National Toxicology Program
Board of Scientific Directors

Report on Carcinogens Subcommittee Meeting

October 14, 2003

Marriott at Metro Center
Bethesda, Maryland

Summary Minutes

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Contents **Page No.**

Attendees

Members Present

Dr. Aaron Blair
Dr. Hillary Carpenter
Dr. Garil Charnley
Dr. Harvey Checkoway
Dr. Elizabeth Delzell
Dr. John Froines
Dr. Howard Frumkin
Dr. Iva Hertz-Picciotto
Dr. Maria Morandi
Dr. Barbara Pence
Dr. James Popp
Dr. Stephen Roberts
Dr. Allan Smith

Members Absent

Dr. George Bonney
Dr. Margaret Karagas

Ad Hoc Expert Consultant

Dr. David Phillips

Agency Staff

Dr. William Allaben, Federal & Drug Administration
Patricia Clutton, Consumer Product Safety Commission
Myra Karstadt, Environmental Protection Agency
Arthur Kutz, Department of Energy
Loretta Shuman, Occupation Safety and Health Administration
Dr. Mark Toraason, National Institute of Occupational Safety & Health

NIEHS Staff

Dr. John Bucher, National Institutute of Environmental Health Sciences
Dr. Larry Hart, National Institute of Environmnetal Health Sciences
Dr. C.W. Jameson, National Institute of Environmental Health Sciences
Dr. Freya Kamel, National Institute of Environmental Health Sciences
Dr. Ruth Lunn, National Institute of Environmental Health Sciences
Dr. Christopher Portier, National Institute of Environmental Health Sciences
Dr. Mary Wolfe, National Institute of Environmental Health Science

Sally Fields, National Institute of Environmental Health Sciences
Shawn Jeter, National Institute of Environmental Health Sciences
Anna Lee Sabella, National Institute of Environmental Health Sciences

Public

Paul Ackerman, Piper Rudnick, LLP
Nancy Beck, OMB
Angus Crane, NAIMA
Sanford Garner, Constella Group
John Hadley, Owens Corning
Cheryl Hogue, Chemical & Engineering News
Pat Phibbs, BNA
Robert Putnam, CITE
Jennifer Sass, NRDC
Kyle Steenland, Emory
Sara Vel, The Rose Sheet
Terry Yoshizumi, Duke University

The National Toxicology Program (NTP) Board of Scientific Counselors Report on Carcinogens (RoC) Subcommittee ("the RoC Subcommittee") held its eighth meeting on October 14, 2003, at the Marriott at Metro Center, 775 12th Street NW, Washington, DC (see Attachments 1-3 for *Federal Register* meeting announcement, agenda and roster, respectively). Members of the RoC Subcommittee present were: Drs. John Froines (Chairperson), Aaron Blair, Hillary Carpenter, Gail Charnley, Harvey Checkoway, Elizabeth Delzell, Howard Frumkin, Iva Hertz-Picciotto, Maria Morandi, Barbara Pence, James Popp, Stephen Roberts, and Allan Smith. Also attending was Dr. David Phillips, a non-voting expert consultant to the RoC Subcommittee. Members not present were Drs. George Bonney and Margaret Karagas. Dr. Froines noted that this was the last meeting for Dr. Phillips, Dr. Smith, and himself.

I. Introduction and Background

Dr. Christopher Portier, Director, Environmental Toxicology Program (ETP) of the National Institute of Environmental Health Sciences (NIEHS) and Associate Director of the NTP, welcomed the RoC Subcommittee members, representatives from the National Center for Toxicological Research of the Food and Drug Administration and from the National Institute for Occupational Safety and Health of the Centers for Disease Control and Prevention, and members of the public in attendance on behalf of Dr. Kenneth Olden, Director of the NIEHS and the NTP. He said the seven nominations to be reviewed were the final group proposed for possible inclusion in the 11th Report on Carcinogens (the 11th RoC). Dr. Portier reviewed topics discussed with the NTP Board of Scientific Counselors at its meeting on September 10-11, 2003. He noted that the NTP is going through a year-long process evaluating its key activities and determining how best to utilize new molecular and computer technologies in its research and testing program to move the program forward over the next 5 to 10 years. He also said the NTP has been examining the use of transgenic animals in cancer hazard identification. This effort has involved the Board, the Technical Reports Review Subcommittee of the Board, industry, academia, the public and the NTP's federal partners. Dr. Portier concluded by reporting that Dr. Olden announced that he would step down as Director of both NIEHS and NTP after a replacement is found, but will continue his research program at the NIEHS. Dr. Portier presented certificates of appreciation to Drs. Froines, Smith and Phillips.

Dr. Froines went over the format for reviewing the nominations. First, an NIEHS/NTP scientist gives an overview for each nomination, including the data related to human cancer, animal cancer, and mechanistic information. The NIEHS/NTP scientist also provides the recommendations and votes of the two Federal scientific review committees: the NIEHS Review

Group for the RoC (RG1) and the NTP Executive Committee Interagency Working Group for the RoC (RG2). Next, persons or groups who submitted written comments prior to the meeting will be identified (copies of all written comments received were distributed to the RoC Subcommittee prior to the meeting and posted on the NTP web site). Next, members of the public who requested time will make oral comments followed by an opportunity for questions from the RoC Subcommittee members. RoC Subcommittee members assigned as primary reviewers for a nomination will next present their remarks and this will be followed by discussion among all RoC Subcommittee members. Finally, the Chair would call for a motion on the recommendation on the nomination for listing in the 11th RoC and the Subcommittee will vote on the recommendation by a show of hands in favor, against, or abstention. Persons voting no or abstaining will asked to state the reason. The Subcommittee's recommendation will be forwarded to the NTP. Dr. Froines reported that Dr. Charnley has a potential conflict of interest with regard to lead and lead compounds and would not participate in the discussion or vote on the nomination.

II. Peer Review of Nominations for Listing in the 11th Report on Carcinogens

X-Radiation and Gamma Radiation

Neutrons

Dr. C.W. Jameson, NIEHS, said the two separate nominations X-radiation & gamma radiation, and neutrons would be presented together because much of the data for these forms of ionizing radiations overlap. The RoC Subcommittee was instructed previously to provide a separate

recommendation on each nomination. The NIEHS nominated X-radiation & gamma radiation, and neutrons for listing in the 11th RoC based on the recent International Agency for Research on Cancer (IARC) classification of these agents as carcinogenic to humans (Group 1). X-rays and gamma rays are composed of high-energy photons, while neutrons are made-up of electrically neutral particles. X-rays have an energy range of 5 keV to 100 keV. Gamma rays have an energy range of 10 keV to 30 meV, are produced by nuclear transformation, and often accompany the emission of alpha or beta particles from a nucleus. Gamma rays are much more penetrating of tissue than X-rays. Neutrons interact with atomic nuclei generating a dense ion path, causing more damage to tissue than a similar dose of X-rays or gamma rays. Dr. Jameson reported that environmental human exposures are primarily from terrestrial sources, nuclear accidents, and nuclear power generation with exposure to neutrons also occurring from cosmic sources. Occupationally, more than five million workers are exposed to ionizing radiation in underground mining, medical facilities, the nuclear industry, and the airline industry. Exposure also occurs during medical diagnostic and therapeutic procedures with the latter usually providing higher exposures. The database for human studies provides sufficient evidence of a strong association for gamma and X-irradiation with leukemia and tumors of the thyroid gland, breast, and lung. The evidence for associations with tumors of the salivary gland, stomach, colon, bladder, ovary, central nervous system, and skin is weaker. The available epidemiology data are not adequate for an evaluation of the carcinogenicity of neutrons in humans.

X-rays, gamma rays, and neutrons have been shown in animal studies to be carcinogenic in all species tested and cause a wide variety of tumors, including those identified in human epidemiology studies: mammary gland, thyroid gland, and leukemia. With regard to *in vivo*

genotoxicity in humans, X-rays and gamma rays have effects on somatic cells, causing chromosomal aberrations (CAs) and gene mutations; however, the data are unclear for germ cells. Data from *in vitro* studies show that X- and gamma radiation cause mutations, CAs, micronuclei, and DNA strand breaks. The data for neutrons are similar, although the genetic damage caused by neutron radiation is qualitatively similar to that caused by X-radiation and gamma radiation, it differs quantitatively. In general, neutron radiation induces chromosomal aberrations, mutations, and DNA damage more efficiently than does X- and gamma radiation; DNA lesions caused by neutron radiation are more severe and repaired less efficiently; and neutron radiation induces higher proportions of complex chromosomal aberrations. Several mechanisms of action are proposed. One proposed mechanism for ionizing radiation is the direct induction of DNA damage, which results in single- and double-strand chromosomal breaks. Epigenetic mechanisms are also proposed.

Dr. Jameson said the RG1 (7 votes) and the RG2 (8 votes) voted unanimously to recommend that X-rays and gamma rays be listed in the 11th RoC as *known to be human carcinogens*, and that neutrons also be listed as *known to be human carcinogens.*

Dr. Terry Yoshizumi, a clinical metals physicist from Duke University Medical Center, who assisted in preparing the background document, discussed radiation dosimetry. Specifically, Dr. Yoshizumi focused on quantities and units, including dose equivalents and effective dose. He said exposure to X-rays and gamma radiation is defined as the number of ionizations in air. This definition of exposure does not apply to neutrons. Dr. Yoshizumi also addressed the issue of tissue weighting factors.

Public Comment

No written comments were received for this meeting and no oral comments were made.

Primary Reviews: X-Radiation and Gamma Radiation

Dr. Checkoway, a primary reviewer, agreed with the proposed listing of *known to be human carcinogens*. He said there is a vast literature documenting unambiguously the carcinogenic effects of both X- and gamma radiation in humans and animals. These forms of radiation have been investigated extensively in human epidemiological studies, perhaps to a greater extent than any other environmental factor. He said excessive risks have been detected consistently for numerous cancer sites.

Dr. Blair, another primary reviewer, agreed with the proposed listing. He noted that the recommendation for listing in the RoC as *known human carcinogens* is supported by evidence of an increased risk for several cancers from exposure to these forms of radiation in both epidemiological and experimental studies. Radiation causes genetic damage in humans and animals, and IARC lists it as a human carcinogen.

Dr. Morandi, also a primary reviewer, agreed with the proposed listing. She noted that more is known about the mechanisms and effects of radiation than probably any other physical agent.

Discussion: The RoC Subcommittee did not have additional discussion on the nomination. Dr. Checkoway moved that X-radiation and gamma radiation be recommended for listing in the 11th

RoC as *known to be human carcinogens* based on sufficient evidence in humans. Dr. Morandi seconded the motion. The motion was accepted unanimously with 11 yes votes.

Primary Reviews: Neutrons

Dr. Roberts, a primary reviewer, agreed with the proposed listing of neutrons as a *known human carcinogen*, although he had some reservation because of the lack of clinical or epidemiological data on the carcinogenic effects of neutrons. He said the general population, as well as specific groups such as airline crews, are exposed primarily through cosmic radiation. He added that neutrons and gamma radiation appear to produce similar effects on DNA and to share the same mode of action.

Dr. Phillips, a primary reviewer, also agreed with the proposed listing, but believed that the data justify the listing of neutrons as *reasonably anticipated to be a human* carcinogen. He suggested that the Subcommittee discuss whether it is justified to list neutrons as *known* since there are no epidemiological data, but there are sufficient data for agents thought to act by identical mechanisms.

Dr. Checkoway, also a primary reviewer, commented that he would classify neutrons as being *reasonably anticipated to be a human carcinogen.* However, he said he would not be against listing as *known* based on similarity of effects to X- and gamma radiation.

Discussion: Dr. Froines said he believes that finding an agent to be a *known human carcinogen* based on mechanistic considerations would not contravene the NTP's guidelines. Dr. Portier

agreed. Dr. Popp reasoned that *known* requires evidence from human studies, but by definition, a human study includes not only epidemiology or clinical studies, but also data derived from studies of tissues or cells from humans exposed to an agent. He argued that the data on genetic effects from humans exposed to neutrons are applicable. Dr. Smith said the known conversion of neutrons to gamma rays in tissues supports Dr. Popp's reasoning. Dr. Portier clarified that the Subcommittee should focus on the neutrons, not the gamma radiation caused by the neutrons, when determining whether to list as a *known* human carcinogen. He also reiterated that human evidence for the NTP does include studies of mechanisms in human cell lines. Dr. Roberts said the parallelism between X-, and gamma radiation and neutrons with regard to the animal and mechanistic data permits the move from *reasonably anticipated* to *known* without invoking production of gamma radiation in tissues by neutrons. Dr. Hertz-Picciotto asked where in the background document is the information Dr. Popp used to support his argument. Dr. Portier responded that beneath the box containing the official listing criteria, there is a paragraph that defines relevant information, which might be considered in assessing whether or not an agent could be considered a human carcinogen. Dr. Checkoway said the information for Hiroshima and Nagasaki provides support for the case that neutrons are probably human carcinogens, but it is not definitive because of the mixture issue.

Dr. Roberts moved that neutrons be recommended for listing in the 11th RoC as *known to be human carcinogens* based on studies of their mechanisms of carcinogenesis that demonstrates neutrons cause genetic damage in humans similar to that caused by X-radiation and gamma radiation, induce chromosomal aberrations in humans, and produce gamma radiation when they

interact with biological materials. Dr. Frumkin seconded the motion, which was accepted unanimously with 11 yes votes.

Lead and Lead Compounds

Dr. C. W. Jameson, NIEHS, presented the nomination and said the NIEHS nominated lead and lead compounds for possible listing in the 11th RoC based on 1) the IARC identification of lead and inorganic lead compounds as possibly carcinogenic to humans, and 2) subsequent publications of human and animal studies on the carcinogenicity of lead and lead compounds. Dr. Jameson described the physical and chemical properties of lead. Elemental lead is a malleable metal and is insoluble in water. Lead compounds are usually in either +2 or +4 valence states. Lead metal is refined from ores; however, the major source of metallic lead in the United States is from the recycling of lead products. The largest use of metallic lead is in storage batteries, while primary uses of lead compounds are in paints, glass, and ceramics. Dr. Jameson reported that several million workers are potentially exposed in the workplace. Workers with frequent high levels of exposure are those involved in battery production and recycling, foundry, smelter and refinery workers, and those who work in the production of leaded glass. Environmentally, lead is found in the earth's crust, air, water, and soil. Dr. Jameson demonstrated graphically from the NHANES II study, the sharp decline in blood lead levels in the United States during the period of 1976-80 when lead was removed as a gasoline additive. A recent NHANES study demonstrated average human blood lead levels of around 2 μg/deciliter.

Dr. Jameson stated that IARC has conducted three assessments of the human cancer literature. The most recent was completed in 1987 and found inorganic lead compounds to be a possible

human carcinogen, (IARC Group 2B). Since 1987, 17 case control and 17 cohort studies have been published, including information about workers with high and most frequent exposure, *i.e.,* battery and smelter workers. Two studies of an environmentally exposed cohort also have been published. The most consistent findings from the occupational studies are for an association of lead and lead compounds with lung cancer, followed by stomach cancer. Dr. Jameson described the findings from meta-analyses published in 1995 and 2000. The 1995 analysis examined case-control and cohort studies and reported significant increases in the relative risk for lung, stomach, and bladder cancer. The 2000 analysis, which focused on eight cohort studies in which high lead exposure was well documented, also found significant increases in relative risk for lung cancer, and stomach cancer. Dr. Jameson discussed the issue of dose-response, noting that the highest risk appears to be observed at the highest exposure levels, but no dose-response relationships have been reported. He addressed the role of confounding factors, especially smoking, since lung is a major cancer site in smokers. Dr. Jameson also noted the concurrent exposure in the workplace to arsenic, a known human carcinogen. Some studies controlled for smoking and still found an association with lung cancer.

Dr. Jameson next discussed studies of cancer in experimental animals. He reported that given by various routes in mice, lead acetate produced renal tumors, lead subacetate induced lung adenomas, and tetraethyl lead caused lymphoma. Lead acetate, subacetate, phosphate, and chromate caused renal tumors in rats, although some of these studies were only designed to investigate renal effects (*i.e.,* only kidney pathology was performed). Lead did not cause mutations in bacteria, and results from test systems using mammalian cells were conflicting. Positive findings of genotoxicity (chromosomal aberrations and DNA damage) were reported in

most mammalian and human *in vivo* studies. Human studies in smelters or battery workers were positive for chromosomal aberrations, sister chromatid exchanges, and micronuclei, although these studies were limited by small sample sizes and lacked information on selection criteria. Finally, Dr. Jameson noted that lead and lead compounds are absorbed through inhalation, ingestion and, to a lesser extent skin, and then distribute to blood plasma and soft tissues with redistribution to bone. Lead and lead compounds are neurotoxic, and cause developmental, reproductive and cardiovascular effects. In addition, genetic damage is probably induced by indirect mechanisms.

Dr. Jameson reported that RG1 voted unanimously (8 yes votes) to recommend that lead and lead compounds be listed in the 11th RoC as *known to be human carcinogens*. The RG2 voted by four yes votes to three no votes to recommend that lead and lead compounds be listed as *reasonably anticipated to be human carcinogens*, with the no voters supporting the *known* classification.

Public Comments: No oral comments were made. Written public comments were received from or on behalf of

- Battery Council International
- Color Pigments Manufacturers Association, Inc.
- Combe, Inc.
- Environmental Defense
- Ethyl Corporation
- International Lead Zinc Research Organization, Inc.
- Lynn H. Ehrke

Discussion: Dr. Froines said tetraethyl lead (TEL) is still being used in gasoline fuel for small aircraft and asked whether the size distribution of lead aerosols, (e.g., fume vs. dust) has been examined with regard to type of cancer found. Dr. Portier introduced Dr. Kyle Steenland, Emory University a consultant to the NTP who helped prepare the epidemiology section of the background document. Dr. Steenland was available to answer questions about the document.

Primary Reviews: Dr. Smith, a primary reviewer, agreed with the proposed listing of lead and lead compounds as *reasonably anticipated to be human carcinogens* based on a lack of conclusive evidence from the epidemiological studies. He thought the majority of the studies relating lead to lung cancer were flawed, due to confounding by exposure to arsenic, and/or other occupational lung carcinogens including nickel, chromium, radon and asbestos. Dr. Smith agreed with the statement on p.69 in the Background Document that "evidence from the totality of epidemiologic studies is consistent with a mild elevation in risk of lung cancer with lead exposure."

Dr. Hertz-Picciotto, also a primary reviewer, said she could only support listing as *reasonably anticipated to be human* carcinogens because virtually all the epidemiological studies failed to control for confounding from smoking and/or occupational carcinogens. She said the major weakness with nearly all of the published papers is that the studies used cohort designs wherein the exposed group of workers is compared to the general population and virtually no information is available about lifestyle factors, in particular, smoking. Dr. Hertz-Picciotto ventured that perhaps more attention should have been given to an association with stomach cancer. Dr.

Froines commented from his experience looking at the size distribution of lead aerosols across a wide range of industries, that workers are exposed mostly to large particles, which are likely to be swallowed.

Dr. Roberts, also a primary reviewer, said the studies in laboratory animals show tumorigenicity from lead compounds in multiple species and sites, which constitutes sufficient evidence in animals, and supports a classification of *reasonably anticipated to be human carcinogens.*

Dr. Delzell, also a primary reviewer, agreed with the proposed listing of lead and lead compounds as *reasonably anticipated to be human carcinogens.* She found the epidemiological data on lung cancer unconvincing because of confounding factors, and added that the data for stomach cancer are simply too sparse to be convincing. She asked for comment from the RoC Subcommittee on the toxicology studies that indicate lead acetate, subacetate, and phosphate are carcinogenic in rodents, and on their relevance to humans.

Dr. Morandi, also a primary reviewer, stated that the animal data suggest that some lead compounds are certainly carcinogenic, but the occupational data lack information on the speciation of exposure. Further, she added that the compliance monitoring in the occupational setting would be monitoring elemental lead, which she did not think is carcinogenic. With regard to the proposed listing, she said there should be careful wording clarifying that there are significant limitations in both the human and animal studies but the evidence to date is weighted toward protecting public health.

Discussion: Dr. Blair noted that in epidemiology studies, the relative risks are not high and there is no clear response related to exposure. He said arsenic is a major confounding problem and asked whether there is evidence of bladder cancer in any of the cohorts. Dr. Smith responded that bladder cancer is minimally increased in the occupational cohorts exposed to arsenic by inhalation, but in drinking water studies there is a remarkably increased risk for bladder cancer. Dr. Froines asked for more discussion on the animal toxicology studies, which would be the basis for listing as *reasonably anticipated.* Dr. Popp said the data in animals for carcinogenicity to the kidney are well established. With regard to hazard identification, Dr. Phillips stated that although the magnitude of the effects is weak, the strength of the association is strong. Dr. Pence said she was struck by the lack of genotoxicity. Questions were raised about the high background levels of lung adenomas in the rodent studies. Dr. Froines asked about the similarity between the animal evidence presented and that used to support the earlier listing of lead acetate and lead phosphate in the RoC as being *reasonably anticipated to be a human carcinogen.* Dr. John Bucher, NIEHS, said the study by Waalkes *et. al.* (*Cancer Research* 55: 5265-5271, 1995), where mice were exposed to lead acetate transplacentally and then during lactation, resulted in increased incidences of renal tubular tumors in the offspring. The RoC Subcommittee discussed what form of lead, the ionic or a salt form, gets into the kidney. Dr. Popp noted that there is no pharmacokinetic data. Dr. Froines said workers in battery plants and secondary smelters are exposed to lead oxides with long term exposure producing severe kidney toxicity.

Dr. Kyle Steenland, Emory University, said he is a consultant to the NTP involved in summarizing the epidemiological data discussed in the background document. He said the evidence constitutes limited evidence of carcinogenicity in humans and, in his opinion, fits a

listing of *reasonably anticipated to be human carcinogens*. Dr. Steenland discussed the occupational studies and the two cancers of interest, lung and stomach. The relative risk for lung cancer is 1.2, which is within the range of what might be expected from smoking. The relative risk for stomach cancer is lower, but still worrisome. Dr. Smith thought that factors associated with socioeconomic status might play a role in stomach cancer. Dr. Steenland concluded by discussing the general population studies. Dr. Smith commented that he thought lead could cause kidney cancer based on animal studies and circulation of lead through the organ. Dr. Steenland agreed, but his group's finding of kidney cancer in one occupational study appears to have been an isolated finding.

Dr. Portier explained that a motion for listing lead and lead compounds would include all lead compounds, including the two currently listed in the RoC, lead acetate and lead phosphate. If the current nomination is approved for inclusion in the 11th RoC, these two compounds would be subsumed into the current listing. Dr. Smith moved that lead and lead compounds be recommended for listing in the 11th RoC as *reasonably anticipated to be human carcinogens* based on limited evidence in humans and sufficient evidence in animals. Dr. Carpenter seconded the motion, which was unanimously accepted with 11 yes votes. Dr. Charnley did not participate in the discussion and vote due to a conflict of interest.

Hepatitis B Virus

Dr. Ruth Lunn, NIEHS, presented the nomination. She said the NIEHS nominated hepatitis B virus (HBV) for listing in the 11th RoC based on overwhelming evidence of a causal association between chronic HBV infection and an increased risk of hepatocellular carcinoma in humans.

HBV is a member of the hepadnaviridae family of viruses, the orthohepadnavirus subgroup, which infects mammals and primarily infects and reproduces in hepatocytes and bile duct cells. Dr. Lunn reported that HBV is a double stranded DNA virus and described the known functions of the component proteins. An important biomarker of chronic infection is the serum levels of HB surface antigen (HbsAg). The incidence of HBV infection has been declining mainly due to a decline among IV drug users and homosexual men and due to the implementation of a vaccine against HBV. The cancer of interest in humans is hepatocellular carcinoma. Hepatocellular carcinoma has a strong male predominance and is increasing in incidence in the United States. Other risk factors for liver cancer include alcohol abuse, hormones, exposure to aflatoxin, and hepatitis C virus (HCV). In most of the epidemiological studies, chronic HBV infection is a risk factor with a biomarker being the HbsAg. In 1994, IARC evaluated the carcinogenicity of HBV in 15 cohort studies and numerous case control studies; all studies reported a strong association even after controlling for potential risk factors. No association for cancer at other sites was found. IARC classified HBV as carcinogenic to humans (Group 1). Dr. Lunn said numerous studies reporting a strong association with liver cancer were published after the IARC review. Donato *et al.* included some of these studies in a meta-analysis that assessed the combination of the effects of HBV and hepatitis C virus (HCV). The summary odds ratio (OR) for HbsAg was 13.7 (confidence intervals of 2.2 to 15.4). People positive for one virus, but negative for the other, had ORs in the 20s, and people positive for both viruses had a much higher OR (135). Dr. Lunn discussed geographical considerations of HBV and HBC. In high-risk areas for hepatocellular carcinoma of the world, HBV is associated with 80% of the cases of hepatocellular carcinoma. In low to intermediate risk areas, such as the United States, HBV is associated with only 25% of cases of hepatocellular carcinoma. HCV is responsible for a larger

percentage of hepatocellular carcinoma than in low and intermediate risk areas.

Dr. Lunn reported that there are few animal studies of HBV because great apes, gibbons and tree shrews are the only animals that can be infected. The results in transgenic mice are conflicting and there is no evidence for the virus causing liver cancer in primates. Studies have shown that chronic infection of other hepadnaviruses, such as ground squirrel and woodchuck hepatitis viruses, cause liver cancer in their natural host species. In terms of the pathogenesis of HBV infection, cell lysis is caused by the immune response to infected hepatocytes. Infections may be transient, acute, or chronic depending on the ability of the immune system to clear hepatocytes. Dr. Lunn emphasized that where HBV is endemic, a major route of infection is maternal to neonatal transmission, and 90% of babies infected *in utero* become chronic carriers, which leads to the high levels of liver cancer in these areas. Dr. Lunn said most of the studies investigating the potential mechanisms of carcinogenesis by HBV show that the virus integrates into random sites in the host's DNA by nonhomologous recombination. This results in several types of alteration of which the most important may be a loss of tumor suppressor activity. The tumor latency in humans is about 30 years. Dr. Lunn concluded by discussing the possible role of the host immune system in the carcinogenesis process.

Dr. Lunn reported that the RG1 (4 votes) and the RG2 (8 votes) voted unanimously to recommend that hepatitis B virus be listed in the 11th RoC as *known to be a human carcinogen.*

Public Comment: No written comments were received and no oral comments were made.

Primary Reviews: Dr. Frumkin, a primary reviewer, agreed with the proposed listing of HBV based on 1) meeting the criteria of a significant exposure with hundreds of millions of people infected globally and at least a million in the United States, and 2) the availability of sufficient evidence of carcinogenicity from studies in humans, which indicates very strong and consistent relationship between exposure to the agent and human liver cancer.

Dr. Carpenter, also a primary reviewer, agreed with the proposed listing as *known to be a human carcinogen.*

Dr. Blair, also a primary reviewer, agreed with the proposed listing as *known to be a human carcinogen.* He felt the listing is supported by clear evidence of a large increased risk for hepatocellular cancer in individuals infected with HBV in many populations.

Dr. Popp, also a primary reviewer, agreed with the proposed listing as *known to be a human carcinogen.*

Discussion: As a prelude to the upcoming review of hepatitis C virus, Dr. Smith said he was unconvinced of the synergy between the two viruses reported in the meta-analysis of Donato *et al (1998).* He argued that this synergy may have been related to the control populations used since synergy was only found in studies that used community control groups and not in studies that utilized hospital controls. Dr. Smith said the community control groups likely do not represent the general population since blood donors are included. Dr. Hertz-Picciotto said the definition of synergy in the background document is incorrect where it states that synergistic

effects are greater than multiplicative effects. She noted that the standard definition of synergistic effects are greater than additive effects but could be less than multiplicative.

Dr. Frumkin moved that hepatitis B virus (HBV) be recommended for listing in the 11th RoC as *known to be a human carcinogen* based on sufficient evidence in humans. Dr. Carpenter seconded the motion, which was accepted unanimously with 12 yes votes.

Hepatitis C Virus

Dr. Lunn presented the nomination and said hepatitis C virus (HCV) is an RNA virus that causes hepatitis. The NIEHS nominated HCV for listing in the 11th RoC based on the IARC classification of HCV as carcinogenic to humans (Group 1) supported by a finding of sufficient evidence of carcinogenicity in humans (hepatocellular carcinoma). The presence of HCV can be detected by measuring HCV antibodies using immunoassays, although viral RNA can be detected by PCR-based assays. Dr. Lunn reported that screening for HCV in blood banks began in the early1980s; since that time the risk of transmission has decreased from about 1 per 200 units to less than 1 per 1,000,000 units. The prevalence of HCV infection among blood donors varies widely geographically. In areas of low infection, which includes the United States, the incidence of HCV has decreased in the last decade from 180,000 to 30,000 cases. The NHANES study determined the prevalence of HCV to be 1.8%, which extrapolates to 3.9 million people in the United States; approximately 2.7 million people in the United States are estimated to be chronically infected. Prevalence of HCV is very low among individuals under 20 and above 50 years old with a peak in prevalence around age 40. The CDC estimates the major risk factor to be illicit drug use. HCV causes acute hepatitis, which in most individuals is asymptomatic and is

characterized by alternating alanine transaminase (ALT) levels. About 75-80% of adults cannot clear the virus and become chronic carriers. The chronic form of HCV can progress to end-stage liver disease, cirrhosis, and cancer after a long latency of 21 to 28 years.

Dr. Lunn discussed the 1994 IARC review which included two cohort and over 20 case-control studies that showed strong evidence of an association with liver cancer among anti-HCV positive individuals. After the IARC evaluation was completed, an additional 26 case-control and eight prospective studies were published. The Donato *et. al* meta-analysis, which she discussed in the HBV review, included HCV. The summary odds ratio for HCV was 11.5. Of the other studies not included in the meta-analysis, nearly all reported elevated risks for HCV-infected individuals. One study reported that alcohol use enhances the carcinogenic effects of HCV. Dr. Lunn mentioned that HCV has six major genotypes, and all six genotypes are associated with liver cancer although 1b appears to be the most strongly associated. HCV is also potentially associated with B-cell lymphoma. Of eight case-control studies and one cohort study, all but one reported an association between B-cell lymphoma and HCV exposure. Dr. Lunn reported that there are a limited number of studies in experimental animals due to the narrow host range (i.e. only a few species are affected). One chimpanzee infected with HCV developed liver cancer. Studies in transgenic mice showed that some lines of mice expressing the HCV core protein or the complete viral polyprotein developed hepatocellular carcinomas. Dr. Lunn said a direct mechanism postulated for HCV causing hepatocarcinogenesis involves the core protein and its activity in transcriptional regulation of cellular promoters and proto-oncogenes. An indirect mechanism may be related to cirrhosis sincet most cases of liver cancer develop in patients with

cirrhosis, and HCV cirrhosis is usually associated with inflammation, fibrosis, and hepatocellular regeneration.

Dr. Lunn reported that RG1 (7 votes) and RG2 (8 votes) voted unanimously to recommend that hepatitis C virus (HCV) be listed in the 11th RoC as *known to be a human carcinogen.*

Public Comment: No public written comments were received and no oral comments were made.

Primary Reviews: Dr. Frumkin, a primary reviewer, agreed with the proposed listing based on the strong association of HCV with hepatocellular carcinoma in humans. He thought the evidence for a possible association of HCV with B-cell lymphoma was equivocal.

Dr. Smith, also a primary reviewer, agreed with the proposed listing based on the widespread human exposure and the overwhelming evidence that HCV is a cause of human hepatocellular carcinoma. As with the HBV review, he disagreed with the conclusion from the meta-analysis that there is a synergistic effect between HBV and HCV, and suggested that these statements be removed from the document.

Dr. Pence, also a primary reviewer, agreed with the proposed listing based on the extensive human exposure and the sufficient evidence in humans for the carcinogenicity of chronic infection with HCV.

Dr. Frumkin moved that hepatitis C virus (HCV) be recommended for listing in the 11th RoC as *known to be a human carcinogen* based on sufficient evidence in humans. Dr. Pence seconded the motion, which was accepted unanimously with 12 votes.

Human Papillomaviruses (HPV): Genital-Mucosal Types

Dr. Lunn presented the nomination and said the NIEHS nominated human papillomaviruses (HPVs) of the genital-mucosal types based on the IARC evaluation. HPVs are non-envelope DNA viruses and members of the papillomaviridae family of viruses. They infect skin and mucous membranes in humans and animals and often cause benign and malignant tumors. HPVs are species specific. She said over 100 HPVs have been identified to date; however, this review is restricted to genital-mucosal types of which there are about 40 that cause genital warts and cervical abnormalities. The literature refers to high-risk and low-risk types. The distinction between the two types is that high-risk types are associated with cervical cancer and low-risk types are associated with warts or low-grade cervical abnormalities. The background document identifies 13 high-risk viruses; however, now the number of high risk viruses is expanding. HPVs are small non-envelope viruses that contain about 8,000 base pairs of double stranded DNA and c-DNA. The c-DNA consists of eight early genes coding for proteins involved in transcription and replication and two late genes coding for structural proteins produced late in the infection cycle. Dr. Lunn said the most sensitive method for detecting HPV infections is to identify its DNA. Other ways to detect infection include visual signs of warts especially flat warts, and viewing cervical cells under a microscope (pap smear).

Dr. Lunn discussed the descriptive epidemiology of HPV infections, noting HPVs are one of the most common sexually transmitted viruses and are transmitted through contact with infected cervical, vaginal, vulvar, penile, and anal epithelium. About 20 million people are infected in the United States with the highest prevalence in young, sexually active populations, with HPV 16 being the most common type. There are 5.5 million new cases of HPV infection each year. Dr. Lunn described the common pathologic terminology for HPV-associated cervical lesions. She showed a diagram of the natural history of HPV infection and the progression of cervical intraepithelial neoplasia (CIN) where about one-third of the most serious lesions (CIN III) lead to invasive cancer. Worldwide, there are over 500,000 cases of cervical cancer per year. In the United States, the incidence of HPV infection varies by ethnic group with the highest rates found in African-Americans. Deaths from cervical cancer in the United States decreased 74% between 1955 and 1992 mainly as a result of screening programs using the Pap smear. In 1995, IARC evaluated HPVs and concluded that HPV 16 and HPV 18 are carcinogenic to humans (Group 1). Evidence suggested that HPV 18 is limited to the cervix, while HPV 16 causes other anogenital cancers. IARC considered HPVs 31 and 33 as probably carcinogenic to humans (Group 2A). Most other types of HPVs (not specified) were classified as possibly carcinogenic to humans (Group 2B). Dr. Lunn reported that since 1995, many epidemiological studies, both case-control and cohort studies, have primarily focused on cervical cancer. Included in this group are 13 case-control studies initiated by IARC in various geographical locations to study the effects of other HPV types and the role of cofactors. The case-control studies and a meta-analysis reported very high odds ratios for cancer for HPVs 16 and 18 and strong associations for eight additional viruses. Also, HPV 16 was associated with vulvar and vaginal cancers with a somewhat weaker association with penile and anal cancers. Many studies of head and neck cancers have suggested

that HPV may have a role in their etiology with the strongest evidence supporting oropharyngeal-related tumors. Finally, a recent study found that 99.7% of all cervical cancers contained detectible HPV.

Dr. Lunn said there are little data on HPV from studies in experimental animals since HPV does not infect them. Animal papillomaviruses do cause cancer in their natural host species. Studies in transgenic mice show that these mice express an HPV gene that causes cancer. With regard to mechanistic studies, HPV can integrate into host DNA and immortalize and transform cells with E6 and E7 proteins playing the largest roles.

Dr. Lunn reported that the RG1 (4 votes) and the RG2 (8 votes) voted unanimously to recommend that some human papillomaviruses (HPV), genital-mucosal types be listed in the 11th RoC as *known to be human carcinogens.*

Public Comment: The American Academy of Dermatology submitted written comments. No oral public comments were made.

Primary Reviews: Dr. Hertz-Picciotto, a primary reviewer, agreed with the proposed listing, but said the wording of the title needs to be changed to reflect the evidence that some HPVs are negative for human cancer. She was quite impressed with the data showing that chromosomal aberrations are observed in infected human cervical cancer cells involving nearly every human chromosome.

Dr. Charnley, also a primary reviewer, agreed with the proposed listing and noted that the exposure criteria were met and there was sufficient evidence for cancer in humans. The major discussion point had to do with classifying the nomination as "some HPV viruses...." as suggested by RG2, since there was weaker or negative evidence for some HPVs.

Dr. Delzell, also a primary reviewer, agreed with the proposed listing under the modification proposed by Dr. Charnley.

Discussion: Dr. Smith commented that the problem with adding "some" to the classification is a concern as to which virus types to omit, because in many cases, the infections are mixed. For example, there may be relative risks for one virus of 60, for another 40, and perhaps for another 70. Dr. Lunn agreed, noting that many patients may be infected with multiple viruses, and perhaps, the real risk factor is type-specific persistence. Dr. Smith said that using "some" is probably the best word, since at this time it is not possible to tease out which types are and are not associated with the cancers.

Dr. Hertz-Picciotto moved that some human papillomaviruses (HPV), genital-mucosal types be recommended for listing in the 11th RoC as *known to be human carcinogens* based on sufficient evidence in humans. Dr. Charnley seconded the motion, which was accepted unanimously with 12 yes votes.

Diazoaminobenzene

Dr. Jameson presented the nomination and said diazoaminobenzene (DAAB) is used as an intermediate in the manufacture of dyes and insecticides. The NIEHS nominated DAAB for possible listing in the 11th RoC based on NTP toxicity studies showing that it is metabolized to benzene, a known human carcinogen, and to aniline, an animal carcinogen. DAAB is used in the preparation of D&C Red No. 33, FD&C Yellow No. 5, and FD&C Yellow No. 6, which are dyes used in foods, drugs and cosmetics and can contain residues of DAAB. It is also used as a polymer additive and a growing agent for the production of foamed polymeric materials. Dr. Jameson said environmental exposures are through dermal or oral routes from residues in foods or cosmetics, while occupational exposure would be dermal or inhalation from the material's use as a chemical intermediate. With regard to human exposure, there is no production information specific to DAAB. He said that the FDA has allowable residue limits for DAAB in dyes used in foods, drugs and cosmetics. No human cancer studies have been reported. There are several oral, dermal and injection studies of cancer in mice published in the late 1940s. Skin and lung tumors were found in the dermal study; however, the studies were considered inadequate due to the small number of animals tested, there being no controls and questions about the identity of the chemical used in these studies. Dr. Jameson reported that DAAB is mutagenic in bacteria with metabolic activation, induces chromosomal aberrations in plants, and induces micronuclei in bone marrow cells of mice exposed *in vivo*.

Dr. Jameson said the NTP conducted metabolism and disposition studies by oral, dermal, and intravenous routes, as well as metabolism studies in human liver slices. Electron spin resonance (ESR) studies were done to investigate formation of the phenyl radical during DAAB

metabolism, and 16-day dermal toxicity studies were conducted in male and female F344/N rats and B6C3F1 mice. The chemical disposition studies were conducted using radiolabeled (^{14}C) DAAB. The chemical was rapidly absorbed from the gastrointestinal tract but poorly absorbed from the skin, and excretion was primarily in the urine. Twenty four hours after a 20 mg/kg oral dose to rats, less than one percent of the dose was retained in various tissues. Benzene metabolites, including phenol, hydroquinone glucoronide, muconic acid, and aniline metabolites were found in the blood of rats, and benzene and aniline metabolites were found in the urine of rats and mice. Also, benzene was detected in the breath of rats and mice. Dr. Jameson showed data on the cumulative excretion of radioactivity in rats and mice after intravenous, oral, and dermal administrations. The majority of the dose was excreted in urine with lesser amounts in the feces and breath. An *in vitro* study with human liver slices and radiolabeled DAAB showed that most of the DAAB remains in the media; about 1-2% is metabolized to aniline and two of its metabolites, as well as two benzene metabolites. ESR studies demonstrated that the 5,5-dimethyl-1-pyrroline-N-oxide -phenyl adduct is formed *in vivo* and *in vitro* and the coenzyme NADPH is required for formation of the radical. The radical was also formed in liver microsomes incubated with the P450 inhibitor, 1-aminobenzotriazole, in the presence of carbon monoxide. Dr. Jameson said these studies provide evidence that DAAB is reductively cleaved by hepatic enzymes to form phenyl radicals. He diagrammed a proposed pathway for metabolism that includes reductive cleavage by a P450 reductase in the gut flora to form the phenyl diazenyl radical and aniline, and the radical is further metabolized to benzene. He concluded by describing 16-day dermal DAAB toxicity studies in rats and mice in which both species metabolized DAAB to benzene and aniline. Erythrocytes and the lymphoid system were

the major targets of toxicity and the toxicity was similar to that expected from exposure to benzene and aniline combined.

Dr. Jameson reported that the RG1 voted unanimously (5 yes votes) and the RG2 voted 8 yes votes to 1 no vote to recommend that diazoaminobenzene (DAAB) be listed in the 11th RoC as *reasonably anticipated to be a human carcinogen.* The negative vote by the RG2 was based on the member feeling that the data did not support listing DAAB in the report.

Public Comment: No public written public comments were received and no oral comments were made.

Primary Reviews: Dr. Popp, a primary reviewer, agreed with the proposed listing of DAAB as *reasonably anticipated to be a human carcinogen* based on very good data that DAAB is metabolized to benzene and aniline in animals and after incubation with human liver microsomes. Otherwise, the information on human exposure is very limited and there is no information on human carcinogenicity. The evidence in animals is similar. Many of the studies date from the 1940s, which creates some uncertainty about what material the animals were exposed to, and the studies included no control animals, so information about background tumor incidences is also lacking.

Dr. Carpenter, also a primary reviewer, agreed with the proposed listing as *reasonably anticipated to be a human carcinogen* and suggested that if benzene, a known human carcinogen,

is a metabolite in animals and in human liver tissue, there could be a rationale for listing DAAB as *known*.

Dr. Phillips, also a primary reviewer, agreed with the proposed listing of DAAB as *reasonably anticipated to be a human carcinogen* based on the data showing benzene to be a major metabolite and on data showing a range in potency of *in vivo* and *in vitro* genotoxicity that indicates it is potentially carcinogenic by a genotoxic mechanism.

Discussion: The RoC Subcommittee had some discussion about the use of data on carcinogenic metabolites in support of listing in the report. Dr. Froines observed that the RoC Subcommittee recommended listing vinyl fluoride and vinyl bromide as known human carcinogens primarily because of their close similarity to vinyl chloride. Dr. Portier commented that the practical consideration of listing DAAB is that the NTP will not devote resources to conducting a two-year bioassay. Dr. Smith noted that benzene itself is not the carcinogen, but rather the DAAB metabolites are the carcinogens. Dr. Froines added that there is a qualitative versus quantitative issue in that the amount of benzene formed *in vivo* and then further metabolized to carcinogenic metabolites may be quite small. Dr. Carpenter agreed. Dr. Hertz-Picciotto said the argument for listing based on the carcinogenic metabolites is compelling to her. Dr. Popp cautioned about overemphasizing the metabolites, because the complete metabolic pathways for DAAB are not known. Dr. Smith opined that if DAAB was metabolized to benzene in humans, then he would support listing it as a human carcinogen. Dr. Froines agreed, but added that it is still a quantitative issue. Dr. Roberts stated that he would be uncomfortable in making an extrapolation in the absence of animal and human data based entirely on DAAB's metabolism to benzene and

its metabolites. Dr. Checkoway concurred with Dr. Roberts. Dr. Blair noted that the data indicate DAAB is metabolized almost exclusively to benzene, aniline and metabolites. Dr. Popp commented that the information on DAAB metabolism is sufficient to support the proposed listing for *reasonably anticipated*, but was concerned that data were lacking on the amount of benzene metabolites that are derived from the DAAB-derived benzene. He said this issue is important because it is still unknown which specific benzene metabolite(s) is carcinogenic. Dr. Phillips agreed that the active metabolite is unknown and it is not found in the urine. Dr. Smith suggested, that lacking biochemical information, perhaps the nomination should be deferred to enable filling the knowledge gaps. Dr. Morandi said she could take either the position that it is *reasonably anticipated* or the position that further studies need to be conducted before it is classifiable Dr. Roberts and Dr. Froines debated the potential interactive effects of aniline and other chemicals present in the body on the metabolism of benzene. Dr. Froines concluded that much of this discussion is speculative and not supported by the data presented. Dr. Popp said there are many documented cases of synergistic or antagonistic interactions among chemicals, although in the present case it is hypothetical. Dr. Hertz-Picciotto wondered whether human data might be developed that could support designating DAAB as a human carcinogen. Dr. Froines responded that at the exposure levels allowed by the FDA, it is unlikely that adequate epidemiological data could be obtained. Dr. Smith thought this nomination is similar to neutrons where there are few human data. Dr. Popp pointed out that with neutrons there are animal data in multiple species showing they are clearly carcinogenic. Dr. Pence asked whether there are data on how the metabolism of DAAB in human liver slices compares with that in liver slices from rats and mice. Dr. Bucher replied that he did not think this comparison has been made; however, the actual amount of benzene converted to benzene metabolites is small. Dr. Froines

concluded that the Subcommittee is not in a position to decide what an acceptable level of risk is and should avoid quantitative determinations, because they are not within the Subcommittee's purview.

Dr. Popp moved that diazoaminobenzene (DAAB) be recommended for listing in the 11th RoC as *reasonably anticipated to be a human carcinogen.* Dr. Morandi seconded the motion, which was accepted by 6 yes votes (Carpenter, Checkoway, Delzell, Hertz-Picciotto, Morandi, Popp) to 4 no votes (Blair, Charnley, Pence, Roberts) with 1 abstention (Smith). Dr. Frumkin was not present. Dr. Froines asked for reasons for the no votes and abstention. Dr. Pence said there was no way to really define exposure or determine to what extent the compound was metabolized to benzene in humans. Dr. Roberts did not think the body of information sufficiently demonstrated that the carcinogenic effects of DAAB is due to its metabolism to benzene, especially in the absence of animal or human data. Dr. Blair thought there was clear evidence that metabolism to benzene occurs in rodents and in human cells; therefore, DAAB should be listed as a known human carcinogen. Dr. Charnley thought the strength of evidence both for exposure and carcinogenicity was weak. Dr. Smith said he abstained because there is insufficient information about the extent of the metabolism of DAAB to benzene.

Dr. Bucher commented that the discussion on DAAB was fascinating because it dealt with a chemical that has almost no human exposure, although exposure might occur in the future. He said alternative animal assays will be used increasingly as the NTP moves into the future and this type of discussion will be much more common.

Dr. Jameson thanked the Subcommittee members for their hard work, thorough discussion, and their time and effort devoted toward reviewing the nominations. Dr. Portier concurred and also thanked colleagues from the other federal agencies in attendance, his staff, and the Report on Carcinogens group for their efforts in making this a successful meeting.

Dr. Froines adjourned the meeting.

Prepared by Dr. Larry Hart and Dr. Mary S. Wolfe

February 17, 2004

notify the Contact Person listed below in advance of the meeting.

Name of Committee: Center for Scientific Review Advisory Committee, Workgroup.

Date: September 22–23, 2003.

Time: 8:30 a.m. to 1 p.m.

Agenda: Discussion of activities to evaluate organization and function of the Center for Scientific Review process.

Place: National Institutes of Health, 6701 Rockledge Drive, Conference Room 6087, Bethesda, MD 20892.

Contact Person: Brent B. Stanfield, PhD, Deputy Director, Center for Scientific Review, National Institutes of Health, 6701 Rockledge Drive, Room 3016, MSC 7776, Bethesda, MD 20892, (301) 435–1114.

Information is also available on the Institute's/Center's home page: *http://www.csr.nih.gov/drgac/drgac.htm*, where an agenda and any additional information for the meeting will be posted when available.

(Catalogue of Federal Domestic Assistance Program Nos. 93.306, Comparative Medicine; 93.333, Clinical Research, 93.306, 93.333, 93.337, 93.393–93.396, 93.837–93.844, 93.846–93.878, 93.892, 93.893, National Institutes of Health, HHS)

Dated: August 4, 2003.

LaVerne Y. Stringfield,

Director, Office of Federal Advisory Committee Policy.

[FR Doc. 03–20294 Filed 8–7–03; 8:45 am]

BILLING CODE 4140–01–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Center for Scientific Review; Notice of Closed Meetings

Pursuant to section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. appendix 2), notice is hereby given of the following meetings.

The meetings will be closed to the public in accordance with the provisions set forth in sections 552b(c)(4) and 552b(c)(6), Title 5 U.S.C., as amended. The grant applications and the discussions could disclose confidential trade secrets or commercial property such as patentable material, and personal information concerning individuals associated with the grant applications, the disclosure of which would constitute a clearly unwarranted invasion of personal privacy.

Name of Committee: Center for Scientific Review Special Emphasis Panel, Prostate Cancer Immunotherapy.

Date: August 13, 2003.

Time: 3:30 p.m. to 4:30 p.m.

Agenda: To review and evaluate grant applications.

Place: National Institutes of Health, 6701 Rockledge Drive, Bethesda, MD 20892 (Telephone Conference Call).

Contact Person: Sharon K. Gubanich, PhD, Scientific Review Administrator, Center for Scientific Review, National Institutes of Health, 6701 Rockledge Drive, Room 4140, MSC 7804, Bethesda, MD 20892, (301) 435–1767.

This notice is being published less than 15 days prior to the meeting due to the timing limitations imposed by the review and funding cycle.

Name of Committee: Center for Scientific Review Special Emphasis Panel, Yeast Genetics.

Date: August 15, 2003.

Time: 2 p.m. to 5 p.m.

Agenda: To review and evaluate grant applications.

Place: National Institutes of Health, 6701 Rockledge Drive, Bethesda, MD 20892 (Telephone Conference Call).

Contact Person: Alexander D. Politis, PhD, Scientific Review Administrator, Center for Scientific Review, National Institutes of Health, 6701 Rockledge Drive, Room 3210, MSC 7848, Bethesda, MD 20892, (301) 435–1150, *politisa@mail.nih.gov.*

This notice is being published less than 15 days prior to the meeting due to the timing limitations imposed by the review and funding cycle.

(Catalogue of Federal Domestic Assistance Program Nos. 93.306, Comparative Medicine; 93.333, Clinical Research 93.306, 93.333, 93.337, 93.393–93.396, 93.837–93.844, 93.846–93.878, 93.892, 93.893, National Institutes of Health, HHS)

Dated: August 4, 2003.

LaVerne Y. Stringfield,

Director, Office of Federal Advisory Committee Policy.

[FR Doc. 03–20298 Filed 8–7–03; 8:45 am]

BILLING CODE 4140–01–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

National Toxicology Program; National Toxicology Program (NTP) Board of Scientific Counselors Meeting; Review of Nominations for Listing in the 11th Edition of the Report on Carcinogens

Pursuant to Public Law 92–463, notice is hereby given of the next meeting of the NTP Board of Scientific Counselors Report on Carcinogens Subcommittee ("the NTP RoC Subcommittee") to be held on October 14–15, 2003, at the Marriott at Metro Center, 775 12th Street, NW., Washington, DC 20005. On October 14, registration will begin at 9 a.m. and the meeting will begin at 9:30 a.m. On October 15, the meeting will begin at 8:30 a.m. Pre-registration is not required; however, persons requesting time to make oral public comments are asked to notify Dr. Mary S. Wolfe, NTP Executive Secretary, prior to the meeting (contact information given below). The agenda covers the peer review of seven nominations for possible listing in the 11th Edition of the Report on Carcinogens ("the 11th RoC"), and includes an opportunity for public input.

Agenda

The meeting of the NTP RoC Subcommittee is scheduled for October 14–15, 2003 and is open to the public with attendance limited to only the available space. Tentatively scheduled for peer review are seven nominations for possible listing in the 11th RoC. These nominations are listed alphabetically in the attached table, along with supporting information and a tentative order of presentation and review. Background documents for each of the nominations have been made available previously to the public on the web and include a summary of the scientific data and information being used to evaluate the nomination. A copy of the background document for each of these nominations is available electronically through the NTP's RoC web site for the 11th RoC at *http://ntp-server.niehs.nih.gov/Newhomeroc/11RoCBkgrnd.html* (select Nominations Under Review in 2003) or can be obtained on CD or in hard copy, as available, from: Dr. C.W. Jameson, Report on Carcinogens, NIEHS, MD EC–14, 79 T.W. Alexander Drive, Building 4401, Room 3118, P.O. Box 12233, Research Triangle Park, NC 27709 (919/541–4096; FAX 919/541–2242; email *jameson@niehs.nih.gov*).

The agenda and a roster of NTP RoC Subcommittee members will be available prior to the meeting on the NTP homepage at *http://ntp-server.niehs.nih.gov/* or upon request from Dr. Wolfe. Following the meeting, summary minutes will also be available electronically at *http://ntp-server.niehs.nih.gov/NewHomeRoc/mtgs.html* and in hardcopy upon request from Dr. Wolfe.

A total of 17 nominations are under consideration for the 11th RoC. Previous notices in the **Federal Register** (July 24, 2001: Volume 66, Number 142, Pages 38430–38432 and March 28, 2002: Volume 67, Number 60, Page 14957) announced the nominations to be reviewed for possible listing in the 11th RoC. This review by the NTP RoC Subcommittee is for the second set of seven nominations identified in those **Federal Register** announcements that have completed review by the NIEHS Review Committee for the Report on

Carcinogens (RG1) and the NTP Executive Committee Interagency Working Group for the Report on Carcinogens (RG2). The RoC Subcommittee reviewed the first 10 nominations to the 11th RoC at a public meeting on November 19–20, 2002, in Washington, DC. Summary minutes of that meeting are available electronically at *http://ntp-server.niehs.nih.gov/NewHomeRoc/mtgs.html* or in hardcopy upon request to the Executive Secretary (contact information below).

Solicitation of Public Comment

This meeting of the NTP RoC Subcommittee is open to the public, and time will be provided for oral public comment on each of the nominations under review. In order to facilitate planning, persons requesting time for an oral presentation on a nomination should notify the Executive Secretary, (Dr. Mary S. Wolfe, P.O. Box 12233, A3–07, Research Triangle Park, NC 27709; telephone 919/541–3971; FAX 919/541–0295; e-mail *wolfe@niehs.nih.gov*) no later than September 29, 2003. Each organization is allowed one time slot for an oral presentation per nomination. Persons registering to make comments are asked to provide, if possible, a written copy of their statement by September 29 so copies can be made and distributed to NTP RoC Subcommittee members for their timely review prior to the meeting. Written statements can supplement and expand the oral presentation, and each speaker is asked to provide his/her name, affiliation, mailing address, phone, fax, e-mail and supporting organization (if any). At least 7 minutes will be allotted to each speaker, and if time permits, may be extended to 10 minutes. Individuals who register to make oral presentations by September 29 will be notified about the time available for their presentation at least one week prior to the meeting. Registration for making public comments will also be available on-site. Time allowed for presentation by on-site registrants may be less than that for preregistered speakers and will be determined by the number of speakers who register at the meeting to give comments. If registering on-site to speak and reading oral comments from printed copy, the speaker is asked to bring 25 copies of the text. These copies will be distributed to the NTP RoC Subcommittee members and supplement the record. All comments received in response to this **Federal Register** notice will be posted on the NTP RoC web site.

Written comments, in lieu of making oral comments, are welcome. All comments must include name, affiliation, mailing address, phone, fax, e-mail and sponsoring organization (if any) and should be received by September 29, 2003, for distribution to the NTP RoC Subcommittee. Written comments received after September 29 will not be considered by NTP RoC Subcommittee members in their reviews.

Solicitation of Additional Information

The NTP would welcome receiving information from completed human or experimental animal cancer studies or studies of mechanism of cancer formation, as well as current production data, human exposure information, and use patterns for any of the nominations listed in this announcement. Organizations or individuals that wish to provide information should contact Dr. C.W. Jameson at the address given above.

Background

The Department of Health and Human Services (DHHS) Report on Carcinogens is a public information document prepared for the U.S. Congress by the National Toxicology Program (NTP) in response to Section 301(b)(4) of the Public Health Service Act, as amended. The intent of the document is to provide a listing of those agents, substances, mixtures or exposure circumstances that are either "known" or "reasonably anticipated" to cause cancer in humans and to which a significant number of people in the United States are exposed. The process for preparation of the RoC has three levels of scientific review. Central to the evaluations of the review groups is the use of criteria for inclusion in or removal of listings from the report. The current criteria for listing in or delisting from the Report is available on the Web at the following web site: *http://ntp-server.niehs.nih.gov/NewHomeRoc/ListingCriteria.html*, or can be obtained in hard copy by contacting Dr. C.W. Jameson at the address listed above. The review process for listing in or delisting from the RoC begins with initial scientific review by the National Institute of Environmental Health Sciences (NIEHS)/NTP Report on Carcinogens Review Committee (RG1), which is comprised of NIEHS/NTP staff scientists. The second scientific review group (RG2) is comprised of representatives from the Federal health research and regulatory agencies that are members of the NTP Executive Committee. The third step is external scientific review at a public meeting by the NTP RoC Subcommittee. Following completion of these reviews and solicitation of public comments through announcements in the **Federal Register** and other media, the independent recommendations of the three scientific review groups and all public comments are presented to the NTP Executive Committee for review and comment. All recommendations and public comments are submitted to the Director, NTP, who reviews them and makes a final recommendation to the Secretary, DHHS, concerning the listing or delisting of substances or exposure circumstances in the RoC. The Secretary has final review and approval authority for the 11th RoC.

Dated: July 30, 2003.

Samuel H. Wilson,

Deputy Director, National Institute of Environmental Health Sciences.

SUMMARY DATA FOR NOMINATIONS TENTATIVELY SCHEDULED FOR REVIEW AT THE MEETING OF THE NTP BOARD OF SCIENTIFIC COUNSELORS REPORT ON CARCINOGENS SUBCOMMITTEE

[October 14–15, 2003]

Nomination to be reviewed/ CAS number	Primary uses or exposures	To be reviewed for	Tentative review order
Diazoaminobenzene (DAAB)/136–35–6.	DAAB is used as an intermediate in the production of dyes, and as a complexing agent, polymer additive and to promote adhesion of natural rubber to steel.	Listing in the 11th RoC	6
Hepatitis B Virus (HBV)	HBV is a small DNA-enveloped virus that along with Hepatitis C Virus causes most parenterally transmitted viral hepatitis.	Listing in the 11th RoC	4
Hepatitis C Virus (HCV)	HCV is an RNA-enveloped virus that along with Hepatitis B Virus causes most parenterally transmitted viral hepatitis.	Listing in the 11th RoC	5

SUMMARY DATA FOR NOMINATIONS TENTATIVELY SCHEDULED FOR REVIEW AT THE MEETING OF THE NTP BOARD OF SCIENTIFIC COUNSELORS REPORT ON CARCINOGENS SUBCOMMITTEE—Continued

[October 14–15, 2003]

Nomination to be reviewed/ CAS number	Primary uses or exposures	To be reviewed for	Tentative review order
Human Papillomaviruses (HPVs), Genital-Mucosal Types.	HPVs are small, non-enveloped viruses that infect oral and genital mucosa. HPV infections are common throughout the world.	Listing in the 11th RoC	3
Lead and Lead Compounds	Major use of metal is in making lead-acid storage batteries. Other common uses include ammunition and cable covering. Lead compounds are used in paint, glass, ceramics, fuel additives, and some traditional cosmetics.	Listing in the 11th RoC	2
Neutrons	Exposure to neutrons normally occurs from a mixed irradiation field in which neutrons are a minor component. The exceptions are exposure of patients to neutron radiotherapy beams and exposures of aircraft passengers and crew.	Listing in the 11th RoC	*1
X-Radiation and GAMMA Radiation.	Exposure to these forms of ionizing radiation comes from a variety of natural (environmental exposure) and anthropogenic sources, including exposure for military, medical, and occupational purposes.	Listing in the 11th RoC	**1

*Note—will be reviewed together with X-Radiation and GAMMA Radiation nomination.
**Note—will be reviewed together with Neutrons nomination.

[FR Doc. 03–20299 Filed 8–7–03; 8:45 am]
BILLING CODE 4140–01–U

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Administration for Children and Families

Technical Assistance to ORR-Funded Refugee Programs and Services for Asylees

AGENCY: Office of Refugee Resettlement (ORR), ACF, DHHS.

ACTION: Notice of availability of FY 2003 discretionary funds for technical assistance in seven categories of programs that assist refugees and one grant for services for asylees.

CFDA Number: The Catalog of Federal Domestic Assistance number for this program is 93.576.

SUMMARY: ORR invites eligible entities to submit competitive applications for cooperative agreements to provide technical assistance to agencies that serve in the following first seven program areas. For Program Area 8, ORR invites eligible applicants to submit applications for a grant to provide services via a Multilingual Information, Referral, and Registration Hotline.

Program Area 1—Technical Assistance for refugee-based Mutual Aid Associations (MAAs), Voluntary Agencies assisting or working with refugee community organizations and other program areas that the Director of ORR may consider as appropriate response to emerging refugee resettlement needs;

Program Area 2—Technical Assistance for Employment Services;

Program Area 3—Technical Assistance for English Language Training and Service Programs;

Program Area 4—Technical Assistance for Refugee Economic Development Activities/Programs;

Program Area 5—Technical Assistance to Enhance Child Welfare Services for Refugee Communities;

Program Area 6—Technical Assistance to Promote Refugee Housing Opportunities;

Program Area 7—Technical Assistance for Crime Prevention Programs; and

Program Area 8—Services for Asylees to be provided via a Multilingual Information, Referral and Registration Hotline.

Applications will be screened and evaluated as indicated in this program announcement. Awards will be contingent on the outcome of the competition and the availability of funds.

Applications will be accepted pursuant to the ORR Director's discretionary authority under section 412(c) of the Immigration and Nationality Act (INA) (8 U.S.C. 1522), as amended.

DATES: The closing date for submission of applications is September 8, 2003. Applications received 30 days after the publication date are considered to be late. See Part IV of this announcement for more information on submitting applications.

Announcement Availability: The program announcement and the application materials are available from Mitiku Ashebir, Office of Refugee Resettlement (ORR), 370 L'Enfant Promenade, SW., 8th Fl., Washington, DC 20447 and from ORR Web site at *http://www.acf.hhs.gov/programs/orr.*

FOR FURTHER INFORMATION CONTACT: Mitiku Ashebir, Division of Community Resettlement (DCR), ORR, Administration for Children and Families (ACF), (202) 205–3602; fax (202) 401–0981; e-mail: *mashebir@acf.hhs.gov* or Daphne Weeden, Office of Grants Management (OGM), (ACF), (202) 401–4577; e-mail: *paqueries-OGM@acf.hhs.gov.*

Application Information: This program announcement consists of four parts:

Part I: Background—Legislative authority, funding availability, applicant eligibility, project and budget periods, length of application, and for each of the nine program areas: Purpose and scope, allowable activities, and review criteria.

Part II: General instructions for preparing a full project description.

Part III: The Review Process—Intergovernmental review, initial ACF screening and competitive review.

Part IV: Application Submission—Application materials, application development, application submission information, certifications, assurances and reporting.

Paperwork Reduction Act of 1995 (Pub. L. 104–13): The public reporting burden for this collection of information is estimated to average 8 hours per response, including the time for reviewing instructions, gathering and maintaining the data needed and reviewing the collection of information. Information collection is included in the following program announcement: OMB

NATIONAL TOXICOLOGY PROGRAM (NTP)
BOARD OF SCIENTIFIC COUNSELORS
REPORT ON CARCINOGENS (RoC) SUBCOMMITTEE MEETING

October 14, 2003

Marriott at Metro Center, Salons C and D
775 12th Street, NW
Washington, DC 20005

October 14, 2003 *Revised 6/17/04*

9:00 A.M. Registration
9:30 A.M. Welcome and Introduction
Review of Nominations to the 11th Report on Carcinogens

REVIEW OF SUBSTANCES FOR LISTING IN OR DELETING/REMOVING FROM THE 11TH REPORT ON CARCINOGENS

Nominations (Case Number)	To Be Reviewed for
X-radiation & Gamma-radiation	Listing in the 11th Report
Neutrons	Listing in the 11th Report
Lead and Lead Compounds	Listing in the 11th Report
Hepatitis B Virus	Listing in the 11th Report
Hepatitis C Virus	Listing in the 11th Report
Human Papillomaviruses, genital-mucosal types	Listing in the 11th Report
Diazoaminobenzene (136-35-6)	Listing in the 11th Report

NATIONAL TOXICOLOGY PROGRAM
BOARD OF SCIENTIFIC COUNSELORS
REPORT ON CARCINOGENS SUBCOMMITTEE

Aaron E. Blair, Ph.D., M.P.H.
Chief, Occupational Epidemiology Branch, EBP, DCEG
National Cancer Institute, NIH
6120 Executive Blvd., EPS 8118
Rockville, MD 20852

George E. Bonney, Ph.D.***
Professor, Director, Statistical Genetics and Bioinformatics Unit
National Human Genome Center at Howard University
2216 Sixth Street, NW, Suite 205
Washington, DC 20059

Hillary M. Carpenter, III, Ph.D.
Toxicologist, Minnesota Department of Health
121 East Seventh Place, Suite 220
P.O. Box 64975
St. Paul, MN 55101

Gail Charnley, Ph.D.
Principal, Health Risk Strategies
826 A Street, SE
Washington, DC 20003

Harvey Checkoway, Ph.D., M.P.H.
Professor, Department of Environmental Health and Epidemiology
Box 357234
School of Public Health and Community Medicine
University of Washington
F-561 Health Sciences Bldg, 1705 NE Pacific St.
Seattle, WA 98195

Elizabeth Delzell, M.S.P.H., S.D.
Professor, Occupational Epidemiology Branch, EBP, DCEG
Department of Epidemiology
School of Public Health
University of Alabama
1665 University Boulevard
Birmingham, AL 35294

John R. Froines, Ph.D.
Professor and Director, UCLA Center for Occupational and Environmental Health
UCLA School of Public Health, Box 951772
650 Charles E. Young Drive
Los Angeles, CA 90095-1772

Howard Frumkin, M.D., Dr. P.H.
Professor, Department of Environmental and Occupational Health
The Rollins School of Public Health, Emory University
1518 Clifton Road, NE
Atlanta, GA 30322

Irva Hertz-Picciotto, Ph.D., M.P.H.
Professor, Department of Epidemiology and Preventive Medicine
University of California-Davis
TB168
Davis, CA 95616

Margaret R. Karagas, Ph.D. ***
Professor, Section of Biostatistics and Epidemiology
Department of Community and Family Medicine
Dartmouth Medical School
7927 Rubin, 462-2, One Medical Drive
Lebanon, NH 03756-0001

Maria T. Morandi, Ph.D., C.I.H.
Assistant Professor of Environmental Sciences
School of Public Health, RAS W624
Houston Health Science Center
University of Texas
1200 Herman Pressler Drive
Houston, TX 77030

Barbara C. Pence, Ph.D.
Professor, Department of Pathology
3601 Fourth Street
Texas Tech University Health Sciences Center
Lubbock, TX 79430

James A. Popp, DVM, Ph.D.
Vice President, Nonclinical Drug Safety Assessment
Pharmacokinetics/Drug Metabolism
Purdue Pharma L.P.
444 Saw Mill River Road
Ardsley, NY 10502

Stephen M. Roberts, Ph.D.
Professor, Center for Environmental and Human Toxicology
University of Florida, Box 110885
Bldg 471, Mowry Rd. Rm. 14
Gainesville, FL 32611-0885

Allan H. Smith, M.D., Ph.D.
Professor of Epidemiology
School of Public Health
University of California, Berkeley
140 Warren Hall
Berkeley, CA 94720-7360

Ad Hoc Expert Consultant

David H. Phillips, Ph.D., DSc, FRCPath
Professor, Institute of Cancer Research
Haddow Laboratories
Cotswold Road
Sutton SM2 5NG, UK

*** not in attendance