UPDATE
National Toxicology Program

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Headquartered at the
National Institute of Environmental
Health Sciences NIH-HHS

What's Inside:

NTP Provides Updates on Cell Phone Studies

Article by Robin Mackar, reprinted from *eFACTOR*, October 2009

On September 14, 2009, toxicologists from the National Toxicology Program (NTP) traveled to Washington to present updates on research supported by NTP and NIEHS related to exposure to radiofrequency energy from the use of cellular telephones. Wireless communication devices are used by more than 270 million Americans, yet there is little known about the potential health effects of long-term exposure to these devices.

In the morning, NTP toxicologist Michael Wyde, Ph.D., presented an overview of the NTP cell phone radiofrequency radiation studies at an "Expert Conference on Cell Phones and Health: Science and Public Policy Questions." The international conference was organized largely by Devra L. Davis, Ph.D., professor of Public Health at the University of Pittsburgh, and supported in part by NIEHS. Chris Portier, Ph.D., associate director at NIEHS, served on the Steering Committee. According to organizers, the goal of the three-day conference was to propose a U.S. research agenda.

Wyde updated the attendees about the three phases of the NTP rodent studies. The three phases of the studies include: (1) a series of pilot studies to establish field strengths that do not excessively raise body temperature; (2) subchronic toxicology studies where rodents are exposed to various non-thermal field strengths for up to two months; and (3) chronic toxicology and carcinogenicity studies where rodents will be exposed for 24 months. Wyde also discussed how the NTP worked with experts from the National Institute of Standards and Technology to design special reverberation chambers for the studies. Cell phone radiation will be administered in 10-minute on/off cycles for up to 20 hours per day. The NTP anticipates the completion and reporting of all phases of the studies by 2014.

In the afternoon, conference participants were invited to attend a U.S. Senate hearing on cell phones and health at the nearby Dirksen Building. NTP Associate Director John Bucher, Ph.D., had the opportunity to represent NIEHS, NTP and the NIH at the hearing. "While the current scientific evidence has not conclusively linked cell phone use with any health problems, we and other scientific organizations evaluating the available studies have concluded that better data are needed to establish any potential health risks from the low-level radiofrequency radiation exposures associated with their use," Bucher said.

Bucher provided an overview of the NTP studies, which he pointed out are designed to clarify any potential hazards, including cancer risk, from exposure to cell phone radiation. He also responded to numerous questions from Senators Tom Harkin and Arlen Specter. Bucher's testimony can be found online. NTP has also prepared a fact sheet on cell phones.

SBIR Opportunities

On August 19, 2009, the National Institutes of Health and the Centers for Disease Control and Prevention released a solicitation for Small Business Innovation Research (SBIR) contract proposals, with a due date of November 9, 2009. Among the topics were several of specific interest to the NTP including:

#106: *Development of Quantitative High Throughput Screens for Environmental Toxicants that Induce DNA Damage.* SBIR project goal is to support the development of quantitative high throughput screens in 1536-well format for the detection of chemicals that induce DNA damage.

#107: *Development of Mid to High-Throughput Toxicological Tests Using Model Organisms.* SBIR project goal is to support the development of mid- to high-throughput alternative models that utilize other model organisms (e.g., *Drosophila melanogaster, Brachydanio rerio, Oryzias latipes*) for evaluating the ability of substances of concern to the NTP to induce toxicological effects (e.g., developmental toxicity, reproductive toxicity, cardiotoxicity, neurotoxicity).

#108: *Integrated Prediction Systems to Support Environmental Toxicological Assessments.* SBIR project goal is to develop a PC and/or Mac-based integrated prediction system to support environment toxicological assessments.

#109: *Incorporation of Metabolism into Quantitative High Throughput Screening (HTS) Assays.* SBIR project goal is to develop high throughput assays (e.g., 384 or 1536-well) that incorporate human or rodent hepatic metabolic capability.

#110: *Development of Quantitative High Throughput Screens for the Detection of Chemicals that Modulate Gap Junction Intercellular Communication.* SBIR project goal is to support the development of quantitative high throughput screens for the detection of chemicals that adversely alter gap junction activities.

#111: *Monitoring* in vivo *Gene Expression Changes After Exposure to Toxicants in Caenorhabditis elegans.* SBIR project goal would be to generate a collection of stable, integrated strains of transgenic C. elegans to monitor the effects of toxicants on gene expression *in vivo*. The collection would include a representative set of targets genes from the signaling pathways known to be affected by exposure to environmental agents (e.g. DNA damage response, unfolded protein response, apoptosis, receptor mediated signaling, etc.). Ideally, several independent lines of low copy number transgenic strains would be generated and out-crossed for several generations.

Additional information can be obtained at:
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-09-137.html

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Upcoming Events

November 2-4, 2009

RoC Expert Panel Meeting

Hilton Raleigh-Durham Airport
4810 Page Creek Lane
Durham, NC

November 19, 2009

NTP Board of Scientific Counselors Technical Reports Review Subcommittee Meeting

NIEHS
111 TW Alexander Drive
Research Triangle Park, NC

December 9-10, 2009

NTP Board of Scientific Counselors Meeting

NIEHS
111 TW Alexander Drive
Research Triangle Park, NC

December 16-18, 2009

CERHR Expert Panel Meeting on Soy Formula

Hilton Alexandria Old Town
1767 King Street
Alexandria, VA

http://ntp.niehs.nih.gov/go/calendar

NTP Board of Scientific Counselors

The NTP Board of Scientific Counselors meeting will be held on December 9-10, 2009, at the NIEHS, 111 TW Alexander Drive, Research Triangle Park, NC. Preliminary agenda items include: research concepts for NTP testing nominations, review of the Host Susceptibility Program, overview of NTP studies on herbals, two concepts for contracts: (1) to provide chemistry support and (2) to conduct reproductive and developmental toxicology and perinatal carcinogenicity studies, NTP evaluation process, and update on activities by the Center for the Evaluation of Risks to Human Reproduction. Meeting information will be posted on the NTP website (http://ntp.niehs.nih.gov/go/165) as it becomes available.

NTP Board of Scientific Counselors Technical Reports Review Subcommittee

The NTP Board of Scientific Counselors Technical Reports Review Subcommittee will meet on November 19, 2009, at the NIEHS, 111 TW Alexander Drive, Research Triangle Park, NC to peer review the findings and conclusions from 6 draft NTP Technical Reports on studies performed in conventional rats and mice.

The draft reports scheduled for review are:

TR 536	Bis(2-chloroethoxy) methane	TR 565	Milk Thistle Extract
TR 563	Pulegone	TR 566	Diethylamine
TR 564	1-Bromopropane	TR 567	Ginseng

Meeting information is available on the NTP web site (http://ntp.niehs.nih.gov/go/15833) or can be obtained by contacting the Executive Secretary (contact information below). Meetings are open to the public and public comment, both written and oral, is welcome on any report.

Contact Information: Dr. Barbara Shane, Executive Secretary, NTP Office of Liaison, Policy and Review, NIH/NIEHS, P.O. Box 12233, MD K2-03, Research Triangle Park, NC 27709; T: (919) 541-4253; shane@niehs.nih.gov

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NTP Testing Program

Request for Study Nominations

With a broad mandate to provide toxicological characterizations for chemicals and other substances of public health concern, the NTP accepts nominations for new toxicological studies at any time. Labor unions, academic scientists, federal and state agencies, industry, and the general public are welcome to make nominations for specific substances or for general issues related to potential human health hazards of occupational or environmental exposures. As available, a rationale for study should accompany the nomination along with background information describing sources of exposure and possible adverse health effects or concerns associated with exposure, the chemical name and the Chemical Abstract Service (CAS) registry number. Details about the nomination review and selection process are available on the NTP web site (http://ntp.niehs.nih.gov, select *Nominations to the Testing Program* under the heading *Testing Information*) or by contacting the NTP Office of Nomination and Selection (contact information below).

Current areas of focus in the NTP's testing program include potential hazards associated with radiofrequency radiation from cellular phones, metals, nanoscale materials, perfluorinated compounds, herbal dietary supplements, photoactive chemicals, brominated flame retardants, certain complex occupational exposures, dioxin-like compounds, contaminants of finished drinking water, and endocrine-active substances.

Contact Information: Dr. Scott A. Masten, Director, NTP Office of Nomination and Selection, NIH/NIEHS, P.O. Box 12233, MD K2-02, Research Triangle Park, North Carolina 27709; T: (919) 541-5710; FAX: (919) 541-3647; email; masten@niehs.nih.gov

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Report on Carcinogens (RoC) Center

Scientific Review of Formaldehyde November 2–4, 2009

A 3-day expert panel meeting for the scientific review of formaldehyde is scheduled for November 2-4, 2009, at the Hilton Raleigh-Durham Airport Research Triangle Park, NC. Formaldehyde is a high-production chemical with a wide array of uses and was selected for review for the 12th RoC (72 FR 26394). The predominant uses of formaldehyde in the United States are in the production of industrial resins and as a chemical intermediate. It is also used as a disinfectant and preservative and in numerous consumer products and is off-gassed from formaldehyde-containing materials such as carpets, paint, and insulation. Formaldehyde (gas) is currently listed in the *11th RoC* as "*reasonably anticipated to be a human carcinogen*." At this public meeting, the expert panel will (1) peer review the draft background document on formaldehyde and (2) provide a recommendation and scientific justification for formaldehyde's listing status in the 12th RoC.

Public comments on the draft background document can be made in writing to the RoC Center, in person at the public meeting, and/or through webconferencing. The deadline for registration to attend the meeting and/or provide oral comments is October 26, 2009. On-line registration for attendance and/or public comments is available on the RoC meeting web site (http://ntp.niehs.nih.gov/go/29679), along with other meeting materials including the draft background document on formaldehyde, or by contacting the RoC Center (see contact information below).

Contact Information: Dr. Ruth M. Lunn, Report on Carcinogens Office, NIH/NIEHS, P.O. Box 12233, MD K2-14, Research Triangle Park, NC 27709; T: (919) 316-4637; FAX: (919) 541-0144; lunn@niehs.nih.gov

Biomolecular Screening Branch

Dr. Raymond Tice, Chief of the NTP Biomolecular Screening Branch, gave the opening plenary presentation at the VII World Congress on Alternatives and Animal Use in the Life Sciences, held in Rome, Italy, from August 30 to September 3, 2009. This Congress, held every two years, was attended by approximately 1000 individuals from over 25 countries. The title of Dr. Tice's presentation was "The U.S. 'Tox21 Community' and the Future of Toxicology Testing." This presentation informed the international scientific, regulatory, and animal welfare communities of the 2008 Memorandum of Understanding between the NTP, the NIH Chemical Genomics Center, and the EPA National Center for Computational Toxicology to collaborate on the research, development, validation, and translation of new and innovative test methods that characterize key steps in toxicity pathways. A central component of this effort is exploration of high throughput screening assays and tests using phylogenetically lower animal species (e.g., fish, worms), as well as high throughput whole genome analytical methods to evaluate mechanisms of toxicity. The goals of the "Tox21 community" are to investigate the use of these new tools to (1) identify mechanisms of chemically induced biological activity, (2) prioritize chemicals for more extensive toxicological evaluation, and (3) develop more predictive models of *in vivo* biological response. Success is expected to result in test methods for toxicity testing that are more scientifically and economically efficient and models for risk assessment that are more biologically based. As a consequence, a reduction or replacement of animals in regulatory testing is anticipated to occur in parallel with an increased ability to evaluate the large numbers of chemicals that currently lack adequate toxicological evaluation.

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NTP Center for the Evaluation of Risks to Human Reproduction (CERHR)

Work continues on the updated evaluation of soy formula. The expert panel will meet on December 16-18, 2009, at the Hilton Alexandria Old Town, 1767 King Street, Alexandria, VA to review and revise the draft expert panel report and reach conclusions regarding whether exposure to soy formula is a hazard to human development. The expert panel will also identify data gaps and research needs. The draft expert panel report is available for public comment and the public is invited to attend the expert panel meeting where time will be set aside for oral comment. The draft expert panel report, Federal Register notice, on-line registration, and materials are available on the CERHR website (http://cerhr.niehs.nih.gov).

Contact Information: Dr. Kristina A. Thayer, Acting Director, NIH/NIEHS, NIH/NIEHS, P.O. Box 12233, MD K2-04, Research Triangle Park, NC 27709; T: (919) 541-5021; FAX: (919) 316-4511; thayer@niehs.nih.gov

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NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM)

ICCVAM-recommended *In Vitro* Ocular Safety Testing Methods Accepted as OECD Test Guidelines

In September, the Organisation for Economic Co-operation and Development (OECD) officially adopted two new international test guidelines that can be used to identify ocular corrosives and severe irritants without the use of live animals. NICEATM and the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) developed the guidelines for the bovine corneal opacity and permeability (BCOP) and isolated chicken eye (ICE) test methods following their acceptance by U.S. Federal regulatory agencies in 2008. Substances that may cause severe irritation or permanent damage to eyes can now be identified using these methods without the use of live animals in the 30 OECD member countries.

After the BCOP and ICE test methods were accepted last year by U.S. Federal agencies (see NIEHS press release, "Newly Approved Ocular Safety Methods Reduce Animal Testing," June 23, 2008, http://www.niehs.nih.gov/news/releases/2008/index.cfm), NICEATM and ICCVAM drafted test guidelines in collaboration with validation organizations in Europe and Japan for submission to OECD. The new test guidelines are designated Test Guidelines 437 (BCOP) and 438 (ICE). This represents the most rapid adoption of new test guidelines by the OECD. The prompt acceptance was due in large part to the comprehensive ICCVAM evaluation of the validation status of the test methods and the involvement of international validation partners in the development of the test guidelines.

Final versions of Test Guidelines 437 and 438 are now available on the NICEATM-ICCVAM website (http://iccvam.niehs.nih.gov/methods/ocutox/ivocutox/OECD.htm) along with information about the NICEATM-ICCVAM evaluation of the BCOP and ICE test methods. Information about the OECD Test Guidelines Program can be found on the OECD website at: http://www.oecd.org/document/40/0,2340,en_2649_34377_37051368_1_1_1_1,00.html.

ICCVAM Recommends Performance Standards and New Versions of the Murine Local Lymph Node Assay to U.S. Federal Agencies

In September 2009, ICCVAM recommendations for the reduced murine local lymph node assay (rLLNA), an updated LLNA test method protocol, and LLNA performance standards were communicated to the heads of Federal agency heads for

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their consideration. Links to these letters are available on the NICEATM-ICCVAM website (http://iccvam.niehs.nih.gov/methods/immunotox/rLLNA.htm). Reponses from agencies are required within 180 days and will be posted on the NICEATM-ICCVAM website as they are received.

ICCVAM recommended that the rLLNA should be routinely considered before conducting the traditional multi-dose LLNA, and used where appropriate to determine the potential of chemicals and products to cause allergic contact dermatitis. Using the rLLNA will reduce animal use by 40% compared to the traditional multi-dose LLNA. ICCVAM also recommended performance standards that can be used to efficiently evaluate the validity of improved and modified versions of the LLNA that are mechanistically and functionally similar to the traditional LLNA. The updated LLNA test method protocol reduces animal use by 20% compared to the original LLNA.The ICCVAM recommendations are provided in the *ICCVAM rLLNA Test Method Evaluation Report* (TMER). More information about the NICEATM-ICCVAM evaluation of the rLLNA and a link to the TMER are on the NICEATM-ICCVAM website.

The ICCVAM-recommended performance standards for the LLNA specify essential test method components, a minimum list of reference substances to evaluate the accuracy and reliability of a modified LLNA, and accuracy and reliability values that must be achieved in order for a modified LLNA to be considered equal to or better than the traditional LLNA. More information about the ICCVAM LLNA performance standards and the LLNA performance standards report are available on the NICEATM-ICCVAM website (http://iccvam.niehs.nih.gov/methods/immunotox/llna_PerfStds.htm).

NICEATM and ICCVAM Scientists Participate at the Seventh World Congress on Alternatives and Animal Use in the Life Sciences

NICEATM and ICCVAM scientists played a prominent role in the recent international meeting dedicated to advancements in the reduction, refinement, and replacement of the use of animals for safety testing. The VII World Congress on Alternatives and Animal Use in the Life Sciences was attended by representatives from industry, regulatory agencies, and animal welfare organizations. (See related article page 4.) The meeting, co-sponsored by NIEHS, was held in Rome, Italy from August 31 to September 3 and emphasized progress made since the last 2007 Congress (Tokyo, Japan) in the development of alternatives for toxicity testing. Four plenary sessions featured updates on recent progress and new initiatives by NICEATM and ICCVAM: (1) a session on the recently signed International Cooperation on Alternative Test Methods agreement, (2) a session on recent progress and future directions of the national validation centers in the U.S. (NICEATM-ICCVAM), Europe (ECVAM), and Japan (JaCVAM), (3) a session on evolving concepts, opportunities, and challenges in validation, and (4) a session providing an update on the recent acceptance of *in vitro* pyrogen tests in the United States and Europe.

NICEATM and ICCVAM scientists also presented eight scientific posters highlighting recent progress in the validation and evaluation of alternative test method activities. The poster presentations, available on the NICEATM-ICCVAM website (http://iccvam.niehs.nih.gov/meetings/7thWC/7WCablst.htm), summarized test method evaluation activities relevant to skin and eye corrosivity and irritation, skin sensitization, pyrogenicity, and endocrine disruptors. They also highlighted NICEATM and ICCVAM's international cooperative activities including the development of internationally harmonized test method performance standards, international validation studies, and efforts toward international regulatory acceptance of *in vitro* alternatives.

September 14-16, 2010 – International Scientific Workshop on Alternative Methods in Vaccine Potency and Safety Testing

NICEATM and ICCVAM are planning a workshop, The International Scientific Workshop on Alternative Methods to Reduce, Refine, or Replace the Use of Animals in Vaccine Potency and Safety Testing, which will be held on September 14-16, 2010, at the William H. Natcher Conference Center at the National Institutes of Health in Bethesda, MD. This workshop will bring together international scientific experts representing relevant stakeholder organizations to review the current status and use of such methods and to prioritize future activities related to research, development, and validation of new alternative methods.

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The goals of the workshop will be to: (1) review the state of the science and current use of alternative methods that can reduce, refine, and/or replace the use of animals in vaccine potency and safety testing and (2) identify priorities for research, development, and validation efforts needed to advance the use of alternative methods for vaccine potency and safety testing while ensuring the protection of human and animal health. Interested stakeholders and members of the public are encouraged to attend. More information about the workshop will be posted on the NICEATM-ICCVAM website (http://iccvam.niehs.nih.gov/meetings/schedule.htm#niceatm) as it becomes available.

Contact Information: Dr. William S. Stokes, Director, NIH/NIEHS, P.O. Box 12233, MD K2-16, Research Triangle Park, NC 27709; T: 919-541-2384; FAX 919-541-0947; niceatm@niehs.nih.gov

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