

# ILSI RISK SCIENCE INSTITUTE

International Life Sciences Institute

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## VIA FACSIMILE

RE: Request for Funding Support of Project on the Use of Non-Tumor Data in Cancer Risk Assessment

Dear Dr. Venezia:

It was a pleasure speaking with you this morning. Per your request, this letter presents a brief proposal requesting funding from the CMA Vinyl Chloride Panel Health Committee for our project on the use of non-tumor data in cancer risk assessment.

Genotoxicity data have been used historically as part of hazard identification (i.e., to classify carcinogens as genotoxic or nongenotoxic) but not as part of the dose-response assessment to quantitatively estimate cancer risk. The current scientific and regulatory climate is such that the use of endpoints other than tumors to quantitatively estimate cancer risk is on the horizon. This project was initiated to address the question of whether and how genotoxicity and other data should be used as part of a cancer risk assessment. A component of the project includes the development of cancer risk assessments for four chemicals using genotoxicity data and other data, and following the draft revisions to the U.S. EPA Cancer Risk Assessment Guidelines. The cost of the project is approximately \$170,000. Partial funding for the project has been provided by the American Petroleum Institute (API) and the U.S. EPA. We are also requesting funding support from a variety of sources from both the private and public sectors. Greater detail about the project is provided below.

On 4 March 1996 a working group of distinguished scientists, (Attachment A) with expertise in genotoxicity and risk assessment met at the ILSI Risk Science Institute (RSI). The group agreed that the qualitative and quantitative use of endpoints other than tumors in a cancer risk assessment is an issue worthy of investigation. Examples of non-tumor endpoints that might be used include genotoxicity (mutagenicity, DNA adduct formation, etc.), cell proliferation, cell death, and others. The working group suggested that the best way to address the issue would be through case studies using the draft revisions to the U.S. EPA Cancer Risk Assessment Guidelines. Four chemicals were nominated for this exercise (aflatoxin, benzene, butadiene and vinyl chloride).

Each case study will include cancer risk estimates derived from: 1) the existing (1986) U.S. EPA Cancer Risk Assessment Guidelines; 2) the proposed revised U.S. EPA guidelines using the  $LED_{10}$  (lower 95% confidence limit on the dose causing a 10% increase in tumor response) as the "point of departure", or the starting point from which to extrapolate down to the low dose-response region; 3) a point of departure from endpoints other than tumors (i.e., DNA adduct formation, cell proliferation, genotoxicity, etc.) that must be mechanistically linked to the observed tumor response; and 4) the use of biologically-based dose-response modeling, if adequate data are available.

Following the development and review of the case studies, RSI plans to hold a workshop, likely in Washington, DC, during late 1996/early 1997, to provide an opportunity to disseminate and discuss the results of the case studies and the implications for inclusion of such data in a risk assessment. The results of the project would be published either in the peer-reviewed literature or in a monograph published by ILSI Press.

As mentioned above, the total project cost is approximately \$170,000. We are requesting funding support from the CMA Vinyl Chloride Panel Health Committee of \$10,000. A rapid response to this request would be most helpful given the time line associated with the project.

Should you have any questions or need any other information, don't hesitate to contact either of us at 202-659-3306. We extend our thanks for your consideration of this request, and look forward to your positive response.

Sincerely,



Gino Scarano, Ph.D.  
Senior Scientist



Jeffery A. Foran, Ph.D.  
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**GENOTOXICITY MEETING**  
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