National Toxicology Program
Board of Scientific Counselors
Report on Carcinogens Subcommittee Meeting

November 19-20, 2002
Hyatt Regency Bethesda, Bethesda, Maryland
Summary Minutes

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Attendees

Members

Dr. George Bonney
Dr. Hillary Carpenter
Dr. Gail Charnley
Dr. John Froines
Dr. Howard Frumkin
Dr. Margaret Karagas
Dr. Rafael Moure-Eraso
Dr. James Popp
Dr. Stephen Roberts
Dr. Allan Smith

Members Absent

Dr. Aaron Blair
Dr. Irva Hertz-Picciotto
Dr. Barbara Pence

Ad Hoc Expert Consultant

Dr. David Phillips

Agency Staff

Dr. William Allaben, Federal & Drug Administration
Dr. Mark Toraason, National Institute of Occupational Safety & Health
Jeffrey Yourick, Federal & Drug Administration
Loretta Schuman, Occupation Safety and Health Administration

NIEHS Staff

Dr. John Bucher, National Institute of Environmental Health Sciences
Dr. Larry Hart, National Institute of Environmental Health Sciences
Dr. C.W. Jameson, National Institute of Environmental Health Sciences
Dr. Ruth Lunn, National Institute of Environmental Health Sciences
Ronald Thomas, National Institute of Environmental Health Sciences
Dr. Mary Wolfe, National Institute of Environmental Health Sciences

Public

William Brinkman, PBI/Gordon Corp.
John Hadley, NAIMA
Eileen Francis, FDC Reports
Angus Crane, NAIMA
Arlean Medeiros, Exxon Mobil Biomedical Sci, Inc.
Jim Felton, LLNL
Anne LeHuray, ACC
Amanda Piccirillo, ACC
Jon Busch, ACC

Clyde Takeguchi, Phoenix Regulatory Assoc.
Michael Babich, U.S. CPSC
Gerhard Gans, BASF Corp.
George Cruzan, ToxWorks
Pat Phibbs, BNA
Vincent Piccirillo, VJP Consulting, Inc.
Linda Loretz, Cosmetic, Toiletry and Fragrance Assn.
William Stott, Dow Chemical

The National Toxicology Program (NTP) Board of Scientific Counselors Report on Carcinogens (RoC) Subcommittee ("the RoC Subcommittee") held its seventh meeting on November 19 and 20, 2002 at the Hyatt Regency Bethesda, 7400 Wisconsin Avenue, Bethesda, Maryland. (Attachment 1: *Federal Register* meeting announcement; Attachment 2: agenda, attachment 3: attending members.) Members of the RoC Subcommittee present were: Drs. John Froines (Chairperson), George Bonney, Hillary Carpenter, Gail Charnley, Howard Frumkin, Margaret Karagas, Rafael Moure-Eraso, 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. Aaron Blair, Irva Hertz-Picciotto, and Barbara Pence. Dr. Froines noted that this was the last meeting for Dr. Moure-Eraso.

I. Introduction and Background:

Dr. Christopher Portier, Director, Environmental Toxicology Program (ETP), National Institute of Environment Health Sciences (NIEHS), welcomed RoC Subcommittee members and members of the public in attendance on behalf of Dr. Kenneth Olden, Director, NIEHS and NTP. Dr. Portier noted that the 10 nominations to be reviewed were proposed for possible inclusion in the 11th Report on Carcinogens (RoC), and reported that the 10th RoC is in the process of being finalized for publication. He emphasized that the RoC is a hazard identification document and a very important part of the process of evaluating agents for carcinogenic hazard in the United States. Dr. Portier thanked the RoC Subcommittee on behalf of the NIEHS and its partners in the NTP, the National Institute of Occupational Safety and Health (NIOSH), and the Food and Drug Administration (FDA), both of whom have representatives present.

Dr. Froines went over the format to be used for reviewing nominations. First, the basis for each nomination is presented by an NIEHS/NTP scientist who discusses the nomination, including data related to human cancer, animal cancer, and mechanistic information, and then provides the recommendations, including the votes of the two Federal review committees, the NIEHS Review Group for the RoC (RG1) and the NTP Executive Committee Interagency Review Group for the RoC (RG2). Dr. Froines

commented that there would be one presentation for the heterocyclic amines but three individual votes. Next, persons or groups who submitted written comments prior to the meeting are identified. Copies of their comments were made available to everyone. Members of the public who have requested time to make oral comments are allowed 7 to 10 minutes after which the RoC Subcommittee can ask questions or make comments. The members of the RoC Subcommittee who have primary review responsibilities for the nomination next present their evaluations. This is followed by further discussion among RoC Subcommittee members and concludes with motions and votes on recommendations to be forwarded to the NTP.

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

1-Amino-2,4-dibromoanthraquinone (ADBAQ)

Dr. Ruth Lunn, NIEHS, presented the nomination and said ADBAQ is an anthraquinone vat dye used in the textile industry and was nominated by NIEHS for listing in the 11th RoC based primarily on the findings from the NTP two-year feeding studies in rats and mice. The chemical is used as a starting material for the manufacture of vat dyes; U.S. production of vat dyes totaled 31 million pounds in 1991. Environmental exposure to ADBAQ occurs when it is released into wastewater from production facilities. Because of its wide use in vat dyes and in the textile industry, there is a high likelihood of mainly dermal industrial exposure. Dr. Lunn reported there are no human cancer studies specific to ADBAQ, but there are some studies on anthraquinone dyes as a class in two populations of workers; one is on Scottish workers showing a small excess in esophageal and prostate cancer. The second study is on New Jersey vat dye workers where there are two case-control studies of lung cancer and central nervous system tumors, and a positive association was found with lung cancer. Limitations of these human studies include a limited power to detect an effect due to the small number of exposed cases and young cohorts and the fact that workers were also exposed to other agents.

Dr. Lunn reported that two-year dietary studies of ADBAQ in F344/N rats and B6C3F1 mice were conducted using technical grade compound (80 to 85 % purity) for the first two months and a 97 % pure preparation the remaining 22 months. Major impurities were anthraquinone and either 2- or 1-aminodibromoanthraquinone. The experimental design included interim sacrifices at 9 and 15 months in rats and 15 months in mice. For mice, there were significantly increased incidences of hepatocellular carcinomas or adenomas, forestomach squamous cell papillomas or carcinomas, and lung alveolar/bronchiolar adenomas or carcinomas in both sexes. For rats, there were significantly increased incidences in one or more dose groups of hepatocellular adenomas or carcinomas, renal tubule adenomas

or carcinomas, transitional cell adenomas or carcinomas of the bladder, and carcinomas of the large intestine. Findings from the interim sacrifice studies were supportive of the findings from the long-term study. Dr. Lunn stated that this bioassay demonstrated *clear evidence of carcinogenic activity* in both sexes of rats and mice.

With regard to genotoxicity, ADBAQ was mutagenic in bacterial strains that revert by frameshift mutations, while mutagenicity was decreased or eliminated by metabolic activation. Mutations were not induced in mouse lymphoma cells. Forestomach and lung tumors induced in rodents by ADBAQ had a higher frequency of *ras* mutations. ADBAQ is absorbed from the gastrointestinal tract and about 97 % is metabolized to unidentified metabolites in animals. With regard to potential mechanisms of carcinogenicity, the larger structural class of quinones has been observed to give rise to reactive oxygen species that may be associated with DNA damage.

Dr. Lunn reported that the RG1 and RG2 voted unanimously (8 votes) to recommend that ADBAQ be listed in the 11th RoC as *reasonably anticipated to be a human carcinogen*.

Public Comment: None.

RoC Subcommittee Discussion: The discussion focused on the purity of the test material in the rodent diets during the first two months of the two-year study. Dr. Smith asked whether the anthraquinone impurity could have caused tumors if the less pure material had been used for the entire study. Dr. John Bucher, NIEHS, said that question could not be answered. Dr. Phillips asked about the purity of other anthraquinones used in chronic studies. Dr. Bucher replied that their purities were variable.

Primary Reviews: Dr. Phillips, a primary reviewer, expressed reservations about the proposed listing because in the NTP study, the ADBAQ administered during the first two months included an animal carcinogen, anthraquinone, as a major impurity. Further, he noted that there were inconsistencies in the sites of increased incidences of some cancers in the epidemiological studies between the Scottish cohorts (esophageal and prostatic tumors) and the U.S. cohorts (lung cancer and CNS tumors).

Dr. Moure-Eraso, also a primary reviewer, agreed with the proposed listing. He thought the high concentrations of ADBAQ, especially for the last 22 months, supported its being the carcinogenic agent.

Dr. Karagas, also a primary reviewer, agreed with the proposed listing based on the data from the two-year studies in rats and mice.

Discussion: There was considerable discussion among members and staff as to the dose of anthraquinone that animals in the ADBAQ study would have received over two years as compared with the doses of anthraquinone that animals received in the two-year studies on that chemical. Dr. Popp pointed out that there were tumor types observed in the ADBAQ studies that were not seen in the studies with anthraquinone, such as intestinal adenomatous polyps in rats and forestomach and lung tumors in mice. Dr. Carpenter stated that it would be misleading to add 'Technical Grade' to the title of the report since for 22 months of the studies a fairly pure compound was being used. Dr. Smith suggested deferral of the motions and votes until the next day so NTP staff could prepare information summarizing the issues relating to the ADBAQ and anthraquinone bioassays for presentation to the RoC Subcommittee. Dr. Moure-Eraso moved that a vote be deferred until the NTP could provide the requested information. Dr. Frumkin seconded the motion, which was accepted unanimously with 9 yes votes.

Resuming the discussion on November 20, 2002, Dr. Bucher presented comparisons of the dose and tumor response data from the anthraquinone and ADBAQ bioassays. He pointed out that where there is concordance in tumor sites between the two studies, almost uniformly the tumor incidences were higher in the ADBAQ studies, and secondly, there were a number of tumors observed in the ADBAQ studies not seen in the anthraquinone studies. Dr. Phillips thanked the NTP for clarifying the tumor responses, but based on the first two months of the ADBAQ studies he could not recommend listing. Drs. Moure-Eraso and Karagas agreed with their previous assessments to list in the 11th RoC.

Dr. Moure-Eraso moved that 1-amino-2,4-dibromoanthraquinone be recommended for listing in the 11th RoC as *reasonably anticipated to be a human carcinogen*. Dr. Frumkin seconded the motion, which was accepted unanimously with 9 yes votes.

Naphthalene

Dr. C.W. Jameson, NIEHS, presented the nomination and said that naphthalene, a polycyclic aromatic hydrocarbon, was nominated by NIEHS for possible listing in the 11th RoC based on the results of NTP two-year bioassays that showed *clear evidence of carcinogenic activity* in male and female rats and *some evidence of carcinogenic activity* in female mice. Principal uses of naphthalene are as chemical intermediates in the production of phthalic anhydride, insecticides, leather tanning chemicals, and surfactants and as a moth repellent in moth balls. Human exposure is by inhalation and dermal routes and

the National Occupational Exposure Survey (NOES) estimates that greater than 100,000 workers are potentially exposed.

With regard to human cancer studies, there are two case studies on naphthalene-exposed individuals; one where laryngeal and other cancers were reported in a group of 15 distillation plant workers in Germany, and the other where colorectal carcinomas were reported in young African men exposed through a naphthalene-containing medicinal. The overall evaluation was that there is insufficient evidence for evaluation of carcinogenicity in humans.

Dr. Jameson reviewed the exposure conditions and findings from the two-year inhalation studies in rats and mice. There was *some evidence* in female mice based on the increased incidences of lung adenomas and adenoma/carcinomas combined in the high dose group. There was *clear evidence* in male rats based on significant increases at all dose levels of adenomas of the respiratory epithelium of the nasal cavity, a rare neoplasm in Fischer rats. In addition, there were dose-related trends for incidences of neuroblastoma, a very rare tumor in Fischer rats, in both males and females, and a significant incidence of this tumor at the high dose in female rats supporting *clear evidence* in female rats. A number of non-neoplastic lesions, primarily of the nose, lungs and olfactory epithelium, were found and considered to be consistent with the neoplastic lesions observed in the bioassays.

Dr. Jameson stated there is little evidence for mutagenic activity, although positive results were obtained in assays for micronucleus formation, chromosomal aberrations and chromosomal recombinations *in vitro*. He said that absorption and disposition studies show metabolites in the urine of workers with good correlation between naphthalene exposure and the amounts of 1-naphthol. Metabolites of naphthalene have been detected in human adipose and breast milk samples. P450 enzymes metabolize naphthalene primarily to two stereoisomers of the 1,2-epoxide, which are further conjugated with glutathione.

Dr. Jameson reported that RG1 voted 6 yes votes to 1 no vote to recommend that naphthalene be listed in the 11th RoC as *reasonably anticipated to be a human carcinogen* with the no vote being based on the mouse data being limited and a question of the relevancy of the nasal tumors in rats to humans. The RG2 deliberations ended in no recommendation after a split vote for listing of 4 yes and 4 no votes. Members voting against the motion felt the mouse data were limited and questioned the relevancy of the nasal tumors in rats to humans. Dr. Jameson noted that the International Agency for Research on Cancer (IARC) recently reviewed naphthalene. IARC found sufficient evidence of carcinogenicity in laboratory animals and proposed to list naphthalene as a Group 2B *possible human carcinogen*.

Dr. Froines stepped down as chairperson for the remainder of this review and Dr. Smith assumed the chairpersonship.

Public Comments: Dr. Vincent Piccarillo, representing the Naphthalene Panel of the American Chemistry Council, stated that an assessment of the carcinogenic potential of naphthalene clearly requires an understanding of genotoxicity and interspecies metabolism, both of which have been studied extensively. He said that issues to be considered are: (1) naphthalene is not likely to be a genotoxic carcinogen with no evidence of mutagenicity in short-term tests and it is protein -- but not DNA -- reactive; (2) species/site selectivity in rodents correlates with susceptibility to cytotoxicity, which in turn appears to correlate with the rates of naphthalene metabolism to the 1,2-epoxide; (3) kinetics of metabolism by recombinant CYP2F (P450 enzymes) from rat and mouse do not differ, while studies conducted at saturating substrate concentrations with human enzymes show activities to be more than 1000-fold lower; and (4) metabolism of naphthalene in lung microsomes from primates (humans and monkeys) is at least an order of magnitude slower than in any rodent species tested. Dr. Picarillo presented data to support these points.

Primary Reviews: Dr. Carpenter, a primary reviewer, agreed with the proposed listing of naphthalene as *reasonably anticipated to be a human carcinogen* based on the findings in rats and to a lesser extent in mice. He saw nothing that would indicate that humans do not have the same mechanisms for carcinogenic activation with sufficient strength of exposure. He thought there was sufficient evidence of both occupational and environmental exposures.

Dr Frumkin, also a primary reviewer, agreed with the proposed listing as *reasonably anticipated to be a human carcinogen* based on the animal carcinogenicity data. He thought there was evidence of exposure. He also thought that the available human evidence was not very helpful for evaluating naphthalene. Although the information provided showed different preferences for metabolic pathways in different species, differences in nasal anatomy between rodents and humans, and the possible role of inflammation, Dr. Frumkin thought there could be a carcinogenic effect in humans.

Dr. Roberts, also a primary reviewer, stated that he had struggled with the animal evidence as to whether it was sufficient to meet the criteria for listing. He felt that the mouse data were not strong, and hoped for a discussion on whether the nasal tumor response in rats was sufficient to drive listing in the RoC. He agreed that there was sufficient human exposure to qualify.

Dr. Froines made a presentation in support of the proposed listing by first concluding that naphthalene meets the criteria for sufficient evidence in experimental animals, particularly under number (3) "to an unusual degree with regard to incidence, site or type of tumor or age at onset" with respect to the rat studies. Further, he argued that the chemical belongs to a well-defined structurally related class of substances, the polycyclic aromatic hydrocarbons, whose members are listed in previous RoCs. Dr. Froines said the main reason he stepped aside as chair to make these remarks was that he considers naphthalene to be a particularly important urban air pollutant as documented by the Agency for Toxic Substances and Disease Registry (ATSDR) providing an issue of public health significance. Dr. Froines also commented on the purported differences in metabolism among species, citing reports in the literature that humans metabolize alkenes to DNA-reactive epoxide intermediates in a similar manner to rodents, and discussed some of the metabolic pathways in detail. Finally, he cited NTP studies where there had been an increase in nasal carcinogenesis.

In further discussion, Dr. Popp emphasized the importance of the neuroblastomas in rats relative to the criteria cited by Dr. Froines and said that it is extremely rare and highly malignant tumor. There ensued considerable discussion among members and staff about the types of statistical analyses used for determining significance in the data from the mouse and rat bioassays. Dr. Phillips cautioned against making a score card for all the genotoxicity tests that have been reported, noting that although the preponderance of the findings, especially in bacterial mutagenesis, are negative, there are some significant positive results. Dr. Roberts commented that Dr. Popp's statements about the rare tumors were helpful and answered his questions on whether the nasal tumor response in rats was sufficient to drive listing in the RoC.

Dr. Carpenter moved to recommend that naphthalene be listed in the 11th RoC as *reasonably anticipated to be a human carcinogen*. Dr. Frumkin seconded the motion, which was accepted unanimously with 9 votes.

Selected Heterocyclic Amines (HCAs): 2-Amino-3,4-dimethylamidazo{4,5-f}quinoline (MeIQ) ; 2-Amino-3,8-dimethylimidazo{4,5-f}quinoxaline(MeIQx); 2-Amino-1-methyl-6-phenylimidazo{4,5-b}pyridine (PhIP)

Dr. Lunn presented the nomination and said that PhIP was nominated for listing by Dr. Sugimura (National Cancer Institute of Japan) and the NIEHS nominated MeIQ and MeIQx based on the 1993 IARC classification that they (each individually) are *possibly carcinogenic to humans* (Group 2B). She reported that the three HCAs are produced during the cooking of meat. Temperature, processing, cooking

time, pH, and type of amino acid present affect their formation with higher temperatures, longer cooking times, and the use of direct heat increasing the amounts. PhIP is the most abundant HCA and is detected in commonly eaten meats in the United States, including beef, chicken and fish.

Dr. Lunn said there are three U.S. cohort studies that measured human intake of HCAs in meat with intake highest for PhIP, ranging from 286 to 457 nanograms (ng)/day. There is some evidence that the cooking methods producing HCAs may be associated with human cancer risk in the lung, stomach, bladder, colon, and breast. There is site concordance for tumors in the colon, breast, and lung from human studies with tumors identified in animal studies; however, these studies cannot separate the effects of HCAs from other major components, such as polycyclic aromatic hydrocarbons (PAHs) that are also found in cooked meats.

Dr. Lunn described the 11 case-control studies from the United States, South America, Sweden and New Zealand and summarized the findings. She noted that there is some evidence that PhIP may increase breast and gastric cancer risk and MeIQx may increase the risk of colon adenoma and lung cancer; however, there are a number of limitations in these studies, including low statistical power, misclassification/measuring errors, recall bias, and confounding.

Dr. Lunn said that HCAs have been studied extensively in experimental animals, mostly in rats and mice, in both long-term and short-term studies. All three were carcinogenic at multiple tumor sites and in multiple species, with tumor profiles being variable, but with some overlap. She added that in general, HCAs are not effective tumor promoters, and other chemicals, dietary factors and interactions of HCA mixtures may be modulating the carcinogenic effects. Further, mice and rats injected with metabolites of PhIP or MeIQ developed tumors.

With regard to genotoxicity, all three HCAs are highly mutagenic and when studied in prokaryotes, rodents, and human (except MeIQx), they showed high degrees of potency. Endpoints included DNA damage, micronuclei formation, sister chromatid exchanges, unscheduled DNA synthesis, and chromosomal aberrations. She noted that HCA-induced adducts in humans occur at dietary relevant doses and have been identified in colon, breast, and prostate tissue following exposure to HCAs. Dr. Lunn reported that following oral ingestion, HCAs are readily absorbed, are distributed to most tissues in humans and animals, especially liver, GI tract, and kidneys, and are excreted by both urinary and fecal routes. The HCAs are detoxified by ring hydroxylation and subsequent conjugation and are activated by N-hydroxylation, followed by esterification leading to the formation of DNA adducts. With regard to

potential mechanisms of carcinogenicity, Dr. Lunn said these adducts may result in mutations. Mutations in protooncogenes and tumor suppressor genes have been observed in mammary, colon, forestomach, Zymbal gland and/or liver tumors in animals exposed to HCAs. Studies using chemical modulators have suggested that oxidative damage and effects on cell proliferation, apoptosis and cell-cycle control may also be factors in HCA-induced carcinogenesis.

Dr. Lunn reported that RG1 voted to recommend that PhIP (5 yes votes to 1 no vote), MeIQx (5 yes votes to 1 no vote), and MeIQ (unanimous - 6 yes votes) be listed in the 11th RoC as *reasonably anticipated to be a human carcinogen*. The dissenting RG1 vote for MeIQx and PhIP was because the member felt that they should be listed as *known to be human carcinogens*. RG2 voted unanimously (8 yes votes) to recommend listing for all three HCAs as *reasonably anticipated to be human carcinogens*.

Public Comments: None.

Primary Reviews: Dr. Smith, a primary reviewer, stated that he had struggled with whether or not there is meaningful human exposure to the HCAs, because when compared with dose levels in rodent bioassay studies, human exposures are on the order of a million times lower. He said he believed a significant number of people are exposed to HCAs, but questioned whether human exposure is significant for listing these compounds. He said he considered several reasons why there might be a potential for higher carcinogenic risk to HCAs for humans than rodents. This included whether humans might be more sensitive to HCAs than rodents or more likely to produce the active metabolite. He said neither of these factors could adequately account for a difference in response for humans versus rodents given the large difference in exposure. Further, there is no evidence for greater human sensitivity due to higher persistence of the metabolites in humans versus rodents. Applying the listing criteria, Dr. Smith said the level of human exposure is not meaningful for MeIQ, and it should not be listed. He added that if a reasonable case could be made for meaningful human exposure and/or much greater sensitivity of humans versus rodents for MeIQx and PhIP, they could be listed.

Dr. Phillips, also a primary reviewer, agreed with the proposed listings based on considerable evidence of human exposures, well proven carcinogenicity in more than one rodent species and at multiple sites, and reasonable assurance that the HCAs are carcinogenic by genotoxic mechanisms.

Dr. Roberts, also a primary reviewer, agreed with the proposed listings based on reasons that closely mirrored those of Dr. Phillips. He said that although the risks from human dietary exposure might be

negligible, the RoC Subcommittee is to identify qualitative hazard and not quantitative risk. With regard to MeIQ, there is human exposure in cigarette smoke.

In clarifying discussion, Dr. Smith asked Dr. James Felton, Lawrence Livermore National Laboratory, to make a few comments. Dr. Felton, an expert on chemistry and toxicology of HCAs, assisted the NTP in the preparation of the background document. Dr. Felton said that Dr. Smith's calculations of human exposure levels are accurate, but cautioned that there are significant subsets of the population that get much higher exposures, perhaps only 50, 000 to 100,000 times below animal doses. He described work from his laboratory using accelerated mass spectrometry and said they can measure in the range of one adduct per 1000 cells. Dr. Smith then said that he would agree that as required by the Congress, significant numbers of people are exposed, at least to MeIQx and PhIP. In response to a question from Dr. Roberts, Dr. Felton replied that he believes human exposure from cigarette smoke to be pretty minimal compared to dietary exposure.
Dr. Frumkin moved that PhIP be recommended for listing in the 11th RoC as *reasonably anticipated to be a human carcinogen*. Dr. Roberts seconded the motion, which was accepted unanimously with 9 yes votes.

Dr. Frumkin moved that MeIQ be recommended for listing as *reasonably anticipated to be a human carcinogen*. Dr. Roberts seconded the motion, which was accepted with 8 yes votes and 1 abstention (Dr. Smith). Dr. Smith said he abstained because he was not convinced that there is meaningful population exposure in the United States.

Dr. Frumkin moved that MeIQx be recommended for listing as *reasonably anticipated to be a human carcinogen*. Dr. Roberts seconded the motion, which was accepted unanimously with 9 yes votes.

Nitromethane

Dr. Jameson presented the nomination and identified nitromethane as the simplest nitroalkane. The NIEHS nominated nitromethane for listing in the 11th RoC based on NTP two-year inhalation studies that showed *clear evidence of carcinogenic activity* in female rats and male and female mice. Its primary uses (85-90%) are in the synthesis of nitromethane derivatives, including pharmaceuticals, agricultural soil fumigants, and industrial antimicrobials. It is also used as a fuel additive in nitro-burning racecars and in nitro-burning model cars and airplanes. Annual production is 16 million pounds by the one U.S. manufacturer, Angus Chemical Company who provided written comments. General population exposures are from cigarette smoke, vapors from engine fuel and exhaust, and environmental

contamination. Occupationally, the NOES estimates that 135,000 male and 46,000 female workers are exposed with current average concentrations in production facilities being about 1 ppm. No human studies relevant to the carcinogenicity of nitromethane were found.

Dr. Jameson described exposure conditions for the NTP two-year inhalation studies in B6C3F1 mice exposed to levels up to 750 ppm and F344/N rats exposed to levels up to 375ppm. In male and female mice, there were significant increases in Harderian gland adenomas with a significant trend test, while in female mice there were significant increases at two doses in hepatocellular adenomas and adenomas or carcinomas with a significant trend test. In high dose females, there were significant increases in adenomas and adenomas or carcinomas of the lung. In female rats, there were significant increases in mammary fibroadenomas, carcinomas or combined tumors with a positive test for trend. Dr. Jameson noted a two-year study in the literature on Long-Evans rats that showed no evidence of carcinogenicity. He said an IARC review in 2000 indicated there is sufficient evidence of carcinogenicity of nitromethane in experimental animals and listed it as *possibly carcinogenic to humans* (Group 2B).

Dr. Jameson reported that nitromethane is not mutagenic *in vivo* or *in vitro*, although it was shown to be positive in a SHE cell transformation assay. No human studies have been reported on absorption, metabolism or excretion of nitromethane and there are minimal *in vivo* studies in animals. *In vitro* studies with rat liver microsomes showed that nitromethane interacts with P450 enzymes to produce formaldehyde. Dr. Jameson commented that for structurally related compounds, tetranitromethane is associated with lung tumors in mice and rats, and 2-nitropropane caused liver tumors in rats; both are listed in the RoC as *reasonably anticipated to be human carcinogens*.

He reported that RG1 (8 votes) and RG2 (9 votes) unanimously recommended that nitromethane be listed in the 11th RoC as *reasonably anticipated to be a human carcinogen*. Dr. Moure-Eraso inquired as to why the study in Long-Evans rats was negative. Dr. Jameson replied that the study was done with lower doses than the two-year study in F344/N rats, but otherwise appears to have been adequately conducted.

Public Comments: None.

Primary Reviews: Dr. Moure-Eraso, a primary reviewer, agreed with the proposed listing noting the animal carcinogenicity data to be incontrovertible. He suggested that NTP urge the manufacturer to initiate epidemiological and exposure assessment studies. Dr. Moure-Eraso said the NOES data (1981-1983) indicate that as many as 180,000 workers were exposed, while the manufacturer claims that no more than 10,000 are currently exposed.

Dr. Bonney, a second primary reviewer, agreed with the proposed listing. He commented on and disagreed with points made in written comments received from the manufacturer who contended that the NTP had not met its own criteria for listing in the RoC.
Dr. Popp, also a primary reviewer, agreed with the proposed listing. He thought that the animal carcinogenicity data are straightforward and he emphasized the mammary tumor findings in female rats, noting that the carcinomas are increased not only with regard to concurrent controls, but are higher compared with the historical control range. Dr. Popp said the real issue has to do with the 20% of production going into fuel and fuel additives and the need for developing exposure data on the motor sport population.

In discussion, Dr. Froines suggested that the NTP could use the OSHA compliance data for information about exposure, and this data as well as any other available sources should be sought and perhaps included in the background document. Dr. Froines lamented the lack of toxicokinetic data.

Dr. Moure-Eraso moved that nitromethane be recommended for listing in the 11th RoC as *reasonably anticipated to be a human carcinogen*. Dr. Bonney seconded the motion, which was accepted unanimously with 9 votes.

Diethanolamine (DEA)
Dr. Lunn presented the nomination and said that diethanolamine (DEA) is a secondary amine used in metalworking fluids and in consumer products. Dr. Frank Mirer, United Auto Workers Union (UAW), nominated DEA for listing based on the results from the NTP two-year dermal study. Since 1960, the production of DEA has been increasing and in 1995 it was over 100,000 tons. Consumer exposure is primarily dermal due to its use as a surfactant in personal care products such as soaps, shampoos, cosmetics and detergents. Occupational exposure is to an estimated 800,000 workers, mostly metalworking fluid workers and is mainly through inhalation, but some dermal exposure also occurs. Dr. Lunn reported that there are no human studies with exposure specifically to DEA and that most epidemiology studies involved workers using metalworking fluids, which are complex mixtures. The most consistent finding in these studies is an excess of stomach cancer, with the next being esophageal cancer. Other sites included liver, pancreas, prostate and larynx; however, the specific effects of DEA can not be separated from the effects of other components in metalworking fluids.

DEA was studied in experimental animals with the two major studies being an NTP two-year bioassay by the dermal route in mice and rats and a 20-week dermal study in female Tg:AC mice possessing an

inducible v-Ha-*ras* gene. No increase in tumor incidence was observed in the transgenic mouse study. In the NTP two-year study in mice, there were increased incidences of liver tumors in both sexes, and the increases were significant at all doses for adenomas, carcinomas and adenomas and carcinomas combined with a significant test for trend . In males there was also a significant increase in blastomas in the liver. In addition, there was an increase in the incidence of renal tumors (adenomas) observed in male mice; however, the increase was in adenomas but not carcinomas. Thus, there was *clear evidence of carcinogenic activity* in male and female B6C3F1 mice. In the NTP two-year study in rats, there was *no evidence of carcinogenic activity* in male and female F344/N rats. Dr. Lunn also described an NTP two-year dermal bioassay in male mice comparing free DEA with DEA condensates of coconut oil acid, lauric acid, and oleic acid.

Dr. Lunn stated that in 2000, the IARC classified DEA as *not classifiable to its carcinogenicity to humans* (Group 3) based on limited evidence of carcinogenicity in experimental animals. DEA is not mutagenic in bacteria and does not appear to be genotoxic in most other markers, although it does induce cell transformation in SHE cells.

DEA is absorbed following dermal administration in rats and mice. It accumulated in tissues with repeated doses, the highest concentrations being in the liver and kidney, and was excreted in urine. An *in vitro* assay showed dermal absorption from human skin. The mechanism for tumor formation has not been fully elucidated. DEA is incorporated into phospholipids, resulting in aberrant phospholipids and disruption of choline utilization. This affect on choline utilization leads to choline deficiency.

Dr. Lunn reported that RG1 (7 yes to 2 no votes) and RG2 (9 yes votes) recommended that DEA not be listed in the 11th RoC. The dissenting RG1 votes thought DEA should be listed as *reasonably anticipated to be a human carcinogen*.

Dr. Popp asked for clarification on why DEA was classified as *limited evidence* by the IARC. Dr. Phillips, who was on the IARC working group, responded that he thought it was *limited* because there was clear evidence of carcinogenicity in only in one tissue of one species.

Public Comments: Dr. William Stott, representing the Alkanolamines Panel of the American Chemistry Council, had several points to make. With regard to the positive findings in the SHE cell assay, the addition of choline eliminates the positive results. This is consistent with choline deficiency induced by DEA being a possible carcinogenic mechanism. With regard to the epidemiological studies, Dr. Stott

stated that important information on alcoholism and liver disease other than cancer is not available in the studies. Further, he said the definition of liver cancer and its coding for epidemiology studies has changed over the years and noted that the increase in cancer in the Eisen study was in biliary tract cancer and not liver cancer.

Dr. Linda Lorentz, Cosmetic, Toiletry, and Fragrance Association, commented that the NTP criteria for listing in the RoC have not been met for listing DEA, which is consistent with the recommendations of RG1 and RG2. The nomination is based on a single positive finding in animals, the occurrence of liver tumors in mice. Dr. Lorentz pointed out that these tumors have a high background rate.

Primary Reviews: Dr. Smith, a primary reviewer, agreed with the recommendation not to list DEA in the RoC. He noted that virtually all of the human workplace carcinogens involve mixed exposures. Dr. Smith said the fact that the only significant tumors in animals are mouse liver tumors detracted from the strength of evidence.

Dr. Popp, also a primary reviewer, agreed with the recommendation not to list. He said the likely presence of known carcinogens, nitrosamines, in metal working fluids obscured attributing carcinogenic effects to DEA.
Dr. Charnley, also a primary reviewer, agreed with the recommendation not to list citing a lack of epidemiological evidence and limited animal data.

Discussion: Dr. Moure-Eraso commented that the doses used in the two-year study in rats were much lower than those used in the mouse study. He wondered whether there might have been a positive carcinogenic finding in rats if the doses given to rats had been more comparable to those administered to mice. Dr. Bucher responded that the doses in the rat study were limited by toxicity to the skin. Dr. Charnley noted that in the subchronic toxicity studies, doses to rats and mice were quite similar and hepatic toxicity was not noted in rats. There were questions about whether the IARC working group in its deliberations about DEA considered the bioassays on fatty acid DEA condensates conducted by NTP. Dr. Phillips replied that the working group was aware of the condensate bioassays but concluded that these studies could not be used in the evaluation of DEA's carcinogenicity because the substances tested were complex mixtures of imprecise composition, the actual DEA content had not been measured, and these studies were not designed as and did not represent conventional bioassays of DEA.

Dr. Charnley moved that DEA not be recommended for listing in the 11th RoC. Dr. Popp seconded the motion, which was accepted by 8 yes votes to 1 no vote (Moure-Eraso). Dr. Moure-Eraso said his reason for opposing the motion is that based on the criteria, DEA should be listed as *reasonably anticipated to be a human carcinogen*.

Cobalt Sulfate

Dr. Lunn presented the nomination and said that cobalt sulfate is an inorganic salt of divalent cobalt. The NIEHS nominated cobalt sulfate based on the two-year inhalation studies by the NTP. Cobalt sulfate is used primarily in electroplating and as a coloring agent. Other uses are in the electrochemical industry, as a drying agent, in animal feed, and in mixtures with fertilizers for use in pastures that are cobalt deficient. Cobalt sulfate is produced by reacting cobalt oxide, hydroxide or carbonate with sulfuric acid. U.S. production in 1983 was 450,000 pounds, while in 2001 imports to the United States were 1,650 metric tons. In terms of human exposure, there is no information specific for cobalt sulfate, but rather on cobalt and cobalt compounds that are inhaled from ambient air and ingested in water and food. Occupationally, there are one million workers who may be exposed. OSHA regulates cobalt at 0.1 mg/m3 per 8-hour time-weighted-average. Dr. Lunn said that in terms of human cancer studies, there are no studies specific to cobalt sulfate, only studies on cobalt and cobalt compounds.

In 1991, IARC concluded that there was inadequate evidence in humans for cobalt and cobalt compounds. IARC identified two cohort studies that showed an excess of lung cancer; however, workers in these cohorts had co-exposure to other carcinogens. Three more current cohort studies reported an excess risk of lung cancer in hard-metal (cobalt and tungsten carbide) workers. Two of these studies reported an excess risk of lung cancer for other cobalt exposure, which was described as cobalt exposure that did not involve co-exposure to tungsten carbide, but was most likely exposure to cobalt metal. In two studies (one was a later follow-up) at a French electrochemical plant, an elevated relative risk of lung cancer was observed in the initial study, but not in the follow-up; however, there was limited power to detect an effect because of the small numbers of cases. Finally, one study of environmental exposure found a positive association between the amount of cobalt detected in nails and esophageal cancer.

Dr. Lunn said that NTP conducted two-year inhalation studies in B6C3F1 mice and F344/N rats using cobalt sulfate heptahydrate. There was *clear evidence of carcinogenic activity* in female and male mice based on increased incidences of lung tumors, *clear evidence of carcinogenic activity* in female rats based on increased incidences of lung and adrenal medullar tumors, and *some evidence of carcinogenic activity* in male rats based on combined incidences of lung adenomas and carcinomas.

With regard to genotoxicity, cobalt sulfate was mutagenic in one out of three *Salmonella* strains, induced cell transformation and micronuclei formation in SHE cells, induced p53 protein expression in mouse fibroblasts, and induced interstrand crosslinks in salmon sperm DNA. The chemical did not induce 8-hydroxy-2'-deoxyguanosine (8-OhdG) adducts in salmon sperm DNA and was not genotoxic in human lymphocytes.

In humans cobalt is absorbed from the gastrointestinal tract, lungs and skin, and distributed throughout the body with the highest concentrations in liver, kidney and heart. It is excreted primarily in urine. Occupational exposure to cobalt is associated with hard-metal pneumoconiosis, asthma and contact dermatitis. There are several possible mechanisms for cobalt-induced carcinogenicity. Cobalt ions may mimic or substitute for essential nutrients, such as Mg, Ca, Fe, Cu, or Zn, thus altering important cellular reactions and functions. Cobalt also inhibits DNA repair, interacts with hydrogen peroxide to form reactive oxygen species that can damage DNA, and may affect DNA synthesis and gene expression.

Dr. Lunn reported that RG1 (9 yes votes) and (8 yes to 1 no vote) recommended that cobalt sulfate be listed in the 11th RoC as *reasonably anticipated to be a human carcinogen*. The dissenting RG2 vote was because the member felt the exposure data in background document needed to be more specific for cobalt sulfate. Dr. Froines commented that IARC reviewed cobalt in 1991 and determined that there was sufficient evidence for carcinogenicity of cobalt metal powder and pure cobalt oxide in experimental animals to classify as *possibly carcinogenic to humans* (Group 2B).

Public Comments: None.

Primary Reviews: Dr. Carpenter, a primary reviewer, agreed with the proposed listing. He thought that there is adequate information on the potential for human exposure, and the findings in experimental animals are sufficient evidence of carcinogenicity. He was a bit concerned about the designation of an essential element as carcinogenic.

Dr. Charnley, also a primary reviewer, did not agree with the proposed listing. She said there is very little information available on human exposure to cobalt sulfate, and generalizing exposure to cobalt metal and cobalt compounds is not appropriate, in part due to the differing water solubilities. Dr. Charnley concluded that the listing should be deferred, because although there is adequate evidence of

carcinogenicity in animals, the NTP has not established that "a significant number of persons residing in the United States are exposed" as required by the Public Health Service Act.

Discussion: Dr. Phillips wondered why this particular salt was nominated, presuming that it is because the NTP had sufficient evidence of carcinogenicity in animals. Dr. Bucher responded that NCI nominated cobalt sulfate as a representative, soluble cobalt salt based primarily on its use in beer and as a pasture and crop plant supplement. Dr. Smith reiterated that the epidemiological studies, some of which are highly suggestive, do not apply to cobalt sulfate. Dr. Frumkin speculated that the population exposed to cobalt and its compounds is probably much larger than is indicated in the background document. Dr. Froines thought there is agreement that the anion is probably the active agent, but the role of soluble versus insoluble salt is not yet resolved.

Dr. Carpenter moved that cobalt sulfate be recommended for listing in the 11th RoC as *reasonably anticipated to be a human carcinogen*. Dr. Frumkin seconded the motion, which was accepted by 8 yes votes to 1 no vote (Charnley). Dr. Charnley said she was not comfortable listing cobalt sulfate separately from the other salts.

Nitrobenzene

Dr. Jameson presented the nomination and said that nitrobenzene is a nitro aromatic compound. The NIEHS nominated nitrobenzene for listing in the 11th RoC based on the IARC finding of sufficient evidence of carcinogenicity in experimental animals and listing as *possibly carcinogenic to humans* (Group 2B). The widest use of nitrobenzene is as a chemical intermediate for the production of aniline, which is used to make dyestuffs and pharmaceutical intermediates. Other uses of nitrobenzene are in production of isocyanates, pesticides, and pharmaceuticals. With regard to human environmental exposures, this would be through release from some of its various applications, its use in shoe and nail polishes, and its use as an industrial solvent with routes of exposure including inhalation, ingestion and dermal. The NOES estimated that over 5,000 workers in the United States are exposed via dermal and inhalation routes. Domestic production of nitrobenzene increased dramatically from 176 million pounds in 1955 to almost 2.4 billion pounds in 2000.

The evidence for human cancers from exposure to nitrobenzene is one case-control study of childhood brain cancer from inferred parental exposure during the postnatal period (from birth to diagnosis). Because of concern about the validity of the exposure assessment and the small number of exposed cases, this study is considered insufficient for an evaluation of the carcinogenicity of nitrobenzene in humans.

In experimental animals, two-year inhalation studies with nitrobenzene vapor were conducted by CIIT in B6C3F1 mice and F344/N rats of both sexes and in male CD rats. Male mice had increased incidences of lung and thyroid follicular cell tumors, and female mice had increased incidences of mammary gland tumors. Male F344 rats had increased incidences of liver and kidney tubular cell tumors and a dose-related trend in thyroid follicular cell tumors and female rats had endometrial stromal polyps and a dose-related trend in liver tumors. Liver tumors were also observed in the male CD rats.

Dr. Jameson said that nitrobenzene is not genotoxic in bacteria. It has been shown to be negative *in vitro* for unscheduled DNA synthesis in rat or human hepatocytes, negative *in vivo* for sister chromatid exchanges and chromosomal aberrations in rat lymphocytes, and positive for chromosomal aberrations *in vitro* in human lymphocytes.

In humans, methemoglobinemia is a major toxic endpoint for exposure to nitrobenzene. In animals and humans, absorption is by dermal and inhalation routes and excretion is in the urine. Metabolism in both animals and humans is by two pathways – oxidation to nitrophenols and subsequent conjugation or reduction to aniline, followed by ring oxidation to aminophenols and subsequent conjugation. Dr. Jameson discussed possible mechanisms of carcinogenicity that are metabolically related - one being reduction to aniline by the microsomal one-electron step mechanism associated with production of reactive free radicals and the other being an oxidation futile reaction involving oxidation of the nitrogen anion radical regenerating nitrobenzene leading to production of superoxide anions. Nitrobenzene is structurally related to five nitroarenes that are listed in the RoC as *reasonably anticipated to be human carcinogens*.

He reported that both RG1 and RG2 voted unanimously (seven votes) to recommend that nitrobenzene be listed in the 11th RoC as *reasonably anticipated to be a human carcinogen*.

Public Comments: None.

Primary Reviews: Dr. Popp, a primary reviewer, agreed with the proposed listing based on the carcinogenicity data in experimental animals. He noted especially the increase in malignant mammary tumors in female mice, adenocarcinomas, and the increases of liver tumors combined in the two strains of male rats. He also commented on the potential for widespread human exposure.

Dr. Phillips, also a primary reviewer, agreed with the proposed listing based on nitrobenzene being a multi-organ, multi-species carcinogen in rodents. He added that there is widespread human exposure, albeit insufficient human study evidence of carcinogenicity.
Dr. Karagas, also a primary reviewer, agreed with the proposed listing based on the carcinogenicity findings in rodents. She commented that a number of urinary metabolites of nitrobenzene have been identified in both humans and animals.

In discussion, Dr. Froines asked Dr. Popp to comment on the carcinogenicity of aniline. Dr. Popp reported there were two bioassays, one by CIIT that resulted in a high incidence of splenic lesions of fibroblastic origin, and the NTP studies showing a mixture of tumors diagnosed as tumors of fibroblastic origin and tumors of endothelial origin.

Dr. Popp moved that nitrobenzene be recommended for listing in the 11th RoC as *reasonably anticipated to be a human carcinogen*. Dr. Carpenter seconded the motion, which was accepted unanimously with 9 yes votes.

4,4'-Thiodianiline

Dr. Jameson presented the nomination and said that thiodianiline is a thioether with two aniline molecules and was nominated by the NIEHS for listing in the 11th RoC based on an IARC finding of sufficient evidence of carcinogenicity in experimental animals and listing as *possibly carcinogenic to humans* (Group 2B). He said the chemical is used almost exclusively as a chemical intermediate in production of several diazo dyes, one of which, C.I. Mordant Yellow 16, has commercial significance in the United States in dying of wool and printing on fabrics. In the past, it was used as an indicator in nerve gas detector programs. There are no data on production levels, and the Pigment and Dyes Association estimates that no more than 'a few hundred pounds' are imported into the United States each year. Dr. Jameson said there are no quantitative data found on occupational exposure; however, it would be estimated that there would have been worker exposure in preparation of the dyes and in the nerve gas detector program.

No human studies of the relationship between exposure to 4,4'-thiodianiline and human cancer have been found. As to experimental animal studies, the NCI conducted 18-month dietary studies at two dose levels in B6C3F1 mice and F344 rats. The conclusions were that thiodianiline was carcinogenic for mice inducing tumors in the liver and thyroid of both sexes and carcinogenic for rats inducing tumors in the liver, thyroid, colon, and ear canal of male rats and thyroid, uterus and ear canal of females. In both sexes

of mice and rats, a majority of the thyroid and liver tumors were carcinomas and demonstrated metastases. Additionally, thiodianiline was shown to produce thyroid follicular cell hyperplasia and adenomas in 24-week studies with both transgenic and non-transgenic mice.
As to genotoxicity, thiodianiline has been shown to be mutagenic in some but not all strains of *Salmonella,* and it induced DNA damage in the brain, liver, urinary bladder and lungs of mice when administered by gavage. Dr. Jameson said there are no data on the absorption, distribution, metabolism, or excretion of thiodianiline in humans.

As to evidence of carcinogenicity of structurally related compounds, 4,4'-oxydianiline and 4,4'-methylenedianiline display similar patterns of tumors and are listed as *reasonably anticipated to be human carcinogens* in the RoC and a*s possibly carcinogenic to humans* by IARC (Group 2B). 4,4'-Methylenebis(2-chloroaniline) is listed as *reasonably anticipated* in the RoC, and is considered "*probably carcinogenic to humans*" (Group 2A) by IARC.

Dr. Jameson reported that RG1 (6 yes to 2 no votes) and RG2 (6 yes to 3 no votes) recommended that 4,4'-thiodianiline be listed in the 11th RoC as *reasonably anticipated to be a carcinogen*. The dissenting votes from these review committees centered on the paucity of exposure data leading to a concern that 4,4'-thiodianiline does meet the criteria for significant human exposure. The RoC Subcommittee asked Dr. Jameson about the extent of human exposure. Dr. Jameson responded that he was unable to get clarification about how the "few hundred pounds' imported yearly are used. He stated that the yellow dye derived from thiodianiline as a nerve gas detector is no longer used for that purpose.

Public Comments: None.

Primary Reviews: Dr. Bonney, a primary reviewer, agreed with the proposed listing based on the strong carcinogenicity data in animals and strong evidence of genotoxicity. He thought that although there appears to be little current human exposure, past exposure appears to be significant enough to meet the criteria for listing.

Dr. Frumkin, also a primary reviewer, agreed with the proposed listing based on the animal carcinogenicity data and evidence of strong genotoxicity. He noted that although current human exposure is unclear, past exposure of U.S. citizens and the potential for delayed toxic effects are sufficient to meet the RoC criteria.

Dr. Carpenter, also a primary reviewer, agreed with the proposed listing based primarily on the animal carcinogenicity findings. He said he had difficulty coming to grips with how extensive the historical human exposures might have been.

Discussion: Dr. Froines said the dyes provide a difficult exposure assessment problem as to when, where, and to what degree they are used and in general they are not regulated. He thought that NIOSH had not done much in evaluating them other than some of the benzidine-based dyes. Dr. Roberts reminded him that it is not the dye that is at issue but rather the precursor chemical. He raised the question of whether significant numbers of people in the United States have been exposed, and further, how many people exposed would define significant. Dr. Portier said that would be the RoC Subcommittee's judgment. Dr. Frumkin opined that past exposure is relevant since there are likely to be long-term, possibly delayed health effects, and he would argue for an inclusive interpretation that even a small number of persons exposed comprises a significant number persons. Dr. Popp didn't disagree, but said the problem is that we have no exposure data. Dr. Smith agreed and added that we do not know the numbers of persons exposed and whether the exposure is trivial. Dr. Moure-Eraso said that regardless of the criteria, it is imperative for public health to alert the non-scientific community about the carcinogenicity of chemicals. Dr. Froines agreed, but said that we do not want to go on record listing compounds for which there is no public health significance. Dr. Carpenter commented that if the material were used in an occupational or industrial setting, one would have to assume there is exposure.

Dr. Phillips had some technical comments on the COMET assay that was used to measure DNA damage and thought that these results favored thiodianiline being a genotoxic carcinogen. Dr. Froines said there seemed to be two positions among the members about human exposure - one being that there has been exposure in the past given that it was used in an occupational setting and the other being that there is simply no evidence. Dr. Portier thanked the RoC Subcommittee for its thoughtful discussion on this issue and added that Dr. Olden would carefully consider these comments before he makes a recommendation to the Secretary.

Dr. Frumkin moved that 4,4'-thiodianiline be recommended for listing in the 11th RoC as *reasonably anticipated to be a human carcinogen*. Dr. Carpenter seconded the motion. Dr. Frumkin urged voting for listing based on the carcinogenic potential of the chemical. The motion was accepted by 5 yes votes (Bonney, Carpenter, Frumkin, Karagas, Moure-Eraso) to 2 no votes (Charnley, Popp) with 2 abstentions (Roberts, Smith). Dr. Charnley said that the evidence does not support the statutory requirements for exposure. Dr. Popp also thought the evidence doesn't meet the exposure criterion as he understands it. Dr. Smith agreed that thiodianiline is a potent animal carcinogen, but the documentation of exposure is

inadequate and would not meet the criterion of a significant number of people. Dr. Roberts agreed with Dr. Smith and said he abstained because there is not enough information to say whether the criteria are met.

Dr. Froines said the lack of adequate human exposure information seems to be a generic issue and urged NTP and NIOSH, and also EPA with regard to environment exposures, interact more to improve the data that the RoC Subcommittee has available for its evaluation. Dr. Portier pointed out that NIOSH and NIEHS have a formal interagency agreement for conducting exposure assessment on specific compounds.

Dr. Portier thanked the RoC Subcommittee members for their deliberations and their time and efforts. He thanked the NTP staff for its efforts in making this a successful meeting.

Meeting was adjourned by Dr. Froines.

Prepared by Dr. Larry Hart

February 25, 2003

and Transplantation Research; 93.856, Microbiology and Infectious Diseases Research, National Institutes of Health, HHS)

Dated: September 13, 2002.

LaVerne Y. Stringfield,

Director, Office of Federal Advisory Committee Policy.

[FR Doc. 02–23956 Filed 9–19–02; 8:45 am]

BILLING CODE 4140–01–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

National Toxicology Program (NTP) Board of Scientific Counselors' Meeting; Review of Nominations for Listing in the 11th 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 November 19 & 20, 2002, at the Hyatt Regency Bethesda, One Bethesda Metro Center, 7400 Wisconsin Avenue, Bethesda, MD 20814. On November 19, registration will begin at 9 a.m. and the meeting will begin at 9:30 a.m. On November 20, 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, Executive Secretary, prior to the meeting (contact information given below). The agenda covers the peer review of 10 nominations for possible listing in the 11th Report on Carcinogens, and includes an opportunity for public input.

Background

The Department of Health and Human Services (DHHS) Report on Carcinogens (RoC) is a public information document prepared 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 peer review. Central to the evaluations of the review groups is the use of criteria for inclusion in or removal of listings from the RoC. The current criteria for listing in or delisting from the report is available on the Internet at the following website: *http://ntp-server.niehs.nih.gov/NewHomeRoc/ListingCriteria.html,* or can be obtained in hard copy by contacting Dr. Jameson at the address listed below. 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 public peer review 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 peer 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 for the 11th RoC.

Agenda

The meeting of the NTP RoC Subcommittee is scheduled for November 19 & 20, 2002. Tentatively scheduled to be peer reviewed are 10 nominated chemicals or exposure circumstances. These nominations are listed alphabetically in the attached table, along with supporting information and a tentative order of presentation and review. Background summary documents for each of the nominations are available to the public and include a summary of the scientific data and information being used to evaluate the nomination. A copy of the draft background summary document for each of these nominations is available electronically through the NTP's homepage at *http://ntp-server.niehs.nih.gov/* (select Report on Carcinogens) 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 Alexander Drive, Building 4401, Room 3118, P.O. Box 12233, Research Triangle Park, NC 27709 (919/541–4096; FAX 919/541–0144; email *jameson@niehs.nih.gov).*

Previous announcements in the **Federal Register** (July 24, 2001: Volume 66, Number 142, Pages 38430–38432 and March 28, 2002: Volume 67, Number 60, Page 14957) called for public comments on the nominations to be reviewed for possible listing in the 11th RoC. These announcements identified a total of 17 nominations. This review by the NTP RoC Subcommittee is for the first set of 10 nominations identified in those **Federal Register** announcements that have completed review by the RG1 and the RG2. The remaining 7 nominations for the 11th RoC will be reviewed by the NTP RoC Subcommittee in 2003. The date and details about that meeting will be published in a future **Federal Register** notice.

Solicitation of Public Comment

The NTP RoC Subcommittee meeting 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 for the meeting, persons requesting time for an oral presentation regarding a particular nomination should notify the Executive Secretary, Dr. Mary S. Wolfe, P.O. Box 12233, A3–01, Research Triangle Park, NC 27709 (telephone 919/541–3971; FAX 919/541–0295; email *wolfe@niehs.nih.gov*) no later than November 4, 2002. 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 November 4th 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, can be extended to 10 minutes. Individuals who register to make oral presentations by November 4th 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 then that for preregistered speakers and will be determined by the number who have registered at the meeting. 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 November 4, 2002 for distribution to the NTP RoC Subcommittee. Written comments received after November 4th 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.

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/* and upon request from Dr. Wolfe. Following the meeting, summary minutes will also be available on the NTP web site (*http://ntp-server.niehs.nih.gov*, select Meetings) and upon request from Dr. Wolfe.

Dated: September 12, 2002.

Samuel 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 NOVEMBER 19 AND 20, 2002

Nomination to be reviewed CAS number	Primary uses or exposures	To be reviewed for—	Tentative review order
1-Amino-2,4-dibromoanthraquinone/ (81–49–2)	1-Amino-2,4-dibromoanthraquinone is an anthraquinone-derived vat dye that is used in the textile industry.	Listing in the 11th RoC	1
Cobalt Sulfate/(10124–43–3)	Cobalt sulfate is used in electroplating and electrochemical industries. It is also used as a colorinig agent for ceramics, a drying agent in inks, paints, varnishes and linoleum, and has been added to animal feed as a mineral supplement.	Listing in the 11th RoC	6
Diethanolamine (DEA)/(111–42–2)	DEA is used in the preparation of surfactants used in liquid laundry, dishwishing detergents, cosmetics, shampoos, and hair conditioners. DEA is also used in metal working fluids, in textile processing, industrial gas purification and as an anticorrosin agent.	Listing in the 11th RoC	5
Naphthalene/(91–20–3)	Naphthalene is used as an intermediate in the synethesis of many industrial chemicals, an ingredient in some moth repellants and toilet bowl deodorants, as an antiseptics for irragatinig animal wounds and to control lice on livestock and poultry.	Listing in the 11th RoC	2
Nitrobenzene/(98–95–3)	Nitrobenzene is used mainly in the produdction of aniline, itself a major chemical intermediate in the production of dyes.	Listing in the 11th RoC	8
Nitromethane/(75–52–5)	Nitromethane is used in specialized fuels, in explosives and in the synthesis of nitromethane derivatives, pharmaceuticals, agricultural soil fumigants and industrial antimicrobials. In the past it was used as a chemical stabilizer to prevent the decomposition of various halogenated hydrocarbons such as metal degreasers and aerosol propellants.	Listing in the 11th RoC	4
Selected Heterocyclic Animes (Three Nominations): (1) 2-Amino-3,4-dimethylimidazo[4,5-f] quinoline (melQ)/(77094–11–2) (2) 2-Amino-3,8-dimethylimidazo[4,5-f] quinoxaline (MelQx)/(77500–04–0) (3) 2-Amino-1-methyl-6-phenylimidazo[4,5-b] pyridine (PhIP)/(105650–23–5)	MelQ, MelQx, and PhIP are heterocyclic amines that are formed during heating or cooking and are found in cooked meats and fish.	Listing in the 11th RoC	[1]3
4,4′-Thiodianiline/(139–65–1)	4,4′-Thiodianiline has been produced commercially since the early 1940s as an intermediate of several diazo dyes.	Listing in the 11th RoC	7

[1] These three nominations will be reviewed together.

[FR Doc. 02–23874 Filed 9–19–02; 8:45 am]
BILLING CODE 4140–01–P

DEPARTMENT OF HOUSING AND URBAN DEVELOPMENT

[Docket No. FR–4737–N–7]

Notice of Proposed Information Collection for Public Comment: HOPE VI—In-Depth Assessment of Family and Neighborhood Outcomes—Wave Two of Panel Study

AGENCY: Office of Policy Development and Research, HUD.

ACTION: Notice.

SUMMARY: The proposed information collection requirement described below has been submitted to the Office of Management and Budget (OMB) for review, as required by the Paperwork Reduction Act. The Department is soliciting public comments on the subject proposal.

DATES: Comment Due Date: November 19, 2002.

ADDRESSES: Interested persons are invited to submit comments regarding this proposal. Comments should refer to the proposal by name and/or OMB approval number and should be sent to: Mildred M. Hamman, Reports Liaison Officer, Public and Indian Housing Department of Housing and Urban Development, 451 7th St., SW., Room 4238 Washington, DC 20410–5000.

FOR FURTHER INFORMATION CONTACT: Mildred M. Hamman, (202) 708–3642, x 4128 or Robert A. Leonard, (202) 708–3700, x4027 for copies of the proposed survey or other documents. These are not a toll-free numbers.

SUPPLEMENTARY INFORMATION: The Department has submitted the proposal for the collection of information, as described below, to OMB for review, as required by the Paperwork Reduction Act (44 U.S.C. Chapter 35, as amended).

This Notice is soliciting comments from members of the public and affected agencies concerning the proposed collection of information to: (1) Evaluate whether the proposed collection of information is necessary for the proper performance of the function of the agency, including whether the information will have practical utility; (2) Evaluate the accuracy of the agency's estimate of the burden of the proposed collection of information; (3) Enhance the quality, utility, and clarity of the information to be collected; and (4) Minimize the burden of the collection of information on those who are to respond; including the use of appropriate automated collection techniques or other forms of information technology, e.g., permitting electronic submission or responses.

This Notice also lists the following information:

Title of Proposal: HOPE VI—In-depth Assessment of Family and Neighborhood Outcomes—Wave Two of Panel Study.

Office: Public Housing Investments in the Office of Public and Indian Housing, HUD

OMB Approval Number: Extension of OMB #2577–0236.

Description of the Need for the Information and its Proposed Use: Questions have been raised among some observers of the HOPE VI program about where the original residents of the developments are living. The purposes of the information collected for this study is to increase knowledge of the ways in which housing choices and outcomes of original residents are affected by revitalization efforts at selected HOPE VI sites. Data gathered will be used by the Urban Institute and Abt Associates to prepare a project report that will allow HUD to begin assessing the benefits of HOPE VI for the original residents, particularly those that may accrue to families choosing to move to other locations, and to provide more guidance to grantees on relocation choices and strategies. This notice covers the second and third waves of a three-wave panel study. The survey for waves 2 and 3 will cover the same topic areas as were addressed in the baseline survey: housing and neighborhood conditions; adult and child health; child education; adult employment, income and hardship; and relocation from public housing.

Form Number: None.

Members of Affected Public: 887 randomly selected original residents of the five selected HOPE VI sites that have received HOPE VI grants between 1998 and 2000 and that have not begun relocating residents.

Frequency of Submission: Once.

Reporting Burden:

	Number of respondents	×	Frequency of response	×	Hours per response	=	Burden hours
Original Residents	887		2		1		1,774

Total Estimated Burden Hours: 1,774.

Status of the Proposed Information Collection: Extension of previous approval.

Authority: Section 3507 of the Paperwork Reduction Act of 1995, 44 U.S.C. 35, as amended.

Dated: September 10, 2002.

Harold L. Bunce,

Deputy Assistant Secretary, for Economics Affairs.

[FR Doc. 02–23932 Filed 9–19–02; 8:45 am]
BILLING CODE 4210–62–M

DEPARTMENT OF HOUSING AND URBAN DEVELOPMENT

[Docket No. FR–4739–N–42]

Notice of Proposed Information Collection: Comment Request; Request for Proposals—Contract Administrators for Project-Based Section 8 Housing Assistant Payments (HAP) Contracts

AGENCY: Office of the Assistant Secretary for Housing-Federal Housing Commissioner, HUD.

ACTION: Notice.

SUMMARY: The proposed information collection requirement described below will be submitted to the Office of Management and Budget (OMB) for review, as required by the Paperwork Reduction Act. The Department is soliciting public comments on the subject proposal.

DATES: *Comments Due Date:* November 19, 2002.

ADDRESSES: Interested persons are invited to submit comments regarding this proposal. Comments should refer to the proposal by name and/or OMB Control Number and should be sent to: Wayne Eddins, Reports Management Officer, Department of Housing and Urban Development, 451 7th Street, SW., L'Enfant Plaza Building, Room 8003, Washington, DC 20410.

FOR FURTHER INFORMATION CONTACT: Deborah Lear, Office of Housing Assistance Contract Administration Oversight, Department of Housing and Urban Development, 451 7th Street SW.,

Attachment 2

NATIONAL TOXICOLOGY PROGRAM (NTP)
BOARD OF SCIENTIFIC COUNSELORS
REPORT ON CARCINOGENS (ROC) SUBCOMMITTEE MEETING
November 19-20, 2002

Crystal Ballroom - Baccarat Suites
Hyatt Regency Bethesda, One Bethesda Metro Center, Washington, DC

November 19, 2002

9:00 A.M. Registration
9:30 A.M. Welcome and Introduction

November 20, 2002

8:30 A.M. Welcome and Introduction

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

Nominations (CAS No.)	Primary Reviewers	NIEHS Staff Presenter	To Be Reviewed for
1-Amino-2, 4-dibromoanthraquinone (81-49-2)	David Phillips Rafael Moure-Eraso Margaret Karagas	Ruth Lunn	Listing in the 11th Report
Naphthalene (91-20-3)	Hillary Carpenter Howard Frumkin Stephen Roberts	C. W. Jameson	Listing in the 11th Report
Selected Heterocyclic Amines (3) *three nominations* 2-Amino-3,4-dimethylimidazo[4,5-f]quinoline (MeIQ)/ (77094-11-2) 2-Amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx) (75500-04-0) 2-Amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) (105650-23-6)	Allan Smith David Phillips Stephen Roberts	Ruth Lunn	Listing in the 11th Report
Nitromethane (75-52-5)	Rafael Moure-Eraso George Bonney James Popp	C. W. Jameson	Listing in the 11th Report
Diethanolamine (DEA) (111-42-2)	Allan Smith James Popp Gail Charnley	Ruth Lunn	Listing in the 11th Report
Cobalt Sulfate (10124-43-3)	Hillary Carpenter Gail Charnley	Ruth Lunn	Listing in the 11th Report
4,4'-Thiodianiline (139-65-1)	George Bonney Howard Frumkin Hillary Carpenter	C. W. Jameson	
Nitrobenzene (98-95-3)	James Popp David Phillips Margaret Karagas	C. W. Jameson	Listing in the 11th Report

Attachment 2

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