AMERICAN CHEMISTRY COUNCIL
LONG-RANGE RESEARCH INITIATIVE

REQUEST FOR PROPOSALS (RfP)

RfP Title  The Impact of Maternal Toxicity on Development of the Nervous, Reproductive, Endocrine, and Immune Systems.

RfP Number  MTH-02-02

Proposal Due Date  January 10, 2003 5:00 p.m. eastern time

INTRODUCTION

The American Chemistry Council’s (the Council) Long-Range Research Initiative (LRI) was created in 1999 to support research to better understand the potential impacts of chemicals on human health, wildlife, and the environment (see www.uslri.org for more information). The LRI supports research in various ways, one of the most important of which is through a competitive research project program of which this RfP is a part.

INQUERIES

More details about the Long-Range Research Initiative can be found on www.USLRI.org. Questions regarding this RfP should be directed in writing, preferably by e-mail to Katherine Craig at ICF Consulting, 9300 Lee Highway, Fairfax, VA 22031, 703-934-3032, KCraig@icfconsulting.com.

DESCRIPTION OF RfP

Purpose

The purpose of this RfP is to encourage the development of data that will help assess the contribution of maternal toxicity to effects seen in developmental safety assessment studies, with emphasis on the potential impacts on the development of the nervous, reproductive, endocrine and/or immune systems.

Background

Interest in protecting the health of children has triggered the need to expand the information that can be obtained from the traditional studies designed to assess the impact of chemicals on development. There is increasing regulatory pressure to determine the impact on the developing nervous, reproductive, endocrine and immune systems. For some of these systems (i.e., the nervous system), specific parameters have already been identified and integrated into guideline studies. While for other systems (i.e., the immune system), there is an ongoing debate over the specific study design that should be employed. In most cases, the ability to integrate new endpoints into existing or slightly modified developmental safety assessment studies is being explored. Safety assessment studies typically require rats and require that the high dose produce effects in offspring or dams. As such, the dams are sometimes exposed to levels of the 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. Therefore, it is possible that changes could be observed in pups that are a consequence of maternal toxicity as opposed to direct developmental toxicity from the chemical being studied.

Maternal toxicity may complicate interpretation of effects on organ systems in the pup by indirectly altering development 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 the development of multiple organ systems, for example, 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 developmental safety assessment studies. For this RfP, the rat is the species of interest because EPA test guidelines for developmental neurotoxicity require rats, and most endocrine, reproductive, and immune study approaches being considered also use rats.

**Research Objectives**

The question of maternal toxicity is multifaceted and could impact on any of a number of important organ systems. Although the objectives are described in three sections for communications purposes, investigators are encouraged to address one or more aspects of this phenomenon.

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, for example, cause changes in food intake, body weight or maternal care in the dams. The research should employ objective indicators of both maternal toxicity/care (e.g., changes in serum chemistry, circulating hormones, hematological values, simple measures of maternal behavior) and pup development (e.g., changes in morphological, physiological, pathological, functional, or behavioral endpoints). A sufficient number of test chemicals or procedures (e.g., chemicals affecting or not affecting maternal toxicity/care, stress) should be employed to distinguish between toxicity in the offspring related directly to maternal toxicity or directly to chemical toxicity. Careful attention should be paid to the collection of dose-response information (as relevant). 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]).

**Developmental Toxicity (general, reproductive, and endocrine systems)**

Study designs in developmental toxicity regulatory studies are guided by the principle that the highest dose level should induce some (e.g., about 10% decrement in body weight gain) maternal toxicity, in order to maximize the potential for detecting toxic responses in the fetus. This study design can potentially lead to two confounding effects that can impair data interpretation: the first is that the highest dose level may be above the range for linear pharmacokinetics, and hence expose the dam and her offspring to levels of the parent compound or metabolites that are not proportional to those seen at lower doses. In fact, if
metabolic capabilities are overwhelmed, the internal dose to the fetus could be appreciably different than predicted from lower dose levels. The second potential confounding factor is that the high dose level could induce some form of systemic toxicity (ranging from simple anorexia to pronounced target organ toxicity in the dam) that in itself may compromise successful outcomes. Research is needed to understand the depth and breadth of these potential confounders, including more reliable indicators of maternal health during various critical periods of development. Ultimately, assessors need to understand what extent of departure from nonlinear kinetics, and what departures from normal maternal physiology are associated with adverse reproductive outcomes that either would not translate down the dose-response curve in a proportional fashion, or that result in secondary effects on development. Thus, this work is rooted in understanding the mechanisms, other than direct toxic effects on the fetus, of high-dose levels used in standard regulatory test guidelines.

Since developmental effects are often only seen at the highest dose level in these studies, this area of research has potentially high impact interpretation of developmental toxicity studies. Previous work has largely focused on the average response of a dose group without further research. Experimental case studies are needed to demonstrate experimental paradigms that can, for example, demonstrate the behavior of biomarkers of maternal health relative to developmental effects as a function of gestational age. It is expected that this research would be conducted in rats and strains that are routinely used in developmental toxicity hazard evaluation studies according to EPA/FDA guidelines. An additional optional facet of this research would be to show how such findings extrapolate to the human situation.

**Developmental Neurotoxicity Endpoints**

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 noted above. 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.

The objectives of research funded under this RfP could be to develop data that will help assess the contribution of maternal toxicity to effects seen in the DNS. Specific areas of interest could 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; (4) mechanistic studies which relate item (3) to items (1) or (2); and (5) decreased brain weight in the presence of reduced body weight.

**Developmental Immunotoxicity Endpoints**
The regulatory pressures over the concerns associated with children's health have thus far had a more modest impact on developmental immunotoxicology than on developmental neurotoxicology. In part, this may be due to the fact that immunotoxicity test guidelines to address the potential for chemically induced immunosuppression (OPPTS 870-7800) were only finalized by the EPA in August 1998. At present, there are currently no validated or widely accepted methods for evaluating the effects of a chemical on the developing immune system, making it difficult to predict which maternal toxicity endpoints are of greatest importance to the current RfP. It is likely that ultimately test guidelines for developmental immunotoxicity will be developed, providing an opportunity to build a strong scientific foundation for them. Maternal toxicity could play a significant role in interpretation of such tests. For example, immune organs in rodents are very sensitive to changes in levels of adrenal corticosteroids, one of the probable outcomes of maternal toxicity.

One of the objectives of research funded under this RfP is to develop data that will help assess the contribution of maternal toxicity to effects seen on the developing immune system of rats. Specific areas of interest could include, but are not limited to, the following aspects: (1) patterns of changes in rat serum chemistry or hematological indicators of maternal toxicity and their relationship to weight and morphology of critical immune organs (e.g., spleen and thymus) in rat pups; (2) patterns of changes in the development of postnatal immunocompetence (e.g., as measured by functional parameters like the T-dependent antibody response, the primary indicator of immunosuppression in the OPPTS 870-7800 guidelines for immunotoxicity) in rat pups or weanlings from dams affected by maternal toxicity; (3) changes in maternal immunocompetence (e.g., as measured by the T-dependent antibody response) associated with maternal toxicity; (4) mechanistic studies which relate items (1) to (2) – e.g., how are changes in immune organ weights related to changes in the development of functional immunocompetence?; and (5) mechanistic studies which relate items (3) to (2) – e.g., how are changes in maternal immunocompetence related to changes in the development of functional immunocompetence in pups.

**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 the nervous, reproductive, endocrine and/or immune systems during the conduct of developmental safety assessment studies in rats. Although there is no requirement to compare effects across multiple organ systems, innovative proposals that do so will be scored accordingly for scientific merit.

**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 reasonable and necessary travel and related expenses. Please include in the proposed travel plan at least one trip to the American Chemistry Council in
Arlington, Virginia, per year for each year of the contract (except for the first year) for the purpose of presenting research results. Foreign travel costs (defined as any travel outside the country of the Contractor’s principal place of business) will require additional approvals.

American Chemistry Council member companies have a time-sensitive legal requirement under the Toxic Substances Control Act (TSCA) to report to the U.S. Environmental Protection Agency (EPA) information “which reasonably supports the conclusion that a substance or mixture presents a substantial risk of injury to health or the environment” (unless the information is already in the public domain). If information you submit results in such TSCA reporting, you shall be informed.

The Office of Management and Budget (OMB) has issued rules and guidelines regarding data and information used in regulations, which require that all data developed with federal funding and used in regulations be available to the public upon request. In addition, quality standards apply to information used for these purposes. The application of these guidelines to federally funded research is clear; however, the application to “third party” supported research (e.g., research sponsored by the American Chemistry Council) has not yet been decided. To help ensure that research pursuant to this Agreement is fully eligible for consideration by the EPA, the Council will require the Contractor to comply with the standards set forth in OMB Circular A-110 (65 Federal Register 14406-14417 (March 16, 2000)). In addition, the Council may require the Contractor to abide by additional OMB or other regulatory information guidelines applicable to research data, even though they are currently undefined. To the extent that this latter requirement imposes additional costs, the budget will be adjusted as mutually agreed to by the parties.

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 cost for the project has been budgeted in the range of $1,100,000. 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.

PROPOSAL GUIDANCE

Proposals must be received by the Council no later than January 10, 2003 5:00 p.m. eastern time. The Project Plan section must be no longer than 15 pages in length, not including literature cited, attachments, and appendices. All proposals must be prepared using the Proposal Form (Attachment A). Budgets, biographies/curricula vitae for the Principal Investigator and all other key personnel, and other submissions specified in the Proposal Form are not part of the 15 page limit. Eight (8) copies of the proposal should be sent to the following address:
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 or nonresponsive proposals will be returned to applicants without further review. Proposals that are complete and within the framework of the RfP 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 proposals:

- Scientific merit and feasibility;
- Expertise of investigator(s); and
- 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 for funding.

For those proposals receiving an overall peer-reviewer rating of excellent or very good, the following criteria will be applied 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; and
- 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 B) with the reviewer’s identifying information deleted and the LRI’s evaluation on the Proposal Selection Form (Attachment C). All applicants will receive a letter of notification regarding the award/non-award decision from the Council on approximately May 2, 2003.
TYPE OF AWARD

The form of award under the LRI is a contract between the Council and the research institution. To be effective, the contract must be executed by both the Council and the research institution.