable and interpretable for the intended use.

Based on the "Preliminary Draft Issues Paper on a Refocus of the Test Guidelines Programme" developed by OECD, BIAC asks that the OECD carefully consider the following points.

1. Setting Priorities in the TG Programme

It may be opportune for OECD to re-evaluate how priorities are set and how these align with available resources. Critical to this effort is to ensure that both the human resources within OECD and those from participating lead organizations are sufficient for the envisioned effort. It sometimes appears that priorities are set without adequate consideration of the common priorities across OECD members and the resources needed over the full time period to see projects to completion. Some sort of commitment from participating lead organizations, perhaps in the form of a written proffer, along with a similar proffer from OECD for each "High Priority" effort may be worthwhile considering. With respect to priorities, OECD may need to revise its process to be more selective to ensure that available resources match the projects and that new projects are not accepted or undertaken without commitment of adequate resources. Those proposing a new TG should be prepared to assume responsibility commensurate with the work. BIAC supports discussing potential modifications of the existing process. Discussions should include consideration of submittal by the lead entity of a timeline, deliverables and resources identified/committed to method standardization and validation as well as draft TG development.

2. Use an Assessment Framework to Guide Decision-Making on High Priority Methods

Calls for new TGs or for substantial revisions to existing TGs often are presented with insufficient clarity as to their need or purpose. Further, fewer, validated, high quality TGs may be

a better output of the TG Programme. BIAC suggests that OECD develop a more rigorous evaluation procedure such that the need would be clearly demonstrated through guidance or a process that OECD could offer. In this regard, we suggest that the appropriate demonstration for “need” is the utility and necessity for a given TG within an assessment framework. The assessment framework should be the guide, and the questions that should be asked for every new proposal could include questions along the lines of:

- Why is the new or revised TG needed?
- What additional information or scientific data is to be obtained and why is this necessary for decision-making using the relevant assessment framework?
- Are there other options rather than a new TG or a revised TG?
- Will the new TG lead to reduction, replacement or refinement of laboratory animal methods?
- How much effort/resources are needed to complete the standardization, validation and TG drafting tasks?

Answers to these types of questions could provide the basis for a prioritization decision. In addition, if these questions cannot be answered satisfactorily for a given proposed TG, then we suggest that the proposal be given low priority until the information becomes available. In this regard, it may be worthwhile for OECD to convene a working group during 2005 to develop the scope of such a decision making tool for OECD TG priority setting.

3. Validation of Test Methods is Absolutely Necessary

BIAC believes that it is absolutely essential for OECD to continue to ensure that all new or revised methods for TGs are scientifically valid – that is, relevant¹ and reliable for their intended purposes before being considered for adoption. OECD should not deviate from this principle. Just as the TG work is core to the OECD EHS Programme, validation is core to the TG Programme.

4. Provisional Acceptance of a TG Based on a Yet-To-Be Validated Method is Inappropriate and Could Cause a Breakdown of Mutual Acceptance of Data

In the “Issues Paper” OECD suggests that it may be possible to consider provisional acceptance of a TG subject to completion of an agreed validation process. BIAC is strongly opposed to such a proposal. First and foremost, the only way to interpret the results of a test method is to understand the relevance and reliability of the measured endpoints. Such an understanding comes primarily from the results generated during methods standardization and validation. There are innumerable instances where new and promising test methods developed in the research lab with one or a few test materials have been shown, upon further analysis with a broader range of substrates or test agents, not to have sufficient reliability or specificity.

Further, provisional acceptance of a TG essentially means provisional acceptance of the data generated by the method as well as decisions flowing from such results. Again, without the requisite degree of scientific data, the same set of data would potentially be interpreted differently in different regions across the globe. Rather than foster mutual acceptance of data, such an approach would foster just the opposite, as each region struggled to develop their own guidance for interpreting data.

¹ The term “relevant”, used in this context, refers to understanding the relevance of a new method with respect to the biological effect of interest, as described in Validation and Regulatory Acceptance of Toxicological Test Methods: A Report of the ad hoc Interagency Coordinating Committee on the Validation of Alternative Methods. March 1997. [NIH Publication No.: 97-3981]. For a given method, relevance must be understood (or at least hypothesized) early on in the development and standardization phase, and then confirmed in the validation phase.

Finally, as we have seen over time, validation efforts also provide needed information on study design and conduct. It could well be envisioned that initial studies conducted on a “provisionally accepted TG” would be found to be deficient or less than optimal after validation is concluded. If such deficiencies were serious, testing would need to be repeated. Thus, rather than be more efficient, such an approach for provisional acceptance followed by validation could well turn out to be less efficient, resulting in unnecessary and duplicative testing and use of lab resources, including laboratory animals.

5. Peer Review is Necessary for Test Methods

There is a need for independent scientific peer review of the data generated or used for validation of test methods. There is no need for the TG Secretariat to always manage the peer review effort, nor is there a need to always exclude the TG Secretariat from including peer review within his or her folio. While the needs and resources should dictate who conducts peer review, the Secretariat must be in a position to affirm that the validation data for a method has indeed undergone adequate peer review, and that OECD member delegations are satisfied with the peer review effort to a point of consensus. Whether or not the Secretariat takes on the responsibility of peer review is primarily an issue of resources. However, peer review is absolutely necessary.

6. Validation Issues for a Broad Variety of Test Methods Should be addressed in OECD Guidance Document (GD) 34

BIAC supports the drafting of GD 34 to achieve the objective of promoting method validation across the entire range of assay types, including QSAR. There is a need to expand GD 34 well beyond the historical context of *in vitro* assays replacing *in vivo* assays. There need to be explicit examples and clear rationales of similarities, differences, and where judgments may be necessary for different types of assays. BIAC suggests that the current draft of Guidance Document 34 tends to be unnecessarily narrow and limited in its scope. Applications of the draft GD in its current form could present a danger of promoting a single, one size fits all model for validation that, in fact, will not apply to many circumstances. This outcome would then hamper, rather than facilitate, the wide practice of assay validation. National authorities and industry are engaged in developing many types of assays, ranging from QSARs, screening or lower tier *in vivo* assays, enhancements to chronic toxicity assays, and ecotoxicity assays on both new vertebrate and invertebrate species – these will all need to be validated before they move into regulatory use. BIAC suggests that great care is needed before rigidly extrapolating existing guidance and principles for the validation of replacement *in vitro* assays to the wide variety of other assays. Careful thought should be exercised as to whether the principles actually apply in different circumstances and to what degree. Examples of these circumstances are 1) when there is or is not a prediction beyond the biological boundaries of a given assay, 2) whether there is simply the need for quantitative data to serve the needs of prioritization and weight of evidence evaluations, and 3) whether there are measured observations of toxicity and not extrapolated predictions.

7. OECD Should Give High Priority to Finalization of the TGs for the Core Methods Identified by the OECD EDTA

On a global basis, BIAC has been an active partner for many years in OECD's Task Force on Endocrine Disruptors Testing and Assessment (EDTA). BIAC has supported a significant portion of the laboratory studies needed for standardization and validation of many of the screening assays envisioned for the EDTA framework (as well as the US EPA's EDSP Tier 1 battery) including the uterotrophic, Hershberger, and enhanced TG407, as well as support of the test chemical repository. We have also supported secondment of technical staff to OECD to assist with the EDTA scientific workload. These activities by BIAC members demonstrate the

importance we put on the need for validated internationally harmonized test methods. This is a common objective that the global chemical industry shares with all OECD member countries.

We are concerned that the once robust activities of the OECD EDTA have now become slow-moving, apparently due in large part to the lack of necessary staff resources within OECD's TG Programme. OECD member countries continue to press for evaluations of endocrine activity of chemical substances and they, as well as the chemical industry and the public at large, need the assurance that the screens and tests used for such evaluations are scientifically sound, relevant and reliable for their intended purpose. The need for the work of the OECD EDTA has not diminished, yet the pace of the program efforts has declined significantly over the last 2-3 years. This has occurred despite the fact that industry funded a short-term position in OECD for a 1-year period to address the backlog of work that accumulated within the OECD EDTA program. Clearly, the work of the OECD EDTA is important and necessary and deserves a high priority within OECD for allocation of the required resources.

Sincerely,



Rainer-Kurt Koch
Chairman
BIAC Chemicals Committee

Dr. Drew Wagner
Principal Administrator
Environment, Health and Safety Division

cc: Robert Visser, Head of Division