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International Agency for Research on Cancer
Lyon, France
E-mail Address for Comment Submissions: cie@iarc.fr

Re: "*Report of the Advisory Group to Recommend Updates to the IARC Monographs: Internal Report 05/001, 4-6 May 2005"*

Dear Sirs,

The American Chemistry Council commends the International Agency for Research on Cancer (IARC) for soliciting widespread review by the scientific community as a whole on the draft language under consideration for revision of the IARC Preamble to the IARC Monographs on the Evaluation of Carcinogenic Risks to Humans.[1] The IARC Monograph process is widely recognized for its contribution over the last 35 years to advancing environmental public health. The scientific rigor and transparency of IARC processes are critical to assuring the most up to date scientific studies and understandings are fully considered and utilized in the Monograph discussions. Opening up the proposed revisions to the Preamble to wider review is appropriate and IARC should consider even more efforts in this regard with respect to the Monographs.

The American Chemistry Council supports IARC's commitment to assessing the potential carcinogenicity of substances, and agrees that a rigorous set of scientifically robust criteria is necessary to guide the process and provide consistency across time and panels. However, we believe that two of the proposed changes do not represent an appropriate scientific approach to this process, and respectfully ask that the Advisory Group give due consideration to the comments below.

1 The American Chemistry Council (ACC or the Council) and its member companies have played an active role in screening and testing chemical substances, developing risk assessments and implementing science-based risk management policies. ACC represents the leading companies engaged in the business of chemistry in the United States. ACC members apply the science of chemistry to make innovative products and services that make people's lives better, healthier and safer. ACC is committed to improved environmental, health and safety performance through health and environmental research and product testing, Responsible Care®, and common sense advocacy designed to address major public policy issues. Chemistry companies invest more in research and development than any other business sector. As a science-driven industry, the business of chemistry – through the Council's Long Range Research Initiative and through research, screening and testing of specific chemicals by individual member companies – provides significant support for scientific research to better understand and characterize the potential risks from chemical exposures.

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Issue 12a: Clarify whether the National Toxicology Program (NTP) studies in male and female rats or mice should be regarded as independent studies capable of providing *sufficient evidence*.

The issue addressed by the Advisory Group is whether an NTP study with male and female rats, for example, can be considered as two independent studies and thus be deemed "sufficient evidence" for carcinogenicity. They state: "This Advisory Group recommends that IARC update its criterion on reproducibility for sufficient evidence of cancer in experimental animals and state clearly that GLP studies in both sexes of a single species may be considered as independent." The Council believes this position of the Advisory Group is deficient in many respects and therefore warrants further deliberation.

Although the Advisory Group is recommending in this report that such a position be adopted by IARC, there is also the following "note" provided at the beginning of the discussion of Issue 21a: "*Some Working Group members recently refused to recognize these as independent studies because they were carried out at the same time in the same laboratory using similar protocols."*

This is a critical point and is supported by the scientific literature on cancer study design in animals: the principles of cancer study design do not support the Advisory Group's opinion that a single study carried out in a single species, in both sexes, at the same time, in the same laboratory and under the same conditions, is actually two independent studies. The principle around which the IARC requirement for two independent studies was established is as current today as when it was initially formulated. Replication in an independent study is a cornerstone of science. Under Good Laboratory Practices (GLPs), each study is required to have a unique protocol. Therefore, if both sexes of an animal species were specified in a single protocol, this would be classified under GLP as a single study. Although GLPs provide a high degree of integrity and certainty in terms of test compound identification, test methods and procedures and documentation of laboratory measurements, GLPs do not supplant the scientific certainty provided by replication in an independent study. Even if studies of each sex of the same species were conducted under separate GLP protocols, but the studies were run simultaneously in the same laboratory using the same procedures and test article dosages, these would need to be viewed as a single study for purposes of an IARC evaluation. Because the carcinogenic process can be influenced by genetics and by exogenous factors, by impurities in test articles, by nutritional factors and by animal husbandry and the lab housing environment, not all of which can be rigorously controlled nor fully appreciated in a single study, the standard of practice which has developed has been that two independent and separate studies are needed to provide the requisite degree of scientific certainty. This standard, based on the foundation of the scientific method – independent replication - has stood the test of time and should remain a hallmark of IARC evaluations.

The scientific consensus on proper cancer study design and interpretation is widely held and is covered well in toxicology textbooks. These texts are consistent in supporting the position that a study performed at the same laboratory, in one species, in both sexes, at the same time, is properly considered as a single independent study, not as two separate evaluations, one in males and one in females. For example, when design of a carcinogenicity study is described, each study is always described as comprising rats or mice exposed for 2 years, and in each species, equal numbers of male and female animals are used.[2] In another

2 See, for example, Ballantyne, B. et al. 1993. *General and Applied Toxicology, volume 2*, Input Typesetting, Ltd.: Wimbledon, UK, chapter 41; Hayes, A.W. 1994. *Principles and Methods of Toxicology, Third Edition*, Raven Press: New York, chapter 19.

text discussing the safety assessment of pharmaceuticals, it is stated: *"The use of two species in carcinogenicity studies is based on the traditional wisdom that no single species can be considered an adequate predicator of carcinogenic effects in humans. Absence of carcinogenic activity in two different species is thought to provide a greater level of confidence that a compound is "safe" for humans than data derived from a single species."*[3]

In another textbook discussing toxicology and safety testing of products for human use, it is stated, "definitive evidence of carcinogenicity is difficult to establish from the results of a single study".[4] Therefore, whether the issue is establishing carcinogenicity or ruling out the possibility of carcinogenicity, the consensus of scientists has been that more than one study, in more than one species, not one study in both sexes, is needed. None of the standard resources on cancer study design suggest that a study in one species, both sexes, could be considered as two independent studies.

The basis for such "standards of practice" is found in the way that an NTP study is designed. The study is designed to limit variability in response among animals in the study in order to maximize the ability to detect a positive response that can be attributed to the test chemical. This is done by rigidly controlling animal husbandry (light/dark cycles, diet, temperature of environment, housing conditions, etc.) and using animals that are genetically similar, from the same species and the same breeding source. These aspects are discussed in detail in Hayes' *Principles and Methods of Toxicology*.[5] By limiting such variability among animals within a single study, any identified cancer response can more likely be attributed to the test chemical rather than the well-established confounding factors in cancer study design of diet, environment, and genetics; these factors are known to be associated with increased cancer risks for certain types of cancer under certain conditions. Therefore, the study design of the NTP studies was not developed in order to produce a study that would be capable, by itself, of defining carcinogenic potential of a test substance. Rather, it was developed in order to maximize the ability to attribute a positive response to the test substance rather than some other confounding factor.

The NTP studies, however, include animals of both sexes in order to attempt to identify the contribution of gender to the response. It is well established that there are differences in the way male and female animals may respond to chemicals, including gender-related differences in carcinogenic potential [6] Further, as pointed out in the IARC Preamble, section 9, under "qualitative aspects," considerations of importance to the Working Group include whether animals of both sexes were used in the study under consideration. The inclusion of animals of both sexes is a characteristic of a single study that makes it adequate for risk assessment. Then, in the same section under the heading "quantitative aspects," it is stated that the probability that tumor will occur may depend on sex of the animal. These statements are fundamental concerns that must be considered. Sex is a characteristic that can affect response. As a result, considering a single study performed in both sexes, in a single laboratory, under the same test conditions, at the same time, does not argue for consideration of the study as two independent evaluations. In fact, with the potential for gender to affect response, if there was a positive carcinogenic response in only one species, the study would need to be repeated in order to clarify whether that response was indeed gender-related.

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3 Gad, S.C. 1995. *Safety Assessment of Pharmaceuticals*, Van Nostrand-Rheinhold: New York, chapter 7, page 168.
4 Chengelis, C.P. et al. 1995. *Regulatory Toxicology*, Raven Press: New York, chapter 3, page 66.
5 Hayes, 1994. *Principles and Methods of Toxicology, Third Edition*, Raven Press: New York, chapter 19.
6 Id.

Furthermore, if a single study in one species that included male and female animals was considered as two independent studies, and thus served as the basis of "sufficient evidence" in an IARC evaluation, an important potential factor may be overlooked: species differences in toxicological response. It is well established that both qualitative and quantitative differences in response to toxic substances may occur among different species.[7] Some of these species-related responses, such as the production of liver tumors after exposure to peroxisome proliferators and nasal tumor development after exposure to formaldehyde, are well documented.[8] It is the potential for such responses to go undetected if only one species, or one sex, was tested that has driven the "standards of practice" and the design of cancer testing requirements to include more than one study in more than one species.

Considering the scientific principles behind cancer study test design and what is known about carcinogenic responses in animals, there is no sound basis to support use of the results of a single study, in one species, in two sexes, as two independent evaluations of carcinogenic potential. Therefore, whether a study is an NTP study or not, studies run on both sexes in the same animal room, using the same species and source of animals, using the same dose solutions, and identical test conditions should be considered a single study. The certainty afforded by replication in an independent study is not fully replaced by the certainty afforded when a study is conducted under GLPs.

Issue 5c. The 2003 Advisory Group recommended that the issues of 'bias of opinion' and'conflict of interests' be discussed in the Preamble.

The proposed preamble indicates that experts with real or perceived conflicts of interest will be excluded from Working Groups but can be "Invited Specialists" (page 4, lines 37-38 and line 42). Invited Specialists cannot serve as meeting chair or subgroup chair, cannot draft text that pertains to cancer data, and cannot participate in the evaluations.

As we explain below, the challenge for IARC is to assure that panels are composed of the most qualified experts, irrespective of affiliation. Affiliation alone should not be taken as synonymous with a conflict of interest. IARC can achieve the Agency's objectives by assuring a balance across affiliations, of equally qualified experts, and by insisting that all potential conflicts be fully and transparently declared. IARC's proposed new policy of including "specialists" in the review process does not achieve this goal. The proposed exclusion of qualified experts based solely on a perception of "commercial interests" is not justified.

Industry's commitment to scientific research and product testing includes employing and working with the highest quality scientists. Many industry-employed scientists have national and international stature in the scientific community, and are leading experts in their disciplines. These scientists are objective, highly skilled professionals. As members of professional associations like the Society of Toxicology, industry scientists adhere to both personal and professional commitments to act in accordance with the codes of ethics of their professions.

The US National Academies' panel selection policy emphasizes that knowledge, training and experience are the foremost considerations, and that no one should be appointed to a panel to represent a particular

7 Klaassen, C.D. 2001. *Casarett & Doull's Toxicology: The Basic Science of Poisons*, sixth edition, chapter 2.
8 Id.

point of view or special interest.[9] Importantly, the NAS states that "[f]or some studies . . . it may be important to have an 'industrial' perspective or an 'environmental' perspective," not because these "sides" need to be represented, but "because such individuals, through their particular knowledge and experience, are often vital to achieving an informed, comprehensive, and authoritative understanding and analysis of the specific problems and potential solutions to be considered by the committee."[10] In many if not most cases, industry scientists will be able to provide just this sort of expertise to IARC Working Groups.

As explained in a recent article addressing just this topic,[11] any discussion of the issue of "commercial interest" must carefully distinguish between conflict of interest and point of view. In general, true conflicts of interest are limited to instances where a person has a concrete financial interest in the subject being addressed. However, an individuals' affiliation or point of view are not, and should not be, viewed as automatic criteria for deselection. The National Academies state: "points of view or positions that are largely intellectually motivated or that arise from the close identification or association of an individual with a point of view of a particular group."[12] Similarly, an EPA Science Advisory Board committee has stated that, "[a]lthough it is possible to avoid conflict of interest, avoidance of bias is probably not possible. All scientists carry bias due, for example, to discipline, affiliation and experience"[13]. Fifteen past presidents of the Society of Toxicology have written in *Risk Policy Report* that, "[o]f course, all scientists have biases; acknowledging this, we as a society must be aware of those biases and seek to ensure balance in the scientific panels whose task is to provide the best possible technical review of complex, important issues."[14]

In its discussion of "conflict of interest," the National Academies' panel selection policy refers to "financial interests," and notes that that these can arise across the board, including regulated entities, the government and non-governmental organizations.[15] Importantly, NAS explains that "biases" should not be disqualifying -- even where a person works for a company with "a general business interest in" the subject of the panel -- unless the person "is totally committed to a particular point of view and unwilling, or reasonably perceived to be unwilling, to consider other perspectives or relevant evidence to the contrary."[16]

As can be seen, therefore, the proposed exclusion for "commercial interests" would logically apply to anyone receiving compensation or support in any manner for their research or investigations on substances considered by IARC, to the extent that their professional livelihood could be involved. Similarly, "commercial interest" would include individuals from NGOs who are dependent on gifts and grants from institutes or foundations or individuals as compensation for work/research on a substance.

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9 "The National Academies Study Process," available at http://www4.nationalacademies.org/news.nsf/isbn/07302001?OpenDocument (NAS 2001).
10 Id.
11 "Assessing the Reliability and Credibility of Industry Science and Scientists," *Envtl. Health Persps*. doi:10.1289/ehp.8417 available via *http://dx.doi.org/* [Online 6 October 2005].
12 NAS 2001.
13 EPA Science Advisory Board Envt'l Health Cmte, letter report re "Review of the Draft Report to Congress 'Characterization of Date Uncertainty and Variability in IRIS Assessments, Pre-Pilot vs post-Pilot,'" EPA-SAB-EHC-LTR-00-007 (Sept. 26, 2000), available at http://www.epa.gov/sab/pdf/ehcl007.pdf.
14 *Risk Policy Report* (Jan. 21, 2002).
15 NAS 2001.
16 Id.

The Council thus suggests that IARC review and consider adopting the National Academies' panel selection policy rather than attempting to implement the problematic, proposed approach regarding "commercial interests."

Yours sincerely,

Original Signed By

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17 Compensation Disclaimer: I am employed full-time by the American Chemistry Council, and as such was compensated for submitting these comments as part of my normal professional duties.