AMERICAN CHEMISTRY COUNCIL
LONG-RANGE RESEARCH INITIATIVE

REQUEST FOR PROPOSALS

RfP Title: Cumulative Risk Assessment for Mixtures Containing Chemicals with Different Modes of Action

RfP Number: RSK-01-03

TIP: Risk Assessment Methods Technical Implementation Panel (RAM TIP)

INTRODUCTION

The Risk Assessment Methods Technical Implementation Panel (RAM TIP) represents one of ten priority research areas, each represented by a Technical Implementation Panel (TIP), identified under the American Chemistry Council’s (the Council) Long-Range Research Initiative (LRI). The RAM TIP identifies research needs for the chemical industry related to the long-term human health risk assessment methodologies for chemicals.

The project described below will enable the chemical industry to better understand the role of the multiple interactions, if any, of chemically disparate structures and functions (modes of action) which would influence the dose-response relationship of chemical-tissue interaction at the same target site and hence the risk associated with combinatorial exposure.

DESCRIPTION OF RfP

Background

The science of risk assessment has continued to evolve from early processes involving determination of risk for single chemicals. Today, there is a growing need for, and implementation of, methods for the conduct of chemical mixture health risk assessment. The National Academy of Sciences (NAS) (NRC report, 1999) has issued recommendations to move away from single chemical assessments towards multiple chemical approaches. Within the regulatory policy realm, EPA’s Science Policy Council (1997) has addressed the need for an overall assessment of multiple chemicals within the context of cumulative risk. EPA’s research strategy for 2000 and beyond has been modified to emphasize research on chemical mixtures. Additional efforts nationally, National Toxicity Program (NTP), and internationally, the International Programme on Chemical Safety (IPCS), are underway to characterize current and develop new comprehensive risk assessment methodology. Regulatory desires for risk assessment of mixtures are now routinely met during site remediation efforts, waste removal projects, and effluent permitting processes. EPA now has Supplemental Guidance for the conduct of health risk assessments of chemical mixtures (2000).

In its development of Supplemental Guidance document, EPA acknowledges there exists considerable uncertainty as to many of the biological premises and information needed to conduct an accurate mixture risk assessment. One of the main areas of uncertainty involves the degree and magnitude of chemical and biochemical interactions, which may occur during co-exposure of two or more chemicals, particularly when each chemical affects the same tissue or organ. In such cases knowledge of component-based interactions in a mixture, particularly as it might relate to their unique or different modes of action, is woefully lacking.

Research sponsored under auspices of the LRI is underway to evaluate interactions of chemicals with similar modes of action occurring at the same target site. This RfP is designed to address scientific shortcomings in our knowledge base of chemical interactions of agents with dissimilar modes of action.
Research Objectives

The objectives of the research funded under this RfP are: (1) to reduce biological uncertainty when assessing cumulative risk and (2) to achieve a better understanding of uncertainty distribution in the evaluation of chemicals with different modes of action, but which affect the same target tissue. In order to provide relevancy of risks associated with the area of combinatorial exposure to be investigated, any research proposals considered under this RfP should have a component which will address chemical interactions under conditions considered physiologically relevant and within an environmentally expectant level of human exposure. Proposals for methods development should consider advanced mathematical approaches leading to reduction of uncertainties in toxicokinetics and toxicodynamics, which can be used to assess cumulative risk.

Scope

To contribute to this goal, the RAM TIP is interested in any or all of the following general areas of research,

1) Identification and demonstration of combinations of biochemical and/or physiological processes that may produce interactions (chemical-to-chemical or chemical-to-tissue) affecting toxicity and determination of risk at physiologically relevant levels. The aim of this research would be to identify and characterize (through literature reviews or experimental study) a list of biochemical and/or physiological processes that may lead to increased toxicity from interaction of structurally unrelated chemicals. Determination of the relevance of such interactions to human risk would be further characterized after confirmation of these interactions at animal exposure levels relevant to man through laboratory experiments.

2) Development of methods for mixture risk estimation for combinations of components with different modes of action capable of affecting the same tissue/target site. This research would involve assessment of multiple chemicals, including those with independent or interacting mechanisms of effect on the same target tissue, and if possible, at the same molecular target site. Preference would be given to projects addressing subchronic and/or systemic effects rather than acute or local (irritation) toxicity.

3) Development of methods for mixture risk estimation for combinations of components with different modes of action capable of affecting tissues at different or multiple sites in the same organism. The research aim of this objective is to advance our understanding and methodology improvement to provide assessment of mixtures that possess component chemicals which themselves affect multiple organs of the same host or which collectively may affect different tissue sites in the same organ.

4) Through laboratory experimentation and development of advanced mathematical models, discern the relationships of time-to-peak effect of chemical interactions and/or the effect of non-concurrent exposures at levels considered physiologically relevant to human risk. Little is known about the effects of peak, intermittent or non-concurrent exposure on chemical interactions within the body, which may affect toxicity and thus risk. The aim of this research would be to evaluate the interrelationships and effect of non-continuous exposure on risk determination of chemical mixtures whose components possess dissimilar modes of action, but are capable of interaction leading to enhanced toxicity.

5) For a series of known chemical interactions related to mixture components, determine the level of magnitude of chemical interaction and characterize the levels at and below which such interactions would be judged significant/insignificant. A number of physiological and/or biochemical interactions are likely to occur at high human exposure levels or under experimental conditions of evaluation. This research would be expected to identify such interactions and experimentally investigate the dependence of
interaction magnitude on total mixture dose and on component fractions. Results would subsequently lead to development of a framework for determination of mixture exposure levels that could affect toxicity at physiologically relevant levels.

SPECIAL REQUIREMENTS

A goal of the LRI is to share broadly the results of funded projects. Thus, it is expected that results be submitted for publication in peer-reviewed scientific journals and presented at scientific meetings, conferences, and/or symposia. The Council’s policy is to support the public release of research findings from the LRI.

All proposals should include costs for preparing manuscripts for submission to peer-reviewed scientific journals and supplying the Council with five reprints of each journal article. Annual progress reports are required for all funded research projects. Any other reporting requirements will be negotiated as part of the development of the research contract.

All proposals should include the costs for travel to the Council’s headquarters in Arlington, VA one time per year for each year of the project, except for the first year of the project (no such trip required). The purpose of such trip(s) is to present project results.

ELIGIBILITY

Proposals may be submitted by any domestic or foreign for-profit, not-for-profit, or non-profit organization, public or private, such as universities, colleges, hospitals, laboratories, or units of federal, state, and local governments.

FUNDS AVAILABLE/PROJECT DURATION

It is anticipated that the award from this solicitation will be a single award; fixed price contract. The total budgeted cost for the project is $150,000 to $200,000 per year up to three years for a maximum cost of $500,000. The project costs are expected to be commensurate with project scope. Proposals should include funds necessary to complete the full scope and deliverables described earlier, including direct and indirect costs (e.g., direct labor, fringe benefits, materials, subcontracts, purchased parts, shipping, indirect costs and rates, fees, status reports, publications, meeting presentations, travel expenses). Projects are expected to begin immediately upon execution of a contract. The duration of the project is expected to be commensurate with the goals of the project. Three years is expected to be the maximum duration, but longer projects will be considered.

GENERAL PROPOSAL PROCESS

All applicants must first submit a preproposal. Those applicants receiving positive reviews from the RAM TIP will be invited to submit a full proposal. Full proposals will be peer-reviewed by independent scientists with expertise appropriate to the RfP. The guidelines and review process for each of these submissions are described in detail below.

PREPROPOSALS

Submission of preproposals is required. Preproposals must be received by the Council no later than November 9, 2001, and must be no longer than six (6) pages in length. Preproposals must be prepared using the Preproposal Form (Attachment A-1). Biographical information (no longer than two pages per person) about the Principal Investigator and all other key personnel, including subcontractors and consultants, should also be submitted as an attachment, which will not be considered part of the six (6) page limit.

One unbound original and ten (10) copies of the preproposal should be sent to the address indicated under submission of full proposals.
The RAM TIP will evaluate each preproposal for relevance to the goals and objectives of the RfP and for consistency with the budget guidance of the RfP. Attachment A-2 is the form that will be used to conduct this evaluation. Principal Investigators will receive a letter by December 24, 2001, either encouraging or discouraging submission of a full proposal, along with a copy of the Preproposal Screening Form (Attachment A-2). Submission of a full proposal upon receipt of a discourage letter is at the discretion of the Principal Investigator.

FULL PROPOSALS

GUIDANCE

Full proposals must be received by the Council no later than March 1, 2002, and must be no longer than fifteen (15) pages in length, not including attachments and appendices. All proposals must be prepared using the Full Proposal Form (Attachment B). Biographies/Curricula Vitae for the Principal Investigator and all other key personnel, including subcontractors and consultants, are not part of the 15 page limit. One unbound and thirteen (13) copies of the proposal should be sent to the following address:

Ms. Cheryl Morton
Managing Director
American Chemistry Council
Long-Range Research Initiative Team
1300 Wilson Blvd.
Arlington, VA 22209

The proposal must be signed by an individual who is authorized to sign on behalf of, and bind your organization to, the proposed rates (including indirect costs). Incomplete proposals will be returned to applicants without further review. Proposals that are complete will be peer-reviewed for scientific merit by independent scientists with expertise appropriate to the subject RfP.

The following criteria will be used by peer reviewers to evaluate full proposals:

- Scientific merit and feasibility
- Expertise of investigator(s)
- Quality Assurance (QA) process and animal care/human subject ethical considerations

Peer reviewers will also assign each proposal an overall rating of “Excellent,” “Very Good,” “Good,” “Satisfactory,” or “Unsatisfactory.” Only proposals that receive an overall rating of “Excellent” or “Very Good” by the peer reviewers will be considered by the RAM TIP for funding.

For those full proposals receiving an overall peer-reviewer rating of excellent or very good, the RAM TIP will apply the following criteria to the proposals for consideration of funding:

- Relevance to the chemical industry, as described in the RfP
- Proposed milestones/timelines
- Appropriateness of the budget/cost-effectiveness
- Use of collaborators/leveraging

AWARD CRITERIA

The criteria that will be used in making awards include receipt of a sufficient number of proposals of scientific merit, as determined by peer review; relevance to the chemical industry, as described in the RfP; availability of funds; and LRI program balance. The Council reserves the right to make no awards under this RfP.

PROPOSAL REVIEW FEEDBACK PROCEDURES
Each applicant will receive a copy of the peer-reviewers’ comments on the Peer-Review Forms (Attachment C) with the reviewer information redacted and RAM TIP’s evaluation on the Proposal Selection Form (Attachment D). All applicants will receive a letter of notification regarding the award/non-award decision from the Council on approximately May 13, 2002.

### SUMMARY OF TIMELINE FOR PROPOSAL SUBMISSION, REVIEW & AWARD

<table>
<thead>
<tr>
<th>Event</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preproposal received at Council</td>
<td>Deadline of November 9, 2001</td>
</tr>
<tr>
<td>Preproposal reviews sent to investigators</td>
<td>Approximately December 24, 2001</td>
</tr>
<tr>
<td>Full proposals received at Council</td>
<td>Deadline of March 1, 2002</td>
</tr>
<tr>
<td>Award Notification</td>
<td>Approximate May 13, 2002</td>
</tr>
</tbody>
</table>

### TYPE OF AWARD

The form of award under the LRI is a contract between the Council and the research institution.

### INQUIRIES

The Council’s website (http://www.americanchemistry.com) contains general information about the Long-Range Research Initiative. Questions regarding this RfP should be directed to Katherine Craig, RAM TIP Consultant Staff Executive, at 9300 Lee Highway, Fairfax, VA 22031, (703) 934-3032, or KatherineCraig@icfconsulting.com