RfP Title: The Impact of Maternal Toxicity in Developmental Neurotoxicity Studies

RfP Number: NT-01-02

TIP: Neurotoxicology Technical Implementation Panel

INTRODUCTION

The Neurotoxicology Technical Implementation Panel (Neuro TIP) represents one of ten priority research areas, each represented by a Technical Implementation Panel, identified under the American Chemistry Council’s (the Council) Long-Range Research Initiative (LRI). The purpose of the Neuro TIP is to advance research that will improve the scientific basis for risk assessment and decision making with respect to potential neurotoxicity of chemicals. The main objectives of the Neuro TIP are to solicit, fund, and contract independent research to address priority issues in developmental neurotoxicology; support communication of the results of TIP-sponsored research regardless of outcome; and to interact and collaborate with fellow scientists worldwide in industry, academia, government, and public interest groups to share knowledge and avoid duplication of effort. Enhancing the relevance, reliability and predictability of current developmental neurotoxicity test methods for use in risk assessment is one of the major themes of the Neuro TIP. The purpose of this specific RfP is to encourage the development of data that will help assess the contribution of maternal toxicity to effects seen in developmental neurotoxicity safety assessment studies.

DESCRIPTION OF RfP

Background

Chemically-induced changes in brain development are a significant public health concern, and the Developmental Neurotoxicity Study (DNS; www.epa.gov/docs/OPPTS_Harmonized/870_Health_Effects_Test_Guidelines/Series/870-6300.pdf) is the primary test used to evaluate potential hazards related to chemical exposure. During the conduct of this test, pregnant female rats are dosed (e.g., through the diet or by gavage) with test substances during pregnancy and lactation, and the offspring are evaluated for changes in the structure and function of the nervous system. Due to the requirement that the high dose produce effects in offspring or dams, the dams are sometimes exposed to levels of test chemicals that produce maternal toxicity as reflected by organ system toxicity, decreased food intake, decreased body weight gain or changes in hematological (or clinical chemistry) parameters. As a result, it is possible that changes in development of brain and/or behavior could be observed in pups that were not a result of direct effects of the chemical on the developing nervous system.

Maternal toxicity may complicate interpretation of the DNS by indirectly altering development of the brain and/or behavior in the pup in a variety of ways. For example, maternal toxicity may adversely affect the ability of the dam to provide appropriate levels of essential nutrients (e.g., protein, essential minerals) to the pup during pregnancy and/or lactation. Stress associated with maternal toxicity may alter levels of circulating hormones (e.g., adrenal corticosteroids) which are known to influence brain development (e.g., suckling behavior, thermoregulation). Maternal toxicity may also affect maternal care (e.g., nurturing, retrieving and grooming of pups). More information is needed to improve the risk assessor’s ability to estimate or quantify the contribution of maternal toxicity to changes observed in offspring during the DNS in rats.
Research Objectives

The objectives of research funded under this RfP should be to develop data that will help assess the contribution of maternal toxicity to effects seen in the DNS. Proposals should be aimed at developing information and objective approaches that can be used in regulated safety studies to help interpret the effects of doses of test chemicals that cause changes in food intake and body weight in the dams. The research should employ objective indicators of both maternal toxicity (e.g., changes in serum chemistry, circulating hormones or hematological values) and pup development (e.g., changes in morphological, pathological or behavioral endpoints). A sufficient number of test chemicals (e.g., chemicals known to affect the development of the nervous system, and chemicals known to not affect the development of the nervous system) should be employed to distinguish between the two types of effects. Careful attention should be paid to the collection of dose-response information. The approach for statistical analysis of the data should be clearly elaborated, and should be consistent with principles of statistical practice (e.g., Muller KE, Barton CN, Benignus VA. Neurotoxicology 1984; 5(2): 113-25) (this paper can be ordered from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=6542184&dopt=Abstract).

Specific areas of interest include, but are not limited to, the following aspects of the impact of maternal toxicity on the development of brain and/or behavior in rats: (1) patterns of changes in rat serum chemistry or hematological indicators of maternal toxicity and their relationship to development of brain and behavior in pups; (2) changes in maternal behavior associated with maternal toxicity; (3) patterns of changes in development of brain and/or behavior characteristics of pups from dams affected by maternal toxicity; and (4) mechanistic studies which relate (3) to (1) or (2); (5) decreased brain weight in the presence of reduced body weight.

Scope

This RfP is designed to fund applied research programs that will generate data useful in supporting methods for evaluating the impact of maternal toxicity on the development of brain and behavior during conduct of the DNS in rats.

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

The award from this solicitation will be fixed price. A maximum of $425,000 per year for a maximum of 3 years is the current budget projection. The Council may fund one or more proposals within this
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.

GENERAL PROPOSAL PROCESS

All applicants must first submit a preproposal. Those applicants receiving positive reviews from the Neuro 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 30, 2001, and must be no longer than five (5) 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 five (5) page limit.

One unbound original and fifteen (15) copies of the preproposal should be sent to the address indicated under submission of full proposals.

The Neuro 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 January 28, 2002, 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 29, 2002, and must be no longer than ten (10) 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 10 page limit. Fifteen (15) 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
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 Neuro TIP for funding.

For those full proposals receiving an overall peer-reviewer rating of excellent or very good, the Neuro 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 the Neuro 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 June 28, 2002.

SUMMARY OF TIMELINE FOR PROPOSAL SUBMISSION, REVIEW & AWARD

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<tr>
<th>Event</th>
<th>Timing</th>
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<tr>
<td>Preproposal received at Council</td>
<td>Deadline of November 30, 2001</td>
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<tr>
<td>Preproposal reviews sent to investigators</td>
<td>Approximately January 28, 2002</td>
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<tr>
<td>Full proposals received at Council</td>
<td>Deadline of March 29, 2002</td>
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<tr>
<td>Award Notification</td>
<td>Approximately June 28, 2002</td>
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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, American Chemistry Council Consultant Neuro TIP Staff Executive, at 9300 Lee Highway, Fairfax, VA 22031, 703-934-3032, or at KatherineCraig@icfconsulting.com.