



**INTERNATIONAL AGENCY FOR RESEARCH ON CANCER  
CENTRE INTERNATIONAL DE RECHERCHE SUR LE CANCER**

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*IARC Monographs Programme*

Dear Dr Sass,

In reply to your letter expressing concern about conflicts of interest among members of this working group, please be assured that IARC is very concerned that the deliberations of Monographs Working Groups are not distorted by conflicts of interest. We are equally concerned whether such interests are financial or are based on any other kind of interest. IARC is a part of the World Health Organization, and follows the rules of the WHO with respect to declaration of financial interests by participants in its meetings. A copy of the WHO declaration of interest form that every participant in our meetings now completes is enclosed.

Please note that the WHO defines conflicts of interest on the first page of this form, and states that declaration of one or more interests may have any of several outcomes, depending on the circumstances. The completed forms are considered confidential and would only be disclosed if the Director General of the WHO decides that this is in the best interests of the Organization, and then only after consultation with the persons involved.

**Evaluation of styrene by the February 2002 working group**

The February 2002 working group consisted of 29 individuals from 15 countries. A list of participants is enclosed, each of whom completed a declaration of interests. Only two individuals, Dr Cruzan and Dr Carlson, declared financial interests, both of which consisted of research support from the styrene industry and consulting to that industry.

Drs Cruzan and Carlson publicly declared their interests to the assembled working group and abstained from evaluations of the strength of evidence for carcinogenicity of styrene, and from the final overall evaluation of that compound. This will be noted in the printed Monograph. I should note that we do not consider that current or previous employment by the Chemical Industry Institute of Toxicology (CIIT; now CIIT Centers for Health Research), Research Triangle Park, NC, *per se* constitutes a declarable interest.

Styrene was previously evaluated as *possibly carcinogenic to humans* (Group 2B) by the IARC Monographs Programme in volume 60 (1994), although at that time there was *inadequate* evidence of carcinogenicity in both humans and experimental animals. At the February 2002 meeting, data on cancer risk in exposed humans were considered to have strengthened to the level of *limited evidence*, but new bioassays did not strengthen the evidence for carcinogenicity in experimental animals. The Working Group recommended that Styrene should remain in Group 2B.

### **Are there adequate provisions for preventing industrial domination of any Monographs meeting?**

We are quite confident that there are adequate provisions against the possibility of industrial domination of an IARC evaluation. First, while individuals who are employed by industry may occasionally be voting members of a working group, there are never more than one or two of them, and they never serve as chairpersons of subgroups or of the meeting. Second, while industrial observers who are accredited to a working group participate in discussions, they do not vote in evaluations; and observers from governmental organizations (such as the U.S. National Cancer Institute and Environmental Protection Agency) also participate fully in discussions. It is not possible for industry employees plus observers to dominate working groups by sheer weight of numbers. Individuals from government or academia who declare financial interests in the form of research funds and possibly consultants from industry are not considered ineligible to serve on working groups if they are permitted to publish their findings without oversight or censorship of any kind from their industrial sponsor. They may be required to abstain from the evaluation of agents in which they have declared an interest.

Exceptions to this policy are companies, or entire industries, known deliberately suppress the truth about health hazards of their products; an example is the tobacco industry. Such companies or industries are not permitted access to Monographs working groups as either members or observers, and a declaration of financial interest in such companies or industries would disqualify any individual from membership.

In this context, it is important to recognize that industry is taking an increasingly important role in funding toxicological and epidemiological research on chemicals and chemical mixtures. To avoid wasteful duplication, government agencies generally avoid repeating studies that are being done by industry. The U.S. National Toxicology Program declined to do carcinogenicity bioassays on styrene for just this reason. The Monographs have always chosen participants in working groups primarily for their expertise, which can best come from those actually participating in research on substances and exposures that are to be evaluated. It is for this reason that industry experts and individuals who have research support from industry may be invited to participate in working groups, subject to the limitations on their numbers that are described above.

## **Comparisons of the IARC Monographs Programme with the U.S. National Toxicology Program's Report on Carcinogens (RoC).**

You expressed concern about the Monographs evaluation of 1,3-butadiene in volume 71 (1999) as *probably carcinogenic to humans* (Group 2A), in comparison to its subsequent listing in the 9<sup>th</sup> [U.S.] Report on Carcinogens (RoC; 2000) as "known to be a human carcinogen." One of us (JR) has explained to you during his visit to your NRDC office in Washington on 1 March 2002 that there was no consensus in that IARC working group about whether all lymphoid and hematopoietic neoplasms should be combined in the evaluation of the two epidemiological studies that were informative. The subsequent RoC decided that these neoplasms *could* be grouped together, and that is the basis for the difference in evaluation. The complex issue of carcinogenicity of the structurally related compounds 1,3-butadiene, isoprene, and chloroprene was the subject of an international scientific meeting in 2001, the proceedings of which have been published (*Chem-Biol. Interactions*, 135-136, 2001). The IARC working group for volume 71, consisting of 31 scientific experts from 12 countries, reviewed not only 1,3-butadiene, but also a total of 121 compounds and groups of compounds. No other evaluation evoked significant differences of opinion within the working group.

When there is a sharp division of opinion in an IARC working group, it always reflects some inadequacy in the available data. Working groups are charged to use their best professional judgement in evaluating strength of evidence, and their decisions must be in accord with the principles described in detail in the Preamble to the Monographs (printed in every volume, and available on-line at <http://monographs.iarc.fr>). When there are marked differences of opinion, it serves as a signal to us that the substance or exposure should be re-evaluated by another working group when additional published data have become available.

### **Is there a tendency by IARC Working Groups to 'downgrade' chemicals?**

You go on to quote Dr Lorenzo Tomatis as expressing concern about IARC's downward evaluation of saccharin in Monographs volume 73 (1999), on the basis of mechanisms of carcinogenicity. You should be aware that the RoC also delisted saccharin, for the same reasons, in its 9<sup>th</sup> Report (2000) in an independent evaluation.

With respect to the participation of industry employees in Monographs working groups, we would call to your attention also that industry employees are often members of National Toxicology Program review boards, including the subcommittee that reviews NTP Technical Reports. Their names are listed in every such report. They are simply required to abstain from reviews of bioassays of substances in which they or their companies have a financial interest. Thus, IARC policy and your own national organization's policy are very similar on the subject of financial interests and suitability for participation on review committees or working groups.

Finally we would note that national health agencies in various countries may or may not agree with IARC Monographs evaluations, and such agencies sometimes assign agents or exposures that IARC has evaluated as "carcinogenic to humans" (Group 1) to lower hazard categories. The 9<sup>th</sup> RoC, for example, lists both "beryllium and certain beryllium compounds" and "nickel and certain nickel compounds" as "reasonably anticipated to be

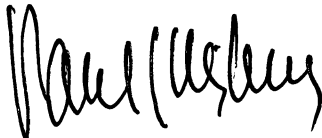
human carcinogens,” and not in its higher category of “known to be a human carcinogen.” Both nickel and beryllium are IARC Group 1 agents.

### Re-evaluation of exposures within the Monographs Programme

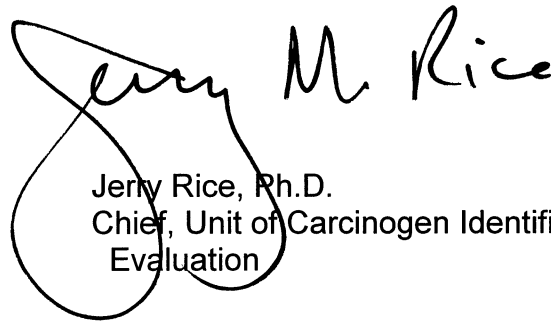
Exposures are chosen for re-evaluation when new data have been published that may change an evaluation, either upwards or downwards. In fact, of the more than 200 evaluations and re-evaluations that were conducted by the IARC Monographs during the past 5 years (1997-2001) 13 previously evaluated agents or exposures were upgraded, two of them to Group 1, while 13 were downgraded. The numbers of upgrades and downgrades were thus equal during this time.

We have shared your letter, and our reply, with Dr Leonard Levy (UK), Chairman of the February 2002 Working Group, and with Dr David Longfellow, who attended the meeting as observer from the U.S. National Cancer Institute. We understand that Dr Levy has already replied to you.

Yours sincerely,



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Director



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Evaluation