The National Toxicology Program UPDATE

January 2003

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

NTP Workshop on Transgenics

The NTP is sponsoring a workshop, ***Genetically Modified Rodent Models for Cancer Hazard Identification: Selecting Substances for Study and Interpreting and Communicating Results***, on February 21, 2003, at the Hamilton Crowne Plaza Hotel, 14th and K Street, NW in Washington, DC. The objectives of this workshop are to solicit comment on

- a process for selection of appropriate nominated substances to undergo cancer hazard evaluation in genetically modified or ***transgenic*** models
- issues related to the proper interpretation of results from "transgenic" cancer models, the implications of these findings for public health decisions, and the most appropriate interpretive language to describe the results of such studies to the scientific/regulatory communities and the public.

This meeting is open to the public subject to available space – interested attendees are asked to contact Ms. Diane Spencer in the NTP Liaison and Scientific Review Office (919-541-2759 or spencer2@niehs.nih.gov). Additional information about the workshop, as available, will be posted on the NTP homepage (http://ntp-server.niehs.nih.gov). The meeting begins with plenary sessions followed by sessions for two different breakouts designed to address the objectives given above. The meeting will conclude with reports from the breakout groups followed by time for open discussion by all attendees.

The agenda provides time for public comment. Details about the submission of written comments and presentation of oral comments are published in the ***Federal Register*** (Vol. 68, No. 1, pages 381-382); this notice is posted on the NTP web site.

The NTP has invested considerable time and resources in addressing whether cancer bioassay results from studies conducted in genetically modified or ***transgenic*** rodent models are useful for identifying chemicals presumed to be of carcinogenic risk to humans. Scientists at the National Institute of Environmental Health Sciences [***Environmental Health Perspectives*** doi:10.1289/ehp.5778 (available at http://dx.doi.org/) online 30 October 2002], have compared results from transgenic mouse cancer assays with the International Agency for Research on Cancer (IARC) and NTP Report on Carcinogens classifications for select chemicals as to their carcinogenic potential for humans. Overall, the transgenic models performed well; however, important issues of experimental design and data interpretation need further attention to enable future regulatory acceptance and use in human risk assessment. The February NTP workshop will begin to address these issues.

NIEHS Receives Leadership Award

The National Institute of Environmental Health Sciences (NIEHS) received the Environment@RTP Environmental Leadership Award in December 2002. This is a new award from the Environment@RTP Committee of the Research Triangle Owners and Tenants Association and the NIEHS is the winner in the category of 2000 employees and less. The Environment@RTP Committee is an organization in the Research Triangle Park, North Carolina dedicated to protecting the environment by sharing best practices, creating joint strategies, minimizing impact on the surrounding community and working with local municipalities to create innovative solutions.

The Leadership Award selection was made by a panel of judges from environmental divisions from Durham and Wake Counties and the State of North Carolina and was moderated by a representative of the Research Triangle Foundation. The panel judged each organization's efforts in the areas of Environmental Management, Sustainable Environmental Results, Leadership and Innovation, Employee Education, and Community Outreach and Voluntary Initiatives. In selecting the NIEHS for this award, the judges noted that they were impressed by the NIEHS' leadership in community outreach, through the purchase and use of a "zero-emissions" electric car by the Facilities Engineering Branch for transportation on campus, the establishment of North Carolina's first vermicomposting program, its extensive, integrated waste management program, and its award-winning employee commute trip reduction efforts.

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NTP Testing Program

The NTP has a broad mandate to provide toxicological characterizations for chemicals and other agents of public health concern. The program continually solicits and welcomes the nomination of agents for study from all interested groups, such as labor unions, academia, federal and state agencies, industry, and the general public.

The NTP Office of Chemical Nomination and Selections handles the receipt of nominations and comments on testing initiatives or nominations (contact information below). As possible, the NTP asks that nominators provide background information describing the agent's use and production, possible adverse health effects or concerns associated with exposure, and the chemical name and Chemical Abstract Service (CAS) registry number. Details about the nomination process are available on the NTP web site (http://ntp-server.niehs.nih.gov, select How to Nominate Substances) or by contacting the NTP Office of Chemical Nomination and Selection.

All nominations undergo several levels of review before the NTP selects agents for study and designs and implements toxicological studies. These steps of review help to ensure that the NTP's testing program addresses toxicological concerns pertinent to all areas of public health and helps maintain balance among the types of agents evaluated.

Current areas of focus in the NTP's testing program include potential safety issues associated with herbal medicines, radio-frequency radiation emissions from cellular telephones, hexavalent chromium in drinking water, photoactive chemicals, certain complex occupational exposures, dioxin-like compounds, contaminants of finished drinking water, and endocrine-disrupting agents.

***Contact information*: Dr. Scott Masten, Office of Chemical Nomination and Selection, NIEHS, P.O. Box 12233, MD A3-07, 111 TW Alexander Dr., Research Triangle Park, NC 27709; T: 919-541-5710; masten@niehs.nih.gov**

10th Edition of the Report on Carcinogens Now Available

The Department of Health and Human Services released and made publicly available the Tenth Edition of the Report on Carcinogens (10th RoC) on December 11, 2002. Prepared by the NTP, the RoC identifies substances -- such as metals, pesticides, drugs, and natural and synthetic chemicals -- and mixtures or exposure circumstances that are ***known*** or are ***reasonably anticipated*** to be human carcinogens, and to which a significant number of Americans are exposed. This edition of the report adds 16 new listings and brings the total of substances in the report ***known*** or ***reasonably anticipated*** to be a cancer hazard to 228. The report makes a distinction between ***known*** human carcinogens, where there is sufficient evidence from human studies, and ***reasonably anticipated*** human carcinogens, where there is either limited evidence of carcinogenicity from human studies and/or sufficient evidence of carcinogenicity from experimental animal studies. The report also identifies current regulations concerning these listings in an attempt to address how exposures have been reduced.

Newly listed as *known* human carcinogens

Steroidal estrogens - A number of the individual steroidal estrogens were already listed as ***reasonably anticipated carcinogens*** in past editions, but this is the first report to list all these hormones as a group. This group of related hormones controls sex and growth characteristics and is commonly used in estrogen replacement therapy to treat symptoms of menopause and in oral contraceptives.

The RoC cites data from human epidemiology studies showing that estrogen replacement therapy is associated with a consistent increase in the risk of endometrial cancer and a less consistent increase in the risk of breast cancer. The RoC also cites evidence suggesting that oral contraceptive use may be associated with increased risk of breast cancer but has protective effects against ovarian and endometrial cancers.

There has been concern expressed that the listing of steroidal estrogens in the RoC as ***known human carcinogens*** may deter use by women who might benefit from their use as estrogen replacement therapy or oral contraceptives. Because of potential benefits not covered in the RoC, personal decisions concerning therapeutic use of carcinogenic agents need to be based on additional information that is beyond the scope of the 10th RoC. The 10th RoC is intended to provide the public and their health care providers with knowledge of these potential risks so that they may weigh the benefits of use of estrogen replacement therapy and oral contraceptives with these risks.

Broad spectrum ultraviolet radiation - is produced by the sun as part of solar radiation and by artificial sources such as sun lamps and tanning beds, in medical diagnosis and treatment procedures, and in industry for promoting polymerization reactions. Individuals can be exposed to UVR from natural (the sun) and artificial sources.

The RoC cites data that indicate a causal relationship between exposure to UVR from natural sources and skin cancer, cancer of the lip and melanoma of the eye. Individuals can be exposed to artificial sources of UVR for cosmetic, medical and occupational reasons and that exposure to these artificial sources (such as sunlamps or sunbeds) is associated with an increased risk of melanoma. The RoC also indicates that skin cancers are observed with increasing duration of exposure and for those persons who experience sunburn.

Wood dust - is created when machines and tools cut, shape and finish wood. Wood dust is particularly prevalent in sawmills, furniture manufacture, carpentry and cabinet making.

The RoC cites data from human epidemiological studies that have consistently demonstrated that wood dust exposure increases the risk of cancers of the nasal cavities and paranasal sinuses.

Nickel compounds - used in many industrial applications as catalysts and in batteries, pigments and ceramics.

The RoC listing is based on sufficient evidence of carcinogenicity from studies in humans, including epidemiological and mechanistic information, that provides evidence of a causal relationship between workers' exposure to nickel compounds and excess mortality from lung and nasal cancers.

Upgraded from *reasonably anticipated* to *known* human carcinogen

Beryllium and beryllium compounds - about 800,000 workers are exposed via inhalation of beryllium dust or dermal contact with products containing beryllium. Workers with the highest potential for exposure include beryllium miners, beryllium alloy makers and fabricators, ceramics workers, missile technicians, nuclear reactor workers, electric and electronic equipment workers, and jewelers.

The RoC listing is based on the observed causal relationship between workers exposed to either beryllium or beryllium compounds and lung cancer. The listing states that higher risks for lung cancer are found in groups with greater exposure or longer time since first exposure. These dose-response patterns support a causal relationship

and cannot be explained by confounding from smoking or other occupational exposures.

Newly listed as *reasonably anticipated* to be human carcinogens

IQ, or 2-amino-3-methylimidazo[4,5-*f*]quinoline – is one of a series of heterocyclic amines formed during direct cooking with high heat of foods, such as meats and eggs, and is also found in cigarette smoke.

The RoC listing is based on findings from oral studies of IQ in experimental animals that produced cancer in multiple organs of multiple species. The report also states that while no adequate human epidemiology studies have been reported that would indicate a human cancer risk specifically associated with exposure to IQ or other HCAs, there are published studies that provide some indication for an increased risk for breast and colorectal cancers related to consumption of broiled or fried foods that may contain IQ and/or other heterocyclic amines.

2,2-bis-(Bromomethyl)-1,3-propanediol (technical grade) - a flame retardant chemical used to make some polyester resins and rigid polyurethane foam is listed as ***reasonably anticipated*** based on long-term animal feeding studies.

The RoC listing is based on findings from long term feeding studies of this chemical in laboratory animals where cancer was observed in multiple organs sites of multiple species of animals.

Ultraviolet A (UVA), Ultraviolet B (UVB) and Ultraviolet C (UVC) Radiation - Broad spectrum ultraviolet radiation contains wavelengths from 100 to 400 nm and is composed of individual components defined as UVA (315 to 400 nm), UVB (280 to 315 nm) and UVC (100 to 280 nm). The major sources of exposure to UVA and UVB are from natural solar radiation and artificial sources such as sunlamps, sunbeds and arc welding. UVC exists in the extraterrestrial solar spectrum, but is completely filtered out by the earth's ozone layer and does not reach the earth's surface. The major source of UVC exposure comes from artificial sources such as germicidal lamps, UV photography, and UV lasers.

The RoC listing of UVA, UVB, and UVC is based on limited evidence of carcinogenicity from studies in humans and sufficient evidence of carcinogenicity from studies in experimental animals that indicate a causal relationship between exposure to UVA, UVB or UVC and skin cancer.

Chloramphenicol – is an antibiotic with restricted use in the United States because it can cause fatal blood disorders.

The RoC listing is based on limited evidence of carcinogenicity from studies in humans showing an increased cancer risk for the occurrence of leukemia after chloramphenicol therapy.

2,3-Dibromo-1-propanol - a chemical used as an intermediate in the production of flame-retardants, insecticides, and pharmaceuticals. Formerly used in the production of TRIS-BP, a now banned flame retardant previously used in children's clothing and other products.

The RoC listing is based on findings from skin painting studies of this chemical on laboratory animals that produced cancer in multiple organs of multiple species.

Dyes metabolized to 3,3'-dimethoxybenzidine - dyes that have been used to color leather, paper, plastic, rubber and textiles.

The RoC listing is based on the fact that 3,3'-dimethoxybenzidine is carcinogenic in male and female rats, has been listed in the RoC since 1983 as ***reasonably anticipated to be a human carcinogen*** and that metabolism of these dyes to release free 3,3'-dimethoxybenzidine is a generalized phenomenon that occurs in all animal species studied.

Dyes metabolized to 3,3'-demethylbenzidine – dyes that have been used in printing textiles, in color photography and as biological stains.

The RoC listing is based on the fact that 3,3'-dimethylbenzidine is carcinogenic in male and female rats, has been listed in the RoC since 1983 as ***reasonably anticipated to be a human carcinogen*** and that metabolism of these dyes to release free 3,3'-dimethylbenzidine is a generalized phenomenon that occurs in all animal species studied.

Methyleugenol - occurs naturally in oils, herbs and spices and is used in smaller amounts in its natural or synthetic form in flavors, insect attractants, anesthetics and sunscreens.

The RoC listing is based on findings from oral studies of this chemical that produced cancer in multiple organs of multiple species of experimental animals.

Metallic nickel - used mainly in alloys with most exposures by inhalation or skin contact in the workplace. The nickel coin does not contain metallic nickel, but does contain a copper-nickel alloy.

The RoC listing is based on findings from studies of this metal in multiple species of experimental animals that produced cancer at multiple organ sites.

Styrene-7,8-oxide - is used in the production of reinforced plastics and as a chemical intermediate for cosmetics, surface coatings, and agricultural and biological chemicals.

The RoC listing is based on findings from oral studies of this chemical that produced cancer in multiple species of experimental animals.

Vinyl bromide - used in polymers in making fabrics for clothes and home furnishings, as well as in leather and metal products, drugs and fumigants.

The RoC listing is based on findings from inhalation studies of this chemical that produced cancer in multiple organs of experimental animals.

Vinyl fluoride - used in making polyvinyl fluoride and related weather-resistant fluoropolymers.

The RoC listing is based on findings from inhalation studies of this chemical that produced cancer in multiple organs of multiple species of experimental animals.

The RoC was mandated by Congress in 1978 recognizing that many cancers are apparently induced by chemicals in the home, workplace, general environment and from the use of certain drugs. The report does not assess the magnitude of the carcinogenic hazard, nor does it address any potential benefits of listed substances such as certain pharmaceuticals. Listing in the report does not establish that a substance presents a risk to persons in their daily lives. Such formal risk assessments are the responsibility of Federal, State, and local health regulatory agencies. The listing of a substance in the RoC is not a regulatory action, but listing may prompt regulatory agencies to consider limiting exposures or uses of a substance.

The report is accessible at http://ntp-server.niehs.nih.gov (select Report on Carcinogens). For available hard copies, email ehponline@niehs.nih.gov, visit http://www.ehponline.org or write Environmental Health Perspectives, Attn: Order Processing, 1001 Winstead Drive, Suite 355, Cary, NC 27513. Requests for hard copies may also be faxed to (919) 678-8696.

Fact sheets – "What is the Report On Carcinogens?" and "Q and A on the RoC" as well as background documents for the new listings can be accessed on the RoC web site.

***Contact information*: Dr. C.W. Jameson, Head, Report on Carcinogens, NIEHS, P.O. Box 12233, MD EC-14, 79 TW Alexander Drive, Research Triangle Park, NC 27709; T: 919-541-4096; jameson@niehs.nih.gov**

Visit NTP at SOT – Booth #329

The NTP will exhibit at the Society of Toxicology 42nd Annual Meeting and ToxExpo being held March 9-13, 2003, at the Salt Palace Convention Center in Salt Lake City, Utah. ToxExpo is the largest gathering of decision-makers charged with developing and implementing toxicological research. It helps to advance the science and application of toxicology by providing important information about products and services in toxicology and related scientific fields.

The NIEHS and ***Environmental Health Perspectives*** (EHP), the NIEHS scientific journal, will also exhibit at ToxExpo. Be sure to check out booths #329 (NTP), #1338 (NIEHS) and #1342 (EHP).

How to Subscribe to the NTP List-server

The NTP Update is issued approximately 4 times each year. To subscribe to the "list-server" and receive the NTP Update as well as other NTP news and announcements electronically, register online at http://ntp-server.niehs.nih.gov or send email to ntpmail-request@list.niehs.nih.gov with the word "subscribe" as the body of the message, or contact the NTP Liaison and Scientific Review Office.

Additional information about the NTP along with announcements of meetings, publications, study results and its centers is available on the Internet at http://ntp-server.niehs.nih.gov.

The Environmental Health Perspectives (EHP) maintains issues of the Report on Carcinogens and the library of NTP Technical Reports and NTP Toxicity Reports and adds new reports as available. To gain access to these reports, contact EHP online at: http://ehp.niehs.nih.gov or call 800-315-3010 or 919-541-3841.

***Contact information*: NTP Liaison and Scientific Review Office, NIEHS, P.O. Box 12233, MD A3-01, Research Triangle Park, NC 27709; T: 919-541-0530; F: 919-541-0295; liaison@starbase.niehs.nih.gov**

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

Review of Ethylene Glycol and Propylene Gycol Is Set

CERHR will hold an expert panel meeting February 11-13, 2003, in Alexandria, Virginia, to evaluate the potential reproductive and developmental toxicities of ethylene glycol and propylene glycol (Federal Register Vol. 67, No. 236, pages 72965 – 72967: December 9, 2002). This meeting is open to the public. Draft expert panel reports on ethylene glycol and propylene glycol are available electronically on the CERHR web site (http://cerhr.niehs.nih.gov) or in hardcopy by contacting CERHR (see contact information below). Additional details, including procedures for submission of written comments or presentation of oral comments at the expert panel meeting, were published in the Federal Register and are available on the CERHR web site.

Ethylene glycol is a high-production-volume chemical used chiefly in the production of polyester compounds. Widespread public exposure occurs through its common use as antifreeze for heating and cooling systems. Propylene glycol, similar in structure to ethylene glycol, is used as antifreeze, in de-icing solutions, and in various paints and coatings. Propylene glycol is also approved for use in various food additives, drugs, and cosmetics.

The CERHR serves as an environmental health information resource. It provides timely and unbiased scientifically sound evaluations of human and experimental evidence for adverse effects on reproduction, including development, which may be caused by agents to which humans are exposed. The CERHR welcomes the nomination of chemicals for future evaluations from all interested individuals and groups at any time. Nominations should include the chemical's name, Chemical Abstract Service (CAS) registry number (if known), and a justification for the nomination. As possible, information on the chemical and its potential reproductive or developmental toxicity is also requested. Nominations can be submitted through the CERHR web site (select Nominate a Chemical) or directly to the CERHR (contact information below). The CERHR also invites submission, at any time, of recent, relevant toxicology or human exposure studies for chemicals under evaluation.

Workshop on Chemical-Induced Thyroid Dysfunction and Human Reproduction

CERHR is planning a workshop to address how best to evaluate the potential for chemical-induced thyroid dysfunction to adversely affect human reproduction. Two primary issues for discussion at this meeting are: (1) the appropriate design of relevant toxicity tests for detecting adverse reproductive effects and (2) the appropriate use of rodent data for predicting effects in humans. This one ***and*** one-half day meeting is planned for late April 2003 in the Washington, DC area. Further details can be obtained from Dr. Michael Shelby, CERHR director (contact information below).

***Contact information*: Dr. Michael Shelby, Director, CERHR, NIEHS, P.O. Box 12233, MD EC-32, 79 TW Alexander Drive, Research Triangle Park, NC 27709; T: 919-541-3455; shelby@niehs.nih.gov**

As the New Year begins, the NTP mourns the deaths during December of three valued scientists: Dr Michael Kohn, Dr. Joel Mahler and Dr. Ghanta Rao. Each will be deeply missed by friends and colleagues. The unique scientific contributions of each are highly valued and the breadth of their talents will be hard to replace.