DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

National Toxicology Program; Announcement of and Request for Public Comment on Substances Nominated to the National Toxicology Program (NTP) for Toxicological Studies and Study Recommendations Made by the NTP Interagency Committee for Chemical Evaluation and Coordination (ICCEC)

SUMMARY: The National Toxicology Program (NTP) continuously solicits and accepts nominations for toxicological studies to be undertaken by the program. Nominations of substances of potential human health concern are received from Federal agencies, the public, and other interested parties. These nominations are subject to several levels of review before selections for testing are made and toxicological studies are designed and implemented. Evaluation by the NTP Interagency Committee for Chemical Evaluation and Coordination (ICCEC) is the initial external review step in the NTP's formal selection process for NTP study nominations. On June 24, 2004, the ICCEC met to review 10 new nominations and make study recommendations. This announcement (1) provides brief background information regarding the substances nominated to the NTP for study, (2) presents the ICCEC's study recommendations from its June 24, 2004 meeting, (3) solicits public comment on the nominations and study recommendations, and (4) requests the submission of additional relevant information for consideration by the NTP in its continued evaluation of these nominations. An electronic copy of this announcement, Internet links to electronic versions of supporting documents for each nomination, and further information on the NTP and the NTP Chemical Nomination and Selection Process can be accessed through the NTP Web site: *http://ntp-server.niehs.nih.gov.*

Review of Study Nominations

Evaluation by the ICCEC is the initial external step in the NTP's formal selection process for NTP study nominations. At its meeting on June 24, 2004, the ICCEC reviewed 10 new nominations for NTP studies. For 7 of these nominations, the ICCEC recommended one or more types of toxicological studies, and for 3 nominations, the ICCEC deferred making specific study recommendations pending review of additional information. The nominated substances with Chemical Abstract Service (CAS) Registry numbers, nomination source, nomination rationale, and specific study recommendations are given in the accompanying tables.

The ICCEC is composed of representatives from the U.S. Consumer Product Safety Commission, U.S. Department of Defense, U.S. Environmental Protection Agency (U.S. EPA), U.S. Food and Drug Administration's National Center for Toxicological Research, National Center for Environmental Health/Agency for Toxic Substances and Disease Registry, National Institutes of Health's (NIH) National Cancer Institute, NIH's National Institute of Environmental Health Sciences (NIEHS), National Institute for Occupational Safety and Health, NIH's National Library of Medicine, and the Occupational Safety and Health Administration. The ICCEC meets once or twice annually to evaluate groups of new study nominations and to make recommendations with respect to both specific types of studies and testing priorities.

Request for Public Comment

Interested parties are invited to submit written comments or supplementary information on the nominated substances and study recommendations that appear in the accompanying tables. The NTP welcomes toxicology and carcinogenesis study information from completed, ongoing, or anticipated studies, as well as information on current U.S. production levels, use or consumption patterns, human exposure, environmental occurrence, or public health concerns for any of the nominated substances. The NTP is also interested in identifying appropriate new animal and non-animal models for mechanistic-based research, and as such, solicits comments regarding the use of specific *in vivo* and *in vitro* experimental models to address scientific questions relevant to the nominated substances or issues under consideration. All information received will be considered by the NTP in its continued review of these nominations. Comments or information should be sent to Dr. Scott Masten (contact information below) by October 19, 2004. Persons responding to this request should include their name, affiliation, mailing address, phone, fax, e-mail address and sponsoring organization (if any) with the submission. Written submissions will be made available electronically on the NTP Web site as they are received.

Send comments or information to Dr. Scott A. Masten, Office of Chemical Nomination and Selection, NIEHS/NTP, P.O. Box 12233, MD A3–07, Research Triangle Park, North Carolina 27709; telephone: (919) 541–5710; FAX: (919) 541–3647; e-mail: *masten@niehs.nih.gov.*

Background

The NTP actively seeks to identify and select for study chemicals and other agents for which sufficient information is not available to adequately evaluate potential human health hazards. The NTP accomplishes this goal through a formal open nomination and selection process. Substances considered appropriate for study generally fall into two broad yet overlapping categories: (1) Substances judged to have high concern as a possible public health hazard based on the extent of human exposure and/or suspicion of toxicity and (2) substances for which toxicological data gaps exist and additional studies would aid in assessing potential human health risks, *e.g.* by facilitating cross-species extrapolation or evaluating dose-response relationships. Input is also solicited regarding the nomination of studies that permit the testing of hypotheses to enhance the predictive ability of future NTP studies, address mechanisms of toxicity, or fill significant gaps in the knowledge of the toxicity of classes of chemical, biological, or physical substances. Substances may be studied to evaluate a variety of health-related effects, including but not limited to reproductive and developmental toxicity, genotoxicity, immunotoxicity, neurotoxicity, metabolism and pharmacokinetics, and carcinogenicity. In reviewing and selecting nominated substances, the NTP also considers legislative mandates that require responsible private sector commercial organizations to evaluate their products for health and environmental effects. The possible human health consequences of anticipated or known human exposure, however, remain the over-riding factor in the NTP's decision to study a particular substance.

The review and selection of substances nominated for study is a multi-step process. A broad range of concerns are addressed during this process through the participation of representatives from the NIEHS, Federal agencies represented on the ICCEC, the NTP Board of Scientific Counselors—an external scientific advisory body, the NTP Executive Committee—the NTP Federal interagency policy body, and

the public. This process is described in further detail in a March 2, 2000 **Federal Register** announcement (Volume 65, Number 42, pages 11329–11331). This multi-step evaluative process provides the NTP with direction and guidance to ensure that its testing program addresses toxicological concerns relative to all areas of public health, and furthermore, that there is balance among the types of substances selected for study (*e.g.*, industrial chemicals, consumer products, therapeutic agents). As such, it should be recognized that at any given time, the new study nominations under consideration do not necessarily reflect the overall balance of substances historically or currently being evaluated by the NTP in its toxicology testing program. For further information on NTP toxicology studies (previous or in progress) visit the NTP Web site at *http://ntp-server.niehs.nih.gov.*

Dated: August 10, 2004.

Samuel Wilson,

Deputy Director, National Institute of Environmental Health Sciences.

Substances Nominated to the NTP for Toxicological Studies and Recommendations Made by the NTP Interagency Committee for Chemical Evaluation and Coordination on June 24, 2004

TABLE 1.—SUBSTANCES RECOMMENDED FOR STUDY *

Substance [CAS number]	Nominated by	Nomination rationale	Recommendations for toxicological studies
Bitter orange extract [No CAS No.].	Private Individual	Consumer exposure through increasing dietary supplement use; suspicion of toxicity; lack of adequate toxicity data.	Toxicological studies: —Developmental toxicity —Physiological responses (*e.g.,* cardiovascular and cerebrovascular) —Subchronic toxicity —Toxicokinetics (of constituents) —Studies alone and in combination with caffeine —Studies in rats and possibly miniature pigs.
n-Buityl glycidyl ether [2426–08–6].	National Institute of Environmental Health Sciences.	Suspicion of toxicity based on structural features; positive results in genetic toxicity studies; substantial potential for human exposure and a lack of chronic toxicity data.	Toxicological studies: —Toxicological characterization including reproductive toxicity, carcinogenicity, and analysis of urinary metabolites —Coordinate with voluntary data development activities of the U.S. EPA.
Di-(2-ethylhexyl)phthalate (DEHP) [118–71–7].	U.S. Food and Drug Administration.	Long-term risks associated with medical exposures of infants have not been clearly elucidated; significant knowledge gaps on the toxicokinetics and effects in fetal and neonatal primates of intravenous exposure; further studies will better define risks and benefits of utilizing non-DEHP-containing products.	Toxicological studies: Tiered research programs to address: —Quantitative studies of toxicokinetics and biotransformation following intravenous exposure in neonatal male non-human primates —Assessment of toxicokinetics, reproductive and immune endpoints following acute and subchronic intravenous exposure to neonatal male rats and nonhuman primates.
Ionic liquids 1-Butyl-3-methylimidazolium chloride [79917–90–1] 1-Butyl-1-methylpyrrolidinium chloride [479500–35–1] *N*-Butylpyridinium chloride [1124–64–7].	University of Alabama Center for Green Manufacturing.	Widespread interest as replacements for volatile organic compounds (VOCs) in various applications; lack of toxicity data.	Toxicological studies: —Toxicological characterization —Coordinate research program with the U.S. EPA.
Perfluorinated compounds class study [Mutliple CAS Nos.].	U.S. Environmental Protection Agency.	Presumed widespread human exposure; known toxicity of certain class members; insufficient information to assess hazard/risk across entire structural class.	Toxicological studies: —Tiered research program to include pharmacokinetics, mechanistic, reproductive toxicity, and carcinogenicity studies (for specific compounds, see supporting document available at *http://ntp-server.niehs.nih.gov/NomPage/noms.html)*
Stachybotrys chartarum [67892–26–2].	Private Individual ..... National Institute of Environmental Health Sciences.	Public concern regarding potential non-infectious adverse health effects of fungal exposures in indoor environments; inadequate toxicological data available evaluating potential systemic toxicity from long-term exposure to this organism under relevant exposure scenarios.	Toxicological studies: —Toxicological characterization including immunotoxicity.
Tungsten trioxide [1314–35–8] and fibrous tungsten suboxides.	National Cancer Institute.	Important industrial raw materials; one of several metals that may form toxic fibrous ''whiskers''; carcinogenic potential of tungsten (vs. cemented tungsten carbide) is not adequately characterized.	Toxicological studies: —Toxicoligical characterization —Genotoxicity —Characterize fiber stability and biopersistence —*In vitro* toxicity to lung cells —Comparative intratracheal toxicity studies with a known hazardous fiber

TABLE 1.—SUBSTANCES RECOMMENDED FOR STUDY *—Continued

Substance [CAS number]	Nominated by	Nomination rationale	Recommendations for toxicological studies
			—Further studies including carcinogenicity will be considered following completion of above.

*** Note:** A recommendation for ''toxicological characterization'' in this table includes studies for genotoxicity, subchronic toxicity, and chronic toxicity/carcinogenicity, as determined to be appropriate during the conceptualization and design of a research program to address toxicological data needs. Though other types of studies (*e.g.*, metabolism, pharmacokinetics, immunotoxicity, reproductive/developmental toxicity) may be conducted as part of a complete toxicological characterization, these types of studies are not listed unless they were specifically recommended.

TABLE 2.—SUBSTANCE FOR WHICH SPECIFIC STUDY RECOMMENDATIONS WERE DEFERRED

Substance [CAS number]	Nominated by	Nominated for	Nomination rationale	Rationale for deferral/further information needed
Butylparaben [94–26–8].	National Institute of Environmental Health Sciences.	—Toxicological characterization including reproductive toxicity studies.	Widespread use in foods, cosmetics, and pharmaceuticals; potential reproductive toxicant; lack of adequate toxicity data.	Further review of data on estrogen receptor binding, pharmacokinetics, dose-response of male reproductive effects, and human exposure.
Decane [124–18–5] ..	National Cancer Institute.	—Carcinogenicity studies.	Widespread industrial use and environmental occurrence as air pollutant; suspicion of carcinogenicity but no adequate carcinogenicity study available.	Review of industry voluntary data development activities coordinated by the U.S. EPA.
Undecane [1120–21–4].	National Cancer Institute.	—Carcinogenicity studies.	Widespread industrial use and environmental occurrence as air pollutant; suspicion of carcinogenicity but no adequate carcinogenicity study available.	Review of industry voluntary data development activities coordinated by the U.S. EPA.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Administration for Children and Families

[Program Announcement No. HHS–2004–ACF–ORR–RE–0004 CFDA 93.576]

ORR Announcement for Services to Recently Arrived Refugees

AGENCY: Office of Refugee Resettlement (ORR), Administration for Children and Families, HHS.

ACTION: Modification to the Standing Announcement published in the **Federal Register** on April 23, 2004 (69 FR 22276). Notice of additional deadline for Priority Area 2—Unanticipated Arrivals, in the Standing Announcement for Services to Recently Arrived Refugees.

SUMMARY: The Office of Refugee Resettlement Standing Announcement for Services to Recently Arrived Refugees, Volume 69, **Federal Register** page number 22276, April 23, 2004, is hereby modified to reflect an additional deadline for the Priority Area 2—Unanticipated Arrivals for FY 2005. This additional deadline encourages applicants to respond to the needs of newly arriving populations.

DATES: October 8, 2004, is the closing date. Please note that all applications must be postmarked by October 8, 2004. Mailed applications postmarked after the closing date will be classified as late. Due to delays in mail delivery to Federal offices, we encourage applicants to use overnight courier service to ensure prompt delivery and receipt.

Announcement Availability: The program announcement and the application materials are available from Sue Benjamin, Office of Refugee Resettlement (ORR), 370 L'Enfant Promenade, SW., 8th Floor West, Washington, DC 20447 and from the ORR Web site at: *http://www.acf.hhs.gov/programs/orr/funding* or *http://www.acf.hhs.gov/grants/open/HHS–2004–ACF–ORR–RE–0004.html*.

Funding Availability: ORR expects to award $1 million in discretionary social service funds.

FOR FURTHER INFORMATION CONTACT: Sue Benjamin, Office of Refugee Resettlement, telephone number 202–401–4851.

Dated: August 11, 2004.

Nguyen Van Hanh,

Director, Office of Refugee Resettlement.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Administration for Children and Families

Notice of Correction for the Modified Standing Announcement for Services to Recently Arrived Refugees

AGENCY: Administration for Children and Families, ACF, DHHS.

Funding Opportunity Title: Modified Standing Announcement for Services to Recently Arrived Refugees.

ACTION: Notice of Correction.

Funding Opportunity Number: HHS–2004–ACF–ORR–RE–0004.

SUMMARY: This notice is to inform interested parties of a clarification made to the Modified Standing Announcement for Services to Recently Arrived Refugees published on Friday, April 23, 2004. The following clarification should be noted:

Clarification of Eligibility for Priority Area 1—Preferred Communities.