

**SUMMARY MINUTES  
NATIONAL TOXICOLOGY PROGRAM  
BOARD OF SCIENTIFIC COUNSELORS  
REPORT ON CARCINOGENS SUBCOMMITTEE  
MEETING  
October 30-31, 1997**

The National Toxicology Program (NTP) Board of Scientific Counselors' Report on Carcinogens Subcommittee (the Subcommittee) held its third meeting on October 30 and 31, 1997, at the National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, North Carolina. (Attachment 1: *Federal Register* meeting announcement; Attachment 2: Agenda and Roster of Members and Expert Consultants.) Members of the Subcommittee are Drs. Arnold Brown (Chairperson), John Bailer, Steven Belinsky, Eula Bingham, Clay Frederick, George Friedman-Jimenez, Carol Henry, Kim Hooper, and Franklin Mirer. Expert Consultant to the Subcommittee is Dr. Hiroshi Yamasaki. Dr. Bingham was present only on October 31. Dr. Henry was unable to attend; however, she was able to provide written reviews which were read into the record. Additionally, for this meeting the Subcommittee was supplemented by the participation of three *ad hoc* Expert Consultants: Drs. Stephen Hecht, University of Minnesota Cancer Centers; Karl Kelsey, Harvard School of Public Health and Medical School; and Shelia Zahm, National Cancer Institute.

- I. Introduction and Background: Dr. George Lucier, Director, Environmental Toxicology Program (ETP), noted that Congress had directed the Department of Health and Human Services to publish a Report on Carcinogens which would contain a list of substances (1) which either are known to be human carcinogens or may reasonably be anticipated to be human carcinogens, and (2) to which a significant number of persons in the United States are exposed. The National Toxicology Program was assigned responsibility for preparing the report. Seven complete reports have been published, and the eighth *Report on Carcinogens* (formerly the *Annual Report on Carcinogens*) will be submitted shortly to the Secretary. Dr. Lucier said that the 14 agents, substances and mixtures to be reviewed by the Subcommittee at this meeting were intended for the ninth *Report* projected for publication in 1999. He commented on the revised criteria, used for the first time by the Subcommittee a year ago, for determining which agents should be listed in or considered for delisting from the Report. These criteria allow for use of mechanistic information along with epidemiological and animal cancer data, permitting use of all relevant information and allowing for scientific judgement to be made. Dr. Lucier reviewed the sources of information supporting the nominations for listing or delisting selected for review. He noted that complex mixtures and exposure circumstances are now considered for inclusion in the *Report*. He concluded by stating that the open review by the Subcommittee allowed the opportunity for public comment.

Dr. Bill Jameson, NIEHS, commented on the preparation of draft background documents for each nomination which were provided to the reviewers as well as to the public. Dr. Jameson noted that written public comments had been received and also provided to the reviewers. Dr. J. Carl Barrett, Scientific Director, NIEHS, thanked the reviewers and the staff and commented on the national and international importance of the Reports in the protection of public health. Dr. Brown went over the

review format to be used with each nomination. Each nomination will be presented by an NIEHS scientist who will discuss the nomination, data relating to human cancer, animal cancer, mechanistic information, summaries of the arguments for or against listing or delisting, and will provide the recommendations, including the votes of the two previous Federal scientific review groups, the NIEHS/NTP Review Group (RG1), and the NTP Executive Committee's Interagency Working Group (RG2). Then the primary reviewer from the Subcommittee will present his/her evaluations of the nominations, followed by the secondary reviewer who should emphasize differences or areas of agreement with the primary reviewer. There will be time for public comments followed by further discussion among the Subcommittee and expert reviewers concluding with motions and votes by Subcommittee members on recommendations to be forwarded to the NTP. Dr. Brown said there had been 16 requests to make formal public statements addressing seven of the 14 nominations, and as well, written comments had been received from a number of individuals and organizations and made available to the reviewers and the public.

## II. Peer Review of Agents, Substances, Mixtures and Exposure Circumstances Nominated for Listing in or Delisting from the 9<sup>th</sup> Report on Carcinogens:

Tetrafluoroethylene—Dr. Joseph Haseman, NIEHS, said that tetrafluoroethylene (TFE) was nominated for listing as *reasonably anticipated to be a human carcinogen* by RG1 because of an NTP 2-year inhalation rodent bioassay study in which TFE increased the incidence of malignant neoplasms at multiple sites in rats and mice. He said potential human exposure is primarily occupational from the production of polyfluoroethylenes and resultant leakage from closed-capture systems. The primary target sites in the NTP study were kidney, liver, and hematopoietic (mononuclear cell leukemia) in rats and liver and histiocytic sarcoma in mice. There were no human cancer data found for this chemical and available genetic toxicity results were negative. Dr. Haseman reported that both RG1 and RG2 recommended unanimously with 10 and eight votes, respectively, that TFE be listed as *reasonably anticipated to be a human carcinogen*.

Dr. Belinsky, the primary reviewer, agreed with the proposed listing. He commented that the summary statement should be amended to accurately describe the *ras* mutation studies since TFE was not negative for the induction of H-*ras* mutations in mouse liver; rather a 15% incidence was found which is significantly lower than seen in controls suggesting that tumors were induced via a *ras* independent pathway. He thought there should be a description of the cytotoxic effects of TFE in human renal proximal tubule cells.

Dr. Hooper, the secondary reviewer, agreed with the proposed listing. He said it would be useful to compare the dose levels in rats and mice with those in the structurally-related tetrachloroethylene which in an NTP study was associated with a similar spectrum of tumors, and then compare dose levels of TFE that produced effects with what would be presumed occupational exposures. Because TFE is an aggressive animal carcinogen, occupationally exposed people should be made aware.

Dr. Belinsky moved that the nomination of tetrafluoroethylene for listing in the *Report* as *reasonably anticipated to be a human carcinogen* be accepted. Dr. Hooper seconded the motion, which was accepted unanimously with five votes.

Cadmium and Cadmium Compounds—Dr. Michael Waalkes, NCI at NIEHS, said that cadmium and cadmium compounds (cadmium) were nominated for listing as *known to be a human carcinogen* (currently listed in the *Report* as *reasonably anticipated to be a human carcinogen*) based on findings of increased risk of cancers in exposed workers or populations and evidence of malignant tumor formation by multiple routes of exposure at various sites in multiple species of experimental animals. He said that cadmium was listed as a Category 1 human carcinogen by the International Agency for Research on Cancer (IARC) in 1993. There is occupational and environmental exposure with most recent estimates that more than half a million workers are exposed to cadmium in the U.S. Cohort studies provide consistent evidence of elevated lung cancer risk in cadmium exposed workers. Cadmium causes a variety of genetic damage including mutations, chromosomal damage, cell transformation, DNA strand breaks, disrupted DNA repair, effects on gene expression, and, in humans, chromosomal aberrations. Dr. Waalkes reported that RG1 voted 7 to 1, and RG2 voted unanimously with 8 votes in favor of the recommendation to list cadmium and cadmium compounds in the 9th *Report on Carcinogens* as *known to be a human carcinogen*.

Dr. Kelsey, the primary reviewer, agreed with the proposed listing but thought the epidemiology studies showed a complex picture in that there is no way to completely determine that human exposure to cadmium can be separated from exposure to arsenic or other compounds. He noted also the conflicting data reported by NIOSH on a cohort from two plants, one where there clearly was a significant risk for lung cancer, the other where exposure to cadmium appeared to have a protective effect. The overall data in support of listing are quite strong including the data on prostate and bladder cancer in humans, the clear carcinogenic effects in animals, the genotoxic data, and mechanistic data.

Dr. Frederick, the secondary reviewer, also commented on the complexity in the epidemiology findings and said that he was influenced in his review by the 1997 British paper that intensively reanalyzed the original NIOSH cohort study. They stated that three possible conclusions could be drawn, two of which were that cadmium oxide and arsenic trioxide together were human lung carcinogens, and the third was that arsenic trioxide was a human lung carcinogen and cadmium was not. Dr. Frederick asked if Dr. Waalkes could provide additional insight. Dr. Waalkes responded that the British study did not (1) adjust for mobility of workers moving into less contaminated areas of the plant, (2) look at a post-1940 employment group when the cadmium feed stock was free of arsenic contamination, whereas one of the authors of the NIOSH study had followed this up and found a significant positive correlation with cadmium exposure levels and lung carcinogenesis. Finally, The British study never mentioned the actual levels of arsenic, while the IARC determined how many of the tumors would be associated with the arsenic exposure, and concluded that of the 24 or so tumors only one or two would be accountable by the levels of arsenic exposure. Dr. Mirer commented on how difficult it is to measure quantitative exposure levels in the occupational setting leading to the likelihood of misclassification errors. There

was further discussion around weighting chemical exposure appropriately relative to job function.

Dr. Kelsey moved that the nomination of cadmium and cadmium compounds for listing in the *Report* as *known to be a human carcinogen* be accepted. Dr. Frederick seconded the motion, which was accepted unanimously with six votes.

Chloroprene—Dr. Jameson said that chloroprene was nominated for listing as *reasonably anticipated to be a human carcinogen* by RG1 based primarily on a NTP 2-year inhalation study which demonstrated that chloroprene was a potent, multiple organ, trans-species carcinogen. Further, chloroprene is structurally related to the known human carcinogen, vinyl chloride, and is the 2-chloro analogue of 1,3-butadiene, currently listed in the *Report* as *reasonably anticipated to be a human carcinogen* and nominated to be changed to *known to be a human carcinogen*. Dr. Jameson reported the environmental release and estimated occupational exposure, reviewed the target sites and levels of evidence for carcinogenicity from the NTP study, and described the limited evidence for carcinogenicity in humans. Chloroprene was negative in a number of genotoxicity assays. However, lung and Harderian gland tumors in chloroprene exposed mice in the NTP study exhibited a high frequency of unique *K-ras* mutations. Dr. Jameson said that RG1 voted 7-0 (with two abstentions) and the RG2 voted unanimously with 8 votes to recommend that chloroprene be listed as *reasonably anticipated to be a human carcinogen*..

Dr. Henry, the primary reviewer, was unable to attend the meeting but had submitted her review, which Dr. Larry Hart, NIEHS, read into the record. Dr. Henry agreed with the proposed listing. She cited the convincing animal data while noting that the concentration of chloroprene cyclic decomposition products comprised less than 0.1% of the chloroprene concentration in the exposure chambers. She thought discussion would have been useful on stability of chloroprene in test samples especially those used in genotoxicity assays. Dr. Henry said that more information about the unique *K-ras* mutations would have helped.

Dr. Bailer, the secondary reviewer, agreed with the proposed listing. He commented that more attention should have been given in the summary statement of the background document to the structural analogy to known carcinogens. He said the human studies were quite weak so characterizing them under “limited evidence” was a fairly generous description. Dr. Frederick wondered as to why the NTP Technical Report on Chloroprene was still in draft form. Dr. John Bucher, NIEHS, responded that this study was one of those where there was evidence for *Helicobacter hepaticus* infection in mice, an infection shown to increase the incidence of liver tumors in male mice. After extensive analysis, the NTP concluded that the infection did not impact on the findings in the chloroprene report and the final report would be published in the near future.

Public Comment: Mr. Michael Lynch, DuPont Dow Elastomers L.L.C., said that his company was the only intentional producer of chloroprene in the United States. He pointed out the existence of a chronic inhalation bioassay of chloroprene sponsored by an industry group in the 1970s and conducted on Syrian golden hamsters for 18 months and Wistar rats for two years. The unpublished study showed that

chloroprene was not carcinogenic in either sex of either species at concentrations up to 50 ppm. In their opinion, the differences in the findings could be attributed to differences in the vapor generation techniques. Dr. Lynch reported that his company and others that produce chloroprene have initiated pharmacokinetic and other studies to better assess human health hazards

Dr. Bailer moved that the nomination of chloroprene for listing in the *Report* as *reasonably anticipated to be a human carcinogen* be accepted. Dr. Frederick seconded the motion, which was accepted unanimously with six votes.

1,3-Butadiene—Dr. Bucher said that 1,3-butadiene was nominated by RG1 for listing as *known to be a human carcinogen* (currently listed in the *Report* as *reasonably anticipated to be a human carcinogen*) based on studies in humans which have consistently found excess mortality from lymphatic and hematopoietic cancers associated with occupational exposure to butadiene, studies in experimental animals which have shown that 1,3-butadiene (butadiene) induces benign and malignant neoplasms at multiple tissue sites in multiple species, and supporting mechanistic data. Specifically, since IARC in 1992 categorized butadiene as probably carcinogenic to humans, new epidemiology data have strengthened the evidence linking exposure with increased human cancer risk, and recent research indicates that the metabolic behavior of butadiene is qualitatively similar in humans and laboratory animals. Dr. Bucher reviewed the information indicating a potentially large exposure of worker, primarily in butadiene monomer manufacturing and in the butadiene styrene synthetic rubber production industry, and emphasized that more recent epidemiology studies addressed many of the limitations of earlier studies, including use of modeling efforts that quantitatively estimated exposure to butadiene and styrene and performance of an interaction study that suggested a negative interaction between styrene and butadiene exposure. Dr. Bucher reported that RG1 voted 9 yes with one abstention and RG2 was unanimous with eight votes in support of listing butadiene as *known to be a human carcinogen*.

Dr. Mirer, the primary reviewer, agreed with the proposed listing. He stated that the epidemiology presents a strong picture if the hematopoietic tumors are considered together and believed there was biological plausibility for doing so. He noted especially the multiple studies finding of Delzell *et al.*, which found an SMR excess and exposure response, and those of Devine and Hartman.

Dr. Zahm, the secondary reviewer, agreed with the proposed listing. She emphasized how the epidemiologic data that have accumulated since the 1992 IARC review support the proposed change in classification for butadiene. In particular, she stressed the strengths of the Delzell *et al.* study which had almost 16, 000 subjects, an excellent exposure assessment, demonstration of dose-response, and evaluation of any confounding by styrene. Dr. Zahm said there were two studies omitted which should be cited, one of which was negative. This study does not detract significantly from the compelling evidence for human carcinogenicity provided by the other studies.

Public Comments. Dr. John Acquavella, Monsanto, representing the International Institute of Synthetic Rubber Producers, Inc., said that he was the project officer for most of the styrene-butadiene rubber (SBR) worker studies that were done. He stated

that the NTP has characterized the butadiene epidemiologic literature as showing a consistent excess of lymphatic and hematopoietic cancers (LHCs) associated with butadiene exposure. He said that, in fact, the epidemiologic literature shows variable results for LHCs. The evidence for leukemia is not consistent across studies, though one large study provides credible, internally consistent evidence of a relationship with butadiene exposure. Dr. Acquavella commented that while two studies show elevated mortality among short-term butadiene monomer workers, the larger study did not find excess mortality for long-term exposed workers and there was no exposure response relationship. In addition, none of the SBR worker studies provide evidence to suggest a relationship between butadiene and non-Hodgkin's lymphoma. He concluded that the butadiene epidemiologic literature should not be characterized as showing a consistent relationship between butadiene exposure and the various LHCs.

Dr. A. Philip Leber, Goodyear Tire and Rubber Company, said that Goodyear's economic interest in butadiene is related to its manufacture of butadiene copolymers used in numerous industrial, consumer, medical device, and food additive products. He contended that the NTP criteria call for sufficient evidence in humans indicating a causal relationship between the agent and human cancer, and briefly cited such evidence for industrial organic chemicals currently listed. He said that for butadiene there is significant question about its causality, as the three worker studies cited in support provide contradictory data. Further, since many chemicals besides butadiene are used within SBR operations, there is the possibility that other chemicals are confounders and likely involved in leukemia etiology in the workers.

Dr. James Swenberg, University of North Carolina, representing the Olefins Panel of the Chemical Manufacturers Association, said he would share a few new findings from his laboratory on the molecular dosimetry and molecular epidemiology of butadiene. He said the metabolism section in the background document should be expanded to reflect epoxy butenediol as the major metabolite in mice, rats and humans. In looking at formation of monepoxide and diepoxide adducts in the liver, at low concentrations rats and mice have identical molecular dosimetry but at 625 ppm, the mouse has over twofold greater numbers of adducts.

Dr. Elizabeth Ward, NIOSH, an author on one of the epidemiologic studies cited was asked by Dr. Brown for any comments. Dr. Ward stated that the Delzell *et al.* study used the best possible epidemiologic methodology and strongly established the association between butadiene exposure and leukemia.

There ensued a discussion about metabolism of butadiene pertaining to differences between mice and rats in formation of reactive metabolites and with regard to which species humans more closely resembled in metabolism of butadiene and formation of reactive metabolites and detoxification products.

Dr. Mirer moved that the nomination of 1,3-butadiene for listing in the Report as *known to be a human carcinogen* be accepted. Dr. Zahm seconded the motion, which was accepted by four yes votes to one no vote (Belinsky) with one abstention (Frederick). Dr. Frederick abstained for reasons of company affiliation.

UV Radiation—Dr. Freja Kamel, NIEHS, said that UV radiation (UVR) was nominated by RG1 for listing as *known to be a human carcinogen* based on the evidence that human studies have shown that exposure to solar radiation is causally related to skin cancer, and that use of sunlamps or sunbeds is associated with skin and eye cancer. She defined UV radiation as the portion of the optical spectrum between 10 and 400 nanometers (nm) with UVA being 315-400 nm, UVB being 280-315 nm, and UVC being from 100-280 nm. The nomination was based on the rather complex 1992 IARC classification, which classified solar radiation as carcinogenic to humans, UVA, UVB, and UVC radiation as well as sunlamps and sunbeds as probably carcinogenic to humans, and fluorescent lighting as not classifiable. Dr. Kamel discussed the various meteorological and personal behavior factors that cause wide variability in dosimetry. She reviewed the various sources of artificial radiation and the types of neoplasms seen with solar and UV radiation, including carcinogenic effects in experimental animals. UV radiation causes genetic damage in human and animal cells with UVC somewhat more potent than UVB, and both considerably more potent than UVA. RG1 voted unanimously with 11 votes to support the proposed listing, while RG2 voted by seven yes to one no votes to defer action until the background document was revised to address the full spectrum of UV radiation.

Dr. Henry, the primary reviewer, was unable to attend the meeting but had submitted her review, which Dr. Hart read into the record. Dr. Henry did not agree with the proposed listing. She noted that the body of evidence supporting the proposed listing was from four positive human studies dating from the mid-1980s or later. Dr. Henry pointed out that the most significant weakness in these studies was the lack of data regarding what the subjects were actually exposed to and how much. In addition, no causal mechanism has been formulated. She concluded that with limited evidence of carcinogenicity in humans, yet sufficient evidence in experimental animals, the most appropriate listing would seem to be *reasonably anticipated to be a human carcinogen*.

Dr. Kelsey, the secondary reviewer, agreed with the proposed listing. He said the data supporting UV radiation as a human carcinogen are clear, consistent and quite striking.

Dr. Kelsey moved that the nomination of UV radiation for listing in the Report as *known to be a human carcinogen* be accepted. Dr. Friedman-Jimenez seconded the motion, which was accepted unanimously with six votes.

Tobacco Smoking—Dr. Bucher said that tobacco smoking was nominated by RG1 for listing in the Report as *known to be a human carcinogen* based on studies in humans which indicate a causal relationship between exposure to tobacco smoke and human cancer. The rationale for nomination included the fact that there have been numerous previous evaluations of human data on cigarette smoking or tobacco smoking and cancer including the cancer societies of various northern European countries, the American Cancer Society, and the Canadian Department of Health and Welfare. In 1964 there was a report issued by the Advisory Committee to the U.S. Surgeon General linking smoking to cancer of the lung, lip, and larynx, and in 1979, the Report of the Surgeon General added cancer of the esophagus to this list. In 1986, the IARC reviewed tobacco smoking and that there was sufficient evidence that tobacco smoke was carcinogenic to humans, and new epidemiology data that have come out continue

to confirm and expand the evidence linking tobacco smoking with known and new tumor types and sites. The IARC review determined that there was also sufficient evidence in animals after inhalation exposure or topical application of tobacco smoke condensates. The review groups, RG1 and RG2, unanimously recommended listing of tobacco smoking as *known to be a human carcinogen*.

Dr. Frederick, the primary reviewer, agreed with the proposed listing and wondered why tobacco smoking had not been listed long ago. He noted that the nomination doesn't address environmental tobacco smoke and assumed that would be brought forward at a future meeting.

Dr. Zahm, the secondary reviewer, agreed with the proposed listing. She said the review document cites numerous studies, utilizing every study design but relying most heavily on cohort studies, which demonstrate that tobacco smoke is a human carcinogen.

Dr. Mirer stated that the sentence in the summary statement that "between 80 to 90 % of all human lung cancers and approximately 30 % of human cancers of all types are attributed to tobacco smoking" should be deleted. He said that more and more occupational and other factors are known to affect lung and other cancer risks, including a number of chemicals and chemical mixtures. Thus the methods of estimation essentially ignore interactions and make no effort to apportion the risks of co-exposures which may be multiplicative. Dr. Friedman-Jimenez disagreed with deleting the statement that 80-90 % of lung cancers are attributable to smoking. In asbestos workers who smoke, you can also have 80 % of cancers attributable to the asbestos exposure; they don't have to add up to 100 %. Dr. Belinsky agreed saying we don't want to diminish the impact that smoking has on cancer rates.

Dr. Frederick moved that the nomination of tobacco smoking for listing in the Report as *known to be a human carcinogen* be accepted. Dr. Zahm seconded the motion, which was accepted unanimously with six votes.

Smokeless Tobacco—Dr. Bucher said that smokeless tobacco was nominated by RG1 for listing in the Report as *known to be a human carcinogen* based on studies in humans which indicate a causal relationship between exposure to smokeless tobacco and human cancer. In 1985, the IARC evaluated the human data and determined that there was sufficient evidence that the oral use of snuffs of the type commonly used in North America and Europe is carcinogenic to humans. There was limited evidence that chewing tobacco of the types commonly used in these areas was carcinogenic. But there were a number of epidemiological studies that did not distinguish between chewing tobacco and snuff, and used as a whole provided sufficient evidence of carcinogenicity for oral use of smokeless tobacco products. Since that time, there have been new epidemiology data that have confirmed the evidence linking exposure with increased human cancer risk. Dr. Bucher said that the IARC found inadequate evidence to evaluate the carcinogenicity of smokeless tobacco products in experimental animals. More recent studies have provided some evidence of carcinogenicity in rats. Finally, there have been studies reporting positive relative risks for tumors at other sites in humans with the oral use of smokeless tobacco products, including rectum, kidney, and most strongly, the prostate. The RG1, with

nine yes votes and one abstention, and the RG2, unanimously with eight votes, recommended listing of smokeless tobacco as *known to be a human carcinogen*.

Dr. Hecht, the primary reviewer, agreed with the proposed listing. He commented that there are large amounts of carcinogens in smokeless tobacco, particularly nitrosamines, and that exposure to these carcinogenic nitrosamines is at least 10 times greater than through any other non-occupational exposure. Dr. Hecht thought the summary document superficial in its coverage of the published literature since 1985, and provided a number of references.

Dr. Bailer, the secondary reviewer, agreed with the proposed listing. He stated that studies which do not adjust or control for smoking should be excluded unless evidence of similar patterns of smoking between cases and controls is available or unless the case for the specificity of cancer site unique to smokeless tobacco can be made. Dr. Hooper asked whether more recent human studies reporting rectal, kidney or prostate cancer could be associated with nitrosamines. Dr. Hecht responded that although nitrosamines are systemic carcinogens, neoplasia of the rectum or prostate have not been demonstrated in animal studies.

Dr. Hecht moved that the nomination of smokeless tobacco for listing in the Report as *known to be a human carcinogen* be accepted. Dr. Bailer seconded the motion, which was accepted unanimously with six votes.

Strong Inorganic Acid Mists Containing Sulfuric Acid—Dr. Jameson said that strong inorganic acid mists containing sulfuric acid were nominated by the International Union, United Auto Workers (UAW), for listing in the Report as *known to be a human carcinogen* based on studies of occupational exposures that indicate a causal relationship between exposure to strong inorganic acid mists containing sulfuric acid and human cancer. Sulfuric acid, itself, is the largest volume chemical produced in the U.S., and yearly, over 770, 000 workers are exposed. Dr. Jameson reported five studies reviewed by the IARC that provided sufficient evidence of increased risk of laryngeal or lung cancer in workers exposed to strong inorganic acid mists containing sulfuric acid. A 10-year followup to one of the larger studies reported laryngeal cancer rates consistent with previous findings from this cohort. He said that there are no adequate experimental animal carcinogenicity studies reported in the literature. The mechanism for carcinogenicity may be related to genotoxicity of the low pH environment. Dr. Jameson said that the RG1 unanimously with eight votes and the RG2 by seven yes to one no votes supported the recommendation to list strong inorganic acid mists containing sulfuric acid as *known to be a human carcinogen*..

Dr. Yamasaki, the primary reviewer, agreed with the proposed listing. He thought the proposed mechanism of an enhanced depurination rate of DNA resulting from the low pH environment to be speculative in that studies from exposed humans indicate increased chromosome aberrations or sister chromatid exchanges, neither of which are linked to depurination.

Dr. Bailer, the secondary reviewer, agreed with the proposed listing. He thought it remarkable to have a case where there were human data to consider but not any adequate animal data.

Public Comment. Dr. James Hathaway, Rhone-Poulenc, Inc., representing the Panel on Inorganic Acid Mists of the CMA, said that they were convinced that the IARC decision to classify occupational exposure to strong inorganic acid mists as a known human carcinogen was flawed in that the cohort and case control studies cited as the basis were flawed. He noted that reanalyses of some of these studies were negative for cancer of the larynx as were other similar studies not cited in the summary document. Dr. Hathaway said that all animal studies were negative for tumors including studies done at the NIEHS at or above the maximum tolerated dose. Thus, the body of evidence is at best characterized as inadequate.

Dr. Hooper asked for comment from staff on the NIEHS studies. Dr. Jameson reported that studies were conducted under contract in the mid-1970s to address issues relating to catalytic converters, and were designed to expose animals to a combination of ozone and sulfuric acid. The results were negative and not published. Dr. Mirer said that an SMR study showing exposure response remains very strong evidence, and a number of indirect assessments detailed in the IARC document further support the conclusions. Dr. Hooper asked whether the primary and secondary reviewers were familiar with the reanalyses mentioned by Dr. Hathaway. Drs. Yamasaki and Bailer said they were and indicated that even though dose-response was lacking or hard to demonstrate the epidemiologic evidence was still quite compelling.

Dr. Yamasaki moved that the nomination of strong inorganic acid mists containing sulfuric acid for listing in the Report as *known to be a human carcinogen* be accepted. Dr. Bailer seconded the motion, which was accepted unanimously with six votes.

Tamoxifen—Retha Newbold, NIEHS, said that tamoxifen was nominated for review by RG1 for listing in the Report as *known to be a human carcinogen* based on epidemiological studies that indicate a causal relationship between exposure to tamoxifen and cancers of the uterine endometrium, and based on the IARC classification of the chemical as a Group 1, “Known Human Carcinogen” in 1996. Tamoxifen as its citrate salt is a pharmaceutical agent that is successfully used as a primary therapy to inhibit metastatic breast cancer and as an adjuvant therapy to prevent the recurrence of breast cancer in both pre- and postmenopausal women. It is known for its nonsteroidal antiestrogenic activity. RG1 and RG2 both recommended that a statement be included with the listing that “there is also conclusive evidence that tamoxifen therapy reduces the risk of contralateral breast cancer in women with a previous diagnosis of breast cancer, and for these women, the benefits clearly outweigh the risks.” Among its other pharmaceutical uses, tamoxifen is being used in chemoprevention trials which enlist disease free women; currently about 16,000, who are at high risk for developing breast cancer are being recruited into these studies. The proposed listing was derived from evaluation of the occurrence of primary uterine cancers diagnosed following tamoxifen treatment for breast cancer. Findings from carcinogenicity studies in animals were supportive of what was seen in humans. A likely mechanism of carcinogenic action is that while tamoxifen acts as an antiestrogen in the breast, accounting for its usefulness in preventing contralateral breast cancer, it acts as an estrogen agonist in the uterus. Other mechanisms may involve DNA adducts, micronuclei formation, increased aneuploidy, and chromosomal

aberrations. The RG1 unanimously with 10 votes and the RG2 with seven yes votes and one abstention recommended listing as *known to be a human carcinogen*.

Since Dr. Brown was to be a primary reviewer for this nomination, he temporarily turned the chair over to Dr. Lucier.

Dr. Brown, the primary reviewer, agreed with the proposed listing. He acknowledged concerns in a recent paper by MacMahon that sufficient attention had not been given to confounding factors such as prior hysterectomy and/or hormone replacement therapy. Dr. Brown stated that he did not believe relative rates of up to 7.5 for endometrial cancers could be disregarded on the basis of confounding factors.

Dr. Kelsey, the secondary reviewer, agreed with the proposed listing, noting that the epidemiologic data present a strong and coherent picture of an association between tamoxifen use and endometrial cancer. He commented on recent data showing that tamoxifen induces DNA adducts at relevant sites including uterine cells. Dr. Kelsey supported inclusion of a risk/benefit statement pertaining to its efficacy in women who have had breast cancer.

Public Comments. Dr. Mark Steinberg, Zeneca Pharmaceuticals, noted that Zeneca was the discoverer and developer of tamoxifen, the most widely prescribed breast cancer treatment in the world. He thought there were two points on which there could be agreement, with the first being that the data do not support an association of tamoxifen with primary hepatocellular carcinomas in humans, and, second, the endometrial cancers seen in women who have taken tamoxifen have a similar stage, grade, and prognosis to those seen in the general population. Dr. Steinberg then spoke of case control studies in breast cancer patients by Dr. Leslie Bernstein which indicated that when data from women who had received unopposed estrogens were eliminated from her analysis, the association between tamoxifen and endometrial cancer virtually disappeared. He said new and emerging data from the chemoprevention trials will support this conclusion. Dr. Steinberg stressed that listing tamoxifen as a human carcinogen will interfere with the patient-physician relationship.

Ms. Joscelyn Silsby, Cancer Research Foundation of America, said the Foundation is a nonprofit organization dedicated to cancer prevention through scientific research, education, and early detection. She wanted to share their perspective on the value of tamoxifen and their belief that labeling it as a substance known to be carcinogenic to humans without further research would be premature at this time. She said the research conducted to date has not established an absolute causal relationship between tamoxifen and endometrial cancer. Ms. Silsby said patients and their families are already informed of the risk of secondary cancers and faced with risk/benefit decisions that would be immensely complicated by the proposed labeling in the Report.

In further discussion by the members, Dr. Brown commented that the charge to the reviewers simply is to look at the data presented and decide whether or not tamoxifen can cause human cancer, in this case, endometrial cancer. He added that there are a number of cancer chemotherapeutic agents which are known human carcinogens, and

as with tamoxifen, it is the duty of the informed physician to clearly present this risk/benefit issue to the patient. Dr. Frederick agreed saying that the social overlay of how the information is used is beyond the scope of this committee.

Dr. Brown moved that the nomination of tamoxifen for listing in the Report as *known to be a human carcinogen* be accepted with the addition of the statement endorsed by IARC, RG1 and RG2 that there is conclusive evidence that tamoxifen reduces the risk of contralateral breast cancer, and that for women with breast cancer, the benefits of tamoxifen are clearly greater than the risks. Dr. Kelsey seconded the motion, which was accepted unanimously with six votes.

Phenolphthalein—Dr. June Dunnick, NIEHS, said that phenolphthalein was nominated by RG1 for listing in the Report as *reasonably anticipated to be a human carcinogen* based on the results of the NTP 2-year dosed feed study in which there were treatment related neoplasms in the kidney and adrenal medulla in male F344 rats, in the adrenal medulla in female rats, histiocytic sarcomas and malignant lymphomas of thymic origin in male and female B6C3F<sub>1</sub> mice, and ovary tumors in female mice. Dr. Dunnick reported that a subset of control thymus and thymic lymphomas from mice were stained with an antibody to p53 tumor suppressor genes and p53 protein accumulation was found in thymic lymphomas from treated mice suggesting that p53 gene alterations were involved. To learn more about mechanisms of phenolphthalein carcinogenicity, the chemical was given in the feed to p53 deficient mice at doses ranging from 200 up to 12,000 ppm for up to six months. (The animal model was developed by Donehower *et al.*) There were large numbers of thymic lymphomas seen in phenolphthalein treated groups, especially in the two highest dose groups which were equivalent to the low and high dose in the 2-year bioassay. Molecular biologic analysis showed loss of the p53 wild allele, while thymuses from animal room controls showed the normal p53 pattern of one null and one wild type allele. Increases in micronuclei formation in p53 transgenic mice were seen at dose levels within 10-20 times recommended human exposure levels. Dr. Dunnick said there are no published epidemiology studies that adequately examine the human cancer risk from exposure to phenolphthalein. The review groups, RG1 by 10 yes to 1 no votes, and RG2 by seven yes votes with one abstention recommended that phenolphthalein be listed in the Report as *reasonably anticipated to be a human carcinogen*.

Dr. Belinsky, the primary reviewer, agreed with the proposed listing. He commented that the doses that induced tumors both in the 2-year bioassay and in the 26-week transgenic studies were significantly higher than any anticipated human exposures and this should be noted in the summary statement.

Dr. Henry, the secondary reviewer, was unable to attend the meeting but had submitted her review, which Dr. Hart read into the record. Dr. Henry agreed with the proposed listing. She commented that in September 1997, the FDA proposed reclassification of the use of phenolphthalein in over-the-counter laxative products from “generally recognized as safe and effective...” to “not generally recognized as safe and effective...” Dr. Henry thought that a brief discussion about the incidence of colorectal cancer in Western societies would help explain why phenolphthalein was a logical substance for NTP to evaluate.

Public Comments. Ms. Laura Zeoli, Novartis Consumer Health Inc., said that Novartis is the manufacturer of Ex-Lax, the largest selling phenolphthalein containing over-the-counter laxative. She stated that Novartis disagrees with the conclusion that phenolphthalein was a potential human carcinogen via a genotoxic mechanism, and requests that any decision on listing in the Report be delayed. Further, while the p53 transgenic mouse may prove to be a valuable research tool, Ms. Zeoli said there is presently significant disagreement among toxicologists on the appropriateness of using these test results quantitatively for extrapolation to the human population and as the basis for a regulatory decision.

Dr. Hart read into the record written statements from Dr. John French, NIEHS, and Dr. Raymond Tice, Integrated Laboratory Systems, both of whom could not be present. Dr. French stated that he disagreed with the Novartis contention that phenolphthalein was not a potential human carcinogen via a genotoxic mechanism. He reported that phenolphthalein given in the diet to male and female B6C3F<sub>1</sub> mice for two years demonstrated the potential for genotoxicity *in vivo* by (1) increasing p53 protein overexpression in the nuclei of thymic lymphomas but not in the thymuses of untreated control mice, and (2) by loss of heterozygosity in mouse chromosome 11 contiguous with the p53 locus. He said that normal p53 tumor suppressor gene function is required for suppression of cancer and homeostatic maintenance of a nonmalignant phenotype in both humans and mice. Data collected to date on the function of p53 and the mechanisms of inactivation of p53 function are consistent between species. Dr. Tice was principal investigator for the project in which the phenolphthalein p53 study was conducted. He said that in a number of *in vivo* mouse studies, phenolphthalein induced a significant increase in the frequency of micronucleated erythrocytes. Based on these results, phenolphthalein is classifiable as an *in vivo* genotoxic agent.

There was some discussion around the loss of the wild type p53 allele in thymic lymphomas from phenolphthalein exposed animals and whether these were comparable with thymuses from control animals. Dr. Dunnick commented that in looking at non-target tissues, the kidney and ear, in animals with thymic tumors, these tissues had one wild type and one null p53 allele.

Dr. Belinsky moved that the nomination of phenolphthalein for listing in the Report as *reasonably anticipated to be a human carcinogen* be accepted. Dr. Mirer seconded the motion, which was accepted unanimously with six votes.

Saccharin—Dr. Robert Maronpot, NIEHS, said that the Calorie Control Council had petitioned the NTP to consider delisting saccharin from the Report based on extensive research supporting the safety of saccharin for human consumption. Saccharin is currently listed as *reasonably anticipated to be a human carcinogen*. Dr. Maronpot listed the extensive food and non-food uses of saccharin and reviewed the regulatory activity in the U. S. and elsewhere, as well as various pronouncements by the IARC and the Joint Expert Committee on Food Additives (JECFA) of the World Health Organization from 1980-1993. In 1984, JECFA determined the no observed effect level (NOEL) for urinary bladder cancer in rats to be 1% in the diet, and they set an estimated temporary average daily intake (ADI) for humans at the upper limit of 2.5

mg/kg body weight. Dr. Maronpot posed the question as to what is different now than before? He said that more papers have been published pertaining to carcinogenicity and, also, the NTP has revised criteria allowing use of mechanistic information in considering listing or delisting. He summarized the essential elements: (1) urinary bladder carcinogen in male rats given high dietary levels for prolonged periods, (2) urinary bladder carcinogen in mice after bladder implants of sodium saccharin-containing cholesterol pellets, (3) thyroid carcinogen in mice given sodium saccharin in water by gavage in one study, and (4) numerous initiation/promotion studies in bladders of rats with many positive. Among data gaps, saccharin has been less rigorously studied in female rats or mice, initiation/promotion studies for bladder cancer in mice are limited, and studies in hamsters and monkeys are inadequate for evaluation. Dr. Maronpot reported that there are numerous epidemiology studies, most of which focus on use of artificial sweeteners, rather than on saccharin alone. Therefore accurate saccharin exposures are generally not very precise or are unknown. Dr. Maronpot described a proposed mechanism of “male rat-specific” urinary bladder carcinogenesis predicated on high concentrations of urinary protein, mucopolysaccharides, and certain electrolytes associated with a calcium phosphate precipitate and a cascade of effects relating to urothelial toxicity, enhanced cell proliferation, and, ultimately, urothelial cancer.

Dr. Maronpot said the RG1 by seven yes to three no votes, and the RG2 by six yes votes to two no votes recommended that saccharin be delisted from the Report. He said that the conclusory paragraph in the background document states that under this proposed mechanism, “the factors thought to contribute to tumor induction by sodium saccharin in rats would not be expected to occur in humans.” Further, “although it is impossible to absolutely conclude that it poses no threat to human health, sodium saccharin is not reasonably anticipated to be a human carcinogen under conditions of general usage as an artificial sweetener.” Dr. Maronpot then spoke of the assumptions pertaining to under conditions of general usage. First, the NOEL in male rats for bladder cancer is 1% equaling 500 mg/kg/day, while in 1993 JECFA set the ADI for adult humans at an upper limit of 5 mg/kg/day, so there is a 100-fold difference between rat and human consumption. However, looking at consumption in children the U.S. Department of Agriculture indicates that children eat approximately twice as much saccharin as adults so therefore in children the difference is half he said. Further, if the surface area metric were used, and if the 90<sup>th</sup> percentile of human consumption were used instead of the average, then the safety factor drops to about 10 to 13-fold. Finally, he noted that the NOEL for cell proliferation in the rat urinary bladder was 1/10<sup>th</sup> that for a tumor response, or 0.1%.

Dr. Hooper, the primary reviewer, said that he was not convinced that the available data established the mechanism of cancer in rodents, nor was it sufficiently clear that it would differ from humans. Better understanding of the mechanisms of bladder cancer in rodents and humans would be helpful. He commented that in rats, the fetus binds four to five times as much saccharin in the bladder as does the maternal animal, while repeated dosing gives higher concentrations in the body than does single large doses. Looking at Dr. Maronpot’s figures, Dr. Hooper said that the rat doses may be only 2 to 5 or 20 to 50 times the average human consumption. He noted that in the two generation study in female rats there are positive results yet no indication of an

amorphous precipitate, and, again in implantation studies in mice, tumor bearing animals were not reported to have an amorphous precipitate.

Dr. Zahm, the secondary reviewer, expressed concern about the lack of two-generational and early life studies in mice, given that this is a substance likely to be heavily consumed by young women, and lack of an explanation for the positive findings in mice. Looking at the epidemiology, she focused on the largest study, the Hoover study, and said there was an excess of bladder cancer risk in the whole group, men and women combined, and there were excesses in some of the subgroups, e.g., nonsmoking women, where there would be a low risk of bladder cancer normally making an increase easier to detect. Dr. Zahm said it was important to note that the studies in the 1970s and 1980s were really artificial sweetener studies with probably heavy exposure to cyclamates. She thought the issue of whether sufficient latency had elapsed since the widespread use of saccharin began was critical, since bladder cancer is believed to have an average latency of 30 years or more. Further, one runs into the competing risk of cause of death as bladder cancer is something where the average age is over 70. Dr. Zahm concluded that there are some troubling subgroup findings that would mean the epidemiology could not be used to say that saccharin does not play a role in bladder cancer.

Public Comments. Dr. Robert Gelardi, President, Calorie Control Council, said that the Council had petitioned the NTP to have saccharin delisted from the *Report on Carcinogens* on the basis of NTP's new criteria incorporating the use of mechanistic data. He stated that the extensive data obtained during the past 20 years on saccharin clearly demonstrate that the bladder tumor findings in rats are not relevant to humans, and added that studies conducted in mice, hamsters, and monkeys have not resulted in any saccharin-related tumor development. Dr. Gelardi reviewed the mechanistic studies in male rats that indicate formation of an amorphous urinary precipitate at high doses lead to bladder tumors. He added that more than 30 human studies indicate saccharin safety at human levels of consumption.

Dr. Michael Jacobson, Executive Director, Center for Science in the Public Interest (CSPI), said that he spoke also on behalf of a number of scientists who cosigned a statement received by the Subcommittee, and who believe that numerous animal and human studies provide sufficient evidence that saccharin poses a risk and the only prudent course for the NTP would be not to delist saccharin. Their first concern was that saccharin causes bladder tumors in rats and at dose levels as low as 0.5% with smaller increases at 0.1%, which is certainly in the range of ingestion by children. Their second concern is that saccharin may cause tumors at sites other than the bladder and there is evidence for this in several rodent studies. Their third concern was that half a dozen case control studies found a significantly higher incidence of bladder cancer in people exposed to artificial sweetener.

Dr. Frederick described studies he did in female mice while at NCTR that were designed to see if mice were sensitive to saccharin and whether saccharin could serve as a promoter for a relatively low dose of a genotoxic carcinogen. Because of the initiation/promotion component, the study was taken out to 33 months, and to give a complete dose-response curve, doses ranged from 0.1 to 5 %. No toxic effects or preneoplastic lesions were seen in the mice. He said the other key issue here is

whether human urine is significantly different from rat urine. Dr. Frederick emphasized that many of the epidemiology studies were dealing with exposure to a mixture of materials, especially cyclamate. Dr. Bailer complained that we are trying to draw conclusions about the potential carcinogenicity of saccharin when most of the human studies involved mixtures of sweeteners. He thought there could be more discussion about the issue of dietary confounders. Dr. Zahm said there are not a lot of strong associations between dietary factors and bladder cancer.

Dr. Bailer asked whether there were any studies that identified possible changes in human bladders analogous to those seen in the male rat. Dr. Brown asked Dr. Samuel Cohen, University of Nebraska Medical Center, if he could address this issue. Dr. Cohen said he would but wanted to first comment on epidemiology studies of which he said the only one that gave a statistical overall risk of bladder cancer in humans was the Howe study, and that study had a major confounding factor, cigarette smoking, which was not taken into account. With regard to changes in the human bladder, Dr. Cohen reported there is only one study, that by Auerbach and Garfinkle published in *Cancer* in the late 1980s. Cigarette smokers were positive controls and showed increased cell proliferation in the bladder, while there was no increased level of proliferation in nonsmokers exposed to high doses of artificial sweeteners. Dr. Cohen gave a discourse on the composition of urine from rats and mice exposed to saccharin, noting that calcium and phosphate levels are 10-20 times lower in mouse than in rat urine, and the form of protein in male rat urine vs female rat urine may be key to formation of the precipitate. In response to a question from Dr. Yamasaki, Dr. Cohen opined that there is not just a quantitative difference between human and rat urine but also a qualitative one.

Dr. Bingham was troubled by the supposition that if there is only a slight increased risk in the overall study population then higher risks among subgroups could be dismissed. Dr. Zahm agreed that within an occupational setting, there are subgroups where the cancer risk may be much higher than the overall cohort. Dr. Mirer stated that all the issues around differences between rodents and humans in urine composition may enter into risk assessment but in terms of hazard identification based on the criteria, the animal data support *reasonably anticipated to be a human carcinogen*, and the epidemiologic data are on the border. Dr. William Allaben, FDA/NCTR, commented that whether or not saccharin remains listed or is delisted there will be no change in how FDA regulates at least until 2002 due to extension of the Congressional moratorium until then. Dr. Friedman-Jimenez pointed out that the subgroups in the Hoover study were determined *a priori* based on other reasoning and not on the data. With regard to the Howe study, he said that in the later reanalysis where smoking was controlled for there was little change in the relative risks. Dr. Hooper returned to mechanistic possibilities that had not been explored with saccharin. He said it binds to proteins, it binds to epidermal growth factor, it is known to be a protease inhibitor, it stimulates increases in P450 enzymes, and it induces ornithine decarboxylase. So until the mechanism of bladder cancer in humans is known he said he would be reluctant to say that rodent findings are not relevant to humans.

Dr. Hooper moved that saccharin not be delisted from the Report as *reasonably anticipated to be a human carcinogen*. Dr. Zahm seconded the motion, which was

accepted by four yes votes (Bingham, Friedman-Jimenez, Hooper, Mirer) to three no votes (Bailer, Belinsky, Frederick).

2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) -- Dr. Arnold Schecter, NIEHS, said that 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) was nominated by RG1 for listing in the Report as *known to be a human carcinogen* (currently listed as *reasonably anticipated to be a human carcinogen*) based on several types of evidence. The nomination took into account the IARC classification of TCDD as a Group 1 “Known Human Carcinogen” (IARC Monograph Vol. 69, 1997). Dr. Schecter described the chemical structure relationships of the dibenzodioxins and dibenzofurans and noted the dioxins are unwanted contaminants in wastes, industrial processes, and various consumer products with general population intake about 95% from food. With regard to epidemiology, he spoke of the combined international cohort and selected industrial cohort studies with high exposure levels focused on by IARC, which included the NIOSH (Fingerhut) study of U.S. chemical workers, the first study to use blood measurements of TCDD as an estimate of exposure. Dr. Schecter then reported on two studies published or in press since the IARC meeting. The first of these was the 15-year cancer mortality followup of an environmental exposure to TCDD in Seveso, Italy (Bertazzi *et al.*), which reported cancer mortality in three zones ranging from highest exposed (Zone A) through next highest exposed (Zone B) to third highest exposed (Zone R). The second study dealt with cancer mortality follow-up of an occupationally exposed Dutch cohort, a portion of whom were accidentally exposed to TCDD (Hooiveld *et al.*). Dr. Schecter summarized the many laboratory animal studies, noting that TCDD causes cancer by multiple routes, in multiple species, multiple strains, both sexes, and in multiple organs and tissues. With regard to mechanism, the scientific consensus is that binding to the aryl hydrocarbon (Ah) receptor is a necessary early step for all known TCDD effects. The Ah receptor is found in the cytoplasm of vertebrate cells from fish to humans. He said that there are numerous Ah receptor responses that have been characterized in experimental systems, many of which are relevant to plausible mechanisms of chemical carcinogenesis. The half-life of elimination for TCDD ranges from 2 to 4 weeks in laboratory rodents to between 5.8 and 11 years in humans. Dr. Schecter summarized the arguments supporting the proposed listing: (1) studies in humans strongly point to a causal association between exposure to TCDD and an increased incidence of cancers in highly exposed occupational cohorts; (2) all studies in rodents have been positive; (3) mechanistic studies support a common mode of action in humans and rodents and body burdens necessary to produce dioxin mediated responses are similar in rodents and human. Arguments against listing TCDD are (1) humans exposed to dioxins are also exposed to mixtures of other carcinogens, and (2) human cancer data alone may not be sufficient to establish causality between dioxin exposure and human cancer. Dr. Schecter reported that RG1 unanimously with 10 votes and RG2 unanimously with eight votes recommended listing TCDD as *known to be a human carcinogen*.

Dr. Yamasaki, the primary reviewer, stated that there is not sufficient evidence of carcinogenicity from studies in humans (epidemiological and mechanistic data combined) to support a causal relationship between TCDD exposure and human cancer. The lack of specific sites make the human data more difficult to interpret. He said that the mechanistic information available to us indicates that TCDD binding to

the Ah receptor is a necessary but not sufficient event for induction of tumors. Since TCDD binding to the Ah receptor induces the transcription of several genes, some of which are involved in cell growth and differentiation, it is biologically plausible that TCDD could induce tumors. Yet, more direct information in exposed humans is needed.

Dr. Frederick, the secondary reviewer, commented that TCDD is the ‘chameleon carcinogen’ as it seems to have different target sites for humans in different groups which have been studied. He demonstrated this by reviewing the tumor data associated with the three zones in the Seveso study. There did not seem to be a common lesion or organ site among the male and female cancer deaths nor did there seem to be correlations with tumors seen in occupational sites other than perhaps soft tissue sarcomas. Dr. Frederick then turned to proposed mechanism of tumor formation. He said that the early steps of TCDD binding to the Ah receptor and to DNA response elements have been elegantly elucidated but are not enough to explain its carcinogenicity.

Public Comments. Ms. Lisa Finaldi, Greenpeace International, said that Greenpeace strongly endorsed the decision by the NTP to consider new scientific evidence on the human carcinogenicity of TCDD. She stated that the recent action by IARC, the dioxin reassessment by EPA, and the conclusion by the Institute of Medicine about dioxin-contaminated herbicides lend support for similar conclusions and action by NTP linking TCDD to cancer in humans. She said Greenpeace recommends that NTP proceed with urgency to acquire sufficient resources for a broad but thorough assessment of all health effects of TCDD and like chemicals, with not only cancer as an outcome, but most urgently the effects of TCDD exposure on the developing fetus and nursing infant as well as the young child and adolescent.

Dr. Raymond Greenberg, Vice President and Provost, Medical University of South Carolina, representing the American Forestry and Paper Association, said the IARC working group concluded that there was limited evidence in humans for the carcinogenicity of TCDD because the associations observed were quite weak compared with those observed for known human carcinogens, the pattern of outcomes was unusual for a human carcinogen, the evidence for a dose-response relationship was quite limited, and there was strong evidence that confounding could not be ruled out.

Dr. Nathan Karch, Karch and Associates, Inc., representing the Chlorine Chemistry Council of the CMA, said that in his view, the epidemiologic evidence does not support a reclassification of TCDD with each key study acknowledging the potential for confounding or bias, a view consistent with EPA’s conclusion. This is marked by the lack of consistent elevations in specific tumor sites among various cohorts. Dr. Karch said the mechanistic data also provided little support in that the mechanism by which TCDD induces cancer in animals is not known, much less in humans.

Mr. Steve Lester, CCHW Center for Health, Environment, and Justice, supported the listing of TCDD as a known human carcinogen based on the strong evidence in human studies of an association, the compelling evidence in animal studies, and the mechanistic data showing a basic similarity between animals and humans. He noted the IARC’s overall conclusion, and the additional evidence from the continuing study

of the Seveso residents. Mr. Lester said this was not a decision about risk assessment but rather about hazard identification and not every single aspect of dioxin's mechanism needs to be known to make this decision.

Mr. Jim Tozzi, Multinational Business Services, Inc., providing staff support to the Center for Regulatory Effectiveness, stated that the proposal to list TCDD as a human carcinogen based on mechanistic data is a clear violation of Health and Human Services regulations. He said the reason for this is that when the criteria were recently revised, the criteria for listing as a known human carcinogen was not changed, and this was stated publically in writing. Thus, he suggested that to use mechanistic data to upgrade human data is not authorized by the law and is subject to judicial review.

There ensued further discussion by the Subcommittee of the epidemiology data. Dr. Hooper said he was not surprised by the wide variety of tumors seen in the Seveso residents and other cohort studies in view of TCDD being a multisite carcinogen in animals and also due to the nature of the purported mechanism. Some of the lack of target organ consistency may relate to the quite different exposure scenarios between the Seveso residents and occupational cohorts. He said the lack of genotoxicity makes defining a carcinogenic mechanism more difficult. Dr. Belinsky said that some of the mechanistic data is not useful and he found the epidemiology data confusing. Dr. Lucier spoke about the pieces of information used by RG1 and RG2 to support the listing. This included the compelling data on animal cancer, the agreement that the Ah receptor was the necessary channel for toxic events in both animals and humans, and the similar body burdens of TCDD associated with tumors in both species. Dr. Mirer said the mechanistic information for humans was not what it could be. Dr. Hooper wondered if deferral of the proposed listing until more human data were available could be an option. Dr. Bailer thought the epidemiological evidence as presented was fairly compelling particularly with all cancers and lung cancer. Dr. Yamasaki said his concern with the lung cancers was the confounding of smoking. Dr. Schecter noted that smoking considered in the NIOSH study and the conclusion was that smoking would contribute a small effect, if any. Dr. Douglas Sharpnack, NIOSH, said that NIOSH does have a policy of classifying TCDD as a potential human carcinogen, and their epidemiologists he thought are not as concerned about site specific epidemiology but place greater weight on the relative risks overall. Dr. Elizabeth Ward, NIOSH, agreed and said that her concern was increased by seeing increased risks of a large number of cancers at a number of sites, and particularly since TCDD causes cancer at multiple sites in animals.

Dr. Yamasaki moved that 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) continue to be listed in the Report as *reasonably anticipated to be a human carcinogen*. Dr. Frederick seconded the motion, which was defeated by three no votes (Bailer, Bingham, Friedman-Jimenez) to two yes votes (Belinsky, Frederick) with two abstentions (Hooper, Mirer). Dr. Mirer said he would like to see a deferral until the epidemiology information could be clarified. Dr. Bingham then moved that TCDD be listed in the Report as *known to be a human carcinogen*. Dr. Bailer seconded the motion, which resulted in a tie vote with three yes votes (Bailer, Bingham, Friedman-Jimenez) to three no votes (Belinsky, Frederick, Hooper) with one abstention (Mirer).

The Chairman, Dr. Brown, then voted yes to break the tie. The final vote was then four yes votes to three no votes with one abstention.

Trichloroethylene -- Dr. Jameson said that trichloroethylene was nominated by RG1 for listing in the Report as *reasonably anticipated to be a human carcinogen* based on evidence by the NTP in 1990 and by Maltoni *et al.* in 1988 where, by inhalation and gavage exposure to laboratory animals, trichloroethylene was demonstrated to be a multiple organ, trans-species carcinogen. Trichloroethylene also is structurally related to the known human carcinogen, vinyl chloride. Dr. Jameson reported environmental exposure to be more than 25 million pounds, and occupationally, more than 400,000 workers are potentially exposed. There is limited evidence of carcinogenicity to humans derived primarily from three cohort studies of workers. There is evidence for genotoxicity in some systems and not in others. Dr. Jameson said there is cancer site concordance between tumors observed in humans and animals, including liver, kidney, and lymphomas. Renal cell carcinomas from trichloroethylene workers exhibited different exon mutation patterns of the von Hippel-Landau (VHL) tumor suppressor gene, a gene associated with renal cell carcinoma, than did non-exposed renal cell carcinoma patients. He said that the glutathione S-transferase enzyme pathway that produces the ultimate electrophile - chlorothioketene - in proximal tubular cells is more prevalent in humans than in rats. Dr. Jameson said that RG1 voted seven to two, and RG2 voted seven to one to recommend that trichloroethylene be listed as *reasonably anticipated to be a human carcinogen*.

Dr. Mirer, the primary reviewer, agreed with the proposed listing. He said the animal data were straightforward and supported the listing. He commented that there were inconsistent tumor site data among the epidemiology studies. Dr. Mirer said the concluding statement supporting the listing implied that one needed to know the mechanism and suggested changing the wording to read "no compelling data indicating that the agent acts through mechanisms which do not operate in humans."

Dr. Kelsey, the secondary reviewer, was not present so as requested, Dr. Hart read his review into the record. Dr. Kelsey agreed with the proposed listing. He said the human data were indeed limited by small numbers, but thought the data on cancers of the kidney to be compelling. Dr. Kelsey thought the mechanistic studies on the VHL gene in exposed workers to be of great interest. The mutational spectra for trichloroethylene workers appeared to be different from that in non-exposed workers. He commented that the genotoxicity and metabolism data indicate there are definite electrophilic metabolites, a fact consistent with mechanistic data indicative of carcinogenic risk.

Dr. Mirer moved that the nomination of trichloroethylene for listing in the Report as *reasonably anticipated to be a human carcinogen* be accepted. Dr. Frederick seconded the motion, which was accepted unanimously with seven votes.

Dyes Metabolized to Benzidine (Benzidine-Based Dyes as a Class) -- Dr. H. B. Matthews, NIEHS, said that benzidine-based dyes were nominated by RG1 for listing in the Report as *known to be a human carcinogen* based on the fact that these dyes are metabolized to a known human carcinogen, benzidine, and on the fact that all

three of the benzidine-based dyes tested induced evidence of liver cancer in rats in 13-week studies. Benzidine-based dyes are readily synthesized by reaction of benzidine with a variety of aromatic amines to form azo linkage, and they are readily metabolically reduced by intestinal microflora to benzidine and the respective aromatic amine(s). He said that animal studies have demonstrated almost complete metabolic conversion to free benzidine in rodents, thus exposure to the benzidine-based dye is equivalent to exposure to an equimolar dose of benzidine. Epidemiological evidence for the carcinogenicity of benzidine-based dyes has been difficult to demonstrate because exposure is almost always associated with co-exposure to benzidine. However, an IARC evaluation concluded that “Although the epidemiological data were inadequate to evaluate the carcinogenicity to man of the individual dyes, they together with the presence of benzidine in the urine of exposed workers provides sufficient evidence that occupational exposure to benzidine-based dyes represents a carcinogenic risk to humans.” He said that benzidine carcinogenicity is attributed to its metabolism to the proximate carcinogen, N-hydroxy-N-acetylbenzidine, in the urinary bladder of humans and liver of rodents. Dr. Matthews said that RG1 by seven yes to one no votes and RG2 by unanimous vote supported the proposed listing.

Dr. Bingham, the primary reviewer, agreed with the proposed listing. She noted that while the U.S. is not producing these dyes, we do buy clothing from all over the world including places where these dyes are still used.

Dr. Hecht, the secondary reviewer, agreed with the proposed listing.

Dr. Bingham moved that the nomination of benzidine-based dyes for listing in the Report as *known to be a human carcinogen* be accepted. Dr. Hecht seconded the motion, which was accepted unanimously with seven votes.