was filed. Appendix M–I–C–3 has been corrected to state that annual reports are to be filed with OBA at the same time that they are filed with the Food and Drug Administration (FDA)—within 60 days of the anniversary of the date the IND went into effect. This filing requirement becomes effective with respect to the first annual safety report filed after January 24, 2002.

Other minor, non-substantive changes have been made to the *NIH Guidelines,* as warranted. In addition, for ease in navigating the document, the *NIH Guidelines* have been fully indexed. The electronic version includes hyperlinks from the index to relevant portions of the body of the document. Thus, when users identify a section of interest in the index, by simply clicking on the title of that section, they will be immediately brought to the corresponding portion of the *NIH Guidelines.*

All of these changes are listed in detail in a Summary of Amendments and Corrections that can be accessed, along with the new version of the *NIH Guidelines,* at: *http://www4.od.nih.gov/oba/rac/guidelines/guidelines.html.*

Dated: May 17, 2002.

Ruth L. Kirschstein,

Acting Director, National Institutes of Health.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

National Toxicology Program (NTP); Availability of Data From Preliminary Studies and Proposed Study Protocols for Cancer Bioassays of Hexavalent Chromium in Rats and Mice; Request for Public Comment and Notice of Public Meeting

Summary

Hexavalent chromium (CAS number 18540–29–9) was nominated to the NTP for study of its potential toxicity and carcinogenicity when administered to animals in drinking water (*see* **Federal Register:** May 7, 2001, Vol. 66, No. 88, pages 23037–23039). Members of the California legislative delegation, the California Environmental Protection Agency, and the California Health and Human Services Agency nominated hexavalent chromium to the NTP for study. The basis for the nomination is a document prepared by the California Environmental Protection Agency's (EPA) Office of Environmental Health Hazard Assessment titled ''Public Health Goal for Chromium in Drinking Water'', a copy of which is available on the NTP's Web site *http://ntp-server.niehs.nih.gov* (*see* NTP Studies of Hexavalent Chromium Compounds under What's New?).

The purpose of this notice is to announce:

(1) The availability of data from studies designed to assess the absorption of chromium by rats, mice and guinea pigs receiving hexavalent chromium, as sodium dichromate dihydrate, in drinking water;

(2) The design and availability of data from 90-day oral toxicity studies in rats and mice receiving hexavalent chromium in drinking water;

(3) A proposed design for 2-year rodent cancer studies of hexavalent chromium in drinking water;

(4) A public meeting to discuss these data and the proposed design for 2-year studies; and

(5) A request for public comments on these data and the proposed design for the 2-year studies.

Public Meeting

A public meeting will be held July 24, 2002 in the Rodbell Auditorium, Rall Building, South Campus, National Institute of Environmental Health Sciences (NIEHS), 111 T.W. Alexander Drive, Research Triangle Park, North Carolina. The meeting will begin at 8:30 AM and is open to the public. Attendance at this meeting is limited only by the space available. Individuals who plan to attend are asked to register with the NTP executive secretary (*see* contact information below). The names of those registered to attend will be given to the NIEHS Security Office in order to gain access to the campus. Persons attending who have not pre-registered may be asked to provide pertinent information about the meeting, *i.e.,* title or host of meeting before gaining access to the campus. All visitors will need to be prepared to show 2 forms of identification (ID), *i.e.,* driver's license and one of the following: company ID, government ID, or university ID. Also those planning to attend who need special assistance are asked to notify the NTP executive secretary in advance of the meeting (*see* contact information below).

A tentative agenda is provided below and includes opportunity for oral public comment. A scientific panel of experts (''the Panel'') will discuss the data, to date, obtained from NTP studies of hexavalent chromium administered as sodium dichromate dihydrate and the proposed study design for 2-year rodent cancer studies (*see* below, NTP Studies). The agenda and roster of the Panel will be available prior to the meeting on the NTP Web site (*http://ntp-server.niehs.nih.gov*) and upon request to the executive secretary at the address given below. Following the meeting, summary minutes will be available electronically on the NTP Web site and in hardcopy upon request to the executive secretary.

Tentative Agenda

8:30 AM
Welcome and introductions

8:40 AM
Overview of the NTP
Hexavalent chromium nomination
NTP studies on hexavalent chromium
Proposed design for 2-year studies
Public comments

Noon
Lunch

1:00 PM
Presentation of remarks by scientific expert panel
General discussion

3:30 PM
Adjourn

Request for Public Comment

The NTP meeting on hexavalent chromium is open to the public and public comment is welcome on the data from the 21-day and 90-day studies, the proposed NTP 2-year study plans, and any other issues related to the evaluation of the toxicity and carcinogenicity of hexavalent chromium in drinking water. Time will be provided at the meeting for oral public comments and persons requesting time for an oral presentation are asked to contact the NTP Executive Secretary Dr. Mary S. Wolfe, (P.O. Box 12233, MD A3–01, Research Triangle Park, NC 27709, phone: 919–541–0530, fax: 919–541–0295, e-mail: *liaison@starbase.niehs.nih.gov*). Persons registering to make oral comments are asked to provide contact information, including name, affiliation, mailing address, phone, fax, e-mail, and supporting organization (if any). Each speaker is also asked to provide, if possible, a written copy of the statement by July 15, 2002, to enable review by the Panel and NTP staff prior to the meeting. The written statement can supplement and may expand the oral presentation. At least seven minutes will be allotted to each speaker, and if time permits, may be extended to ten minutes. Each organization is allowed one time slot for an oral presentation. Registration for making public comments will also be available on-site. If registering on-site to speak and reading comments from printed copy, the speaker is asked to provide 15 copies of the statement. These copies

will be distributed to the Panel and NTP staff and will be used to supplement the record.

Written comments, in lieu of an oral presentation, are also welcome. The comments should include contact information, including name, affiliation, mailing address, phone, fax, e-mail, and sponsoring organization (if any) and preferably be received by July 15, 2002, to enable review by the Panel and NTP staff prior to the meeting as well as to supplement the record.

NTP Studies

Hexavalent chromium (CAS number 18540–29–9) was nominated to the NTP for study of its potential toxicity and carcinogenicity when administered to animals in the drinking water. Hexavalent chromium is a known human carcinogen (*http://ntp-server.niehs.nih.gov*, see Report on Carcinogens). It has been proposed that the reduction of hexavalent chromium to the trivalent form in the gut provides a physiological barrier such that when exposure to hexavalent chromium occurs from drinking water, the absorption of hexavalent chromium would not be sufficient to cause cancer. Public comments received in response to the earlier **Federal Register** notice (*see* above) suggested that this reductive mechanism would be expected to be more effective in humans and other animals lacking an anatomical forestomach than in rats and mice that have a forestomach.

To address these considerations, the NTP carried out studies in which rats, mice and guinea pigs (which lack a forestomach) received drinking water containing sodium dichromate dihydrate for 21 days. After that time, the animals were sacrificed and blood, kidney and bone were collected and analyzed for total chromium. The complete protocol and data from these studies are available on the NTP Web site (*http://ntp-server.niehs.nih.gov*).

Additionally, the NTP has completed 90-day toxicity studies of standard design in which F344/N rats and B6C3F1 mice of both sexes received control water or one of 5 concentrations (62.5, 125, 250, 500, or 1000 mg/L) of hexavalent chromium in their drinking water. The studies included measurements of clinical chemistry indices and the animals received a complete histopathological evaluation. The protocol outline for these studies is also available on the NTP Web site and data from the 90-day studies are anticipated to be available on the NTP Web site approximately one month prior to the meeting.

Also available on the NTP Web site is a draft protocol that outlines 2-year toxicity and carcinogenicity studies of hexavalent chromium in rats and mice. The NTP will establish the final design for these studies following completion and evaluation of the 90-day studies, evaluation of the data for total chromium tissue concentration from the 21-day studies, and consideration of input from the Panel, all written received in response to this notice, and oral public comments received at the public meeting.

Background

Chromium is a naturally occurring element, present in several valence states. The most common valence states are trivalent (Chromium III), hexavalent (Chromium VI), and elemental chromium (0). Chromium III is an essential nutrient forming part of a complex known as the glucose tolerance factor. Chromium compounds are stable in the trivalent state and occur in nature most commonly at this oxidation level. Hexavalent chromium compounds are the next most stable forms, although these rarely occur in nature and are typically associated with anthropogenic (human activities) sources.

Hexavalent chromium is more toxic than trivalent chromium, and is absorbed from the gut more readily than trivalent chromium. Hexavalent chromium is an oxidant and it reduces to trivalent chromium, passing through the intermediate reactive V and IV valence states. The toxicity of hexavalent chromium is thought to result from either direct binding of these intermediates to cellular constituents or through the generation of free radicals.

Prolonged inhalation of hexavalent chromium is an established cause of occupational lung cancer in chromate production workers and people engaged in the manufacture of chromate pigments. This finding is supported by inhalation studies in rats and mice that have shown lung tumors following exposure to calcium chromate or sodium dichromate.

Orally administered chromium compounds are relatively poorly absorbed, with most estimates in the range of 0.5 to 2%. The absorption of trivalent chromium is approximately one quarter that of the hexavalent form. Hexavalent chromium reduces to trivalent chromium in the stomach, and this reduction may potentially limit its systemic availability. This ''protective'' mechanism is not complete, however, because studies have shown that orally administered hexavalent chromium, when given at doses far below those where trivalent chromium showed no adverse effect, caused liver and kidney toxicity. Other concerns with hexavalent chromium given orally involve gastrointestinal effects. Acute gastritis is a common finding in humans who accidentally or intentionally ingested various hexavalent chromium compounds. Also, in a study reported in 1968, a small increase in primarily benign forestomach papillomas was seen in mice exposed to potassium chromate in the drinking water at 9 mg/kg Chromium VI for three generations over 880 days.

Dated: May 16, 2002.

Kenneth Olden,

Director, National Toxicology Program.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

National Toxicology Program; Announcement of Availability of Background Documents for Substances Nominated for Listing in the Report on Carcinogens, Eleventh Edition

Availability of Background Documents

The National Toxicology Program (NTP) announces the availability of the background documents for four nominations under consideration for listing in the Report on Carcinogens (RoC), Eleventh Edition (''the Eleventh RoC''). The background documents are available for the nominations: *Cobalt Sulfate, Diethanolamine, Nitromethane*, and *4,4'-Thiodianiline*. They can be obtained electronically on the NTP Web site: *http://ntp-server.niehs.nih.gov* (select Report on Carcinogens) or in hardcopy by contacting Dr. C. W. Jameson at the following address: National Toxicology Program, Report on Carcinogens, 79 Alexander Drive, Building 4401, Room 3118, P.O. Box 12233, Research Triangle Park, NC 27709; phone: (919) 541–4096, fax: (919) 541–0144, e-mail: *jameson@niehs.nih.gov*.

The background documents for these four nominations are the first to be released for nominations under consideration for the Eleventh RoC. These documents are being made available at this time in response to the October, 1999 public meeting that discussed the preparation and review of the Report on Carcinogens where concerns were expressed regarding the need to increase the time allotted for public review and comment on the RoC