SUMMARY MINUTES
OF THE
DECEMBER 2-3, 1998

NATIONAL TOXICOLOGY PROGRAM
BOARD OF SCIENTIFIC COUNSELORS
REPORT ON CARCINOGENS SUBCOMMITTEE MEETING

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The National Toxicology Program (NTP) Board of Scientific Counselors' Report on Carcinogens (RoC) Subcommittee (the Subcommittee) held its fourth meeting on December 2 and 3, 1998, 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.) Members of the Subcommittee are Drs. Arnold Brown (Chairperson), John Bailer, Steven Belinsky, Eula Bingham, Clay Frederick, George Friedman-Jimenez, Stephen Hecht, Carol Henry, Kim Hooper, Karl Kelsey, Michele Medinsky, Franklin Mirer, Jose Russo, and Shelia Zahm. Expert Consultant to the Subcommittee is Dr. Hiroshi Yamasaki. Dr. Friedman-Jimenez was present only on December 2.

I. Introduction and Background: Dr. George Lucier, Director, Environmental Toxicology Program (ETP), stated that Congress in 1978 mandated the Department of Health and Human Services (DHHS) to publish a Report on Carcinogens, and regularly update the Report, which would contain a list of substances (1) which either are known to be human carcinogens or may reasonably anticipated to be human carcinogens, and (2) to which a significant number of persons in the United States are exposed. The NIEHS was assigned responsibility for preparing the report. Between 1978 and 1996, seven reports were published, while the 8th *Report on Carcinogens* was published in 1998. Dr. Lucier highlighted several recent activities relevant to the *Report on Carcinogens* . First was to increase the opportunity for public input. Part of this had to do with formation of the Report on Carcinogens (RoC) Subcommittee in 1996 as a component of the NTP Board of Scientific Counselors. Prior to 1996, activities relevant to the listing process were done within the Federal government. The new subcommittee added another step of outside scientific peer review in an open meeting with greater opportunity for hearing public comments. Also, in 1996, the criteria for listing were revised to explicitly allow use of mechanistic information. Dr. Lucier described how the criteria were revised to include the consideration of all relevant information, including mechanisms, when applying the criteria, and that this impacted both categories with regard to listing as a *known* or *reasonably anticipated to be human carcinogen* or delisting from the report. He said that in the case of *known to be a human carcinogen* , it can include molecular epidemiology data, clinical data as well as traditional epidemiological data. A particular interest is whether or not an agent acts by a relevant mode of action for cancer in people. With regard to the *reasonably anticipated to be a human carcinogen* category, the use of mechanistic information can be used to list something in the absence of a positive animal or epidemiological study. On the other hand, an agent can be delisted from the *Report* if there is convincing evidence that the mechanism by which it produces cancer in experimental animals does not operate in humans. Dr. Lucier noted that in 1998, the review process was expanded to include consideration of exposure circumstances, some of which will be considered in this meeting. Dr. Lucier briefly reviewed the process leading up to listing in or delisting from the report. Nominations can come from anyone, and once received are reviewed by the NIEHS for substance, credibility and merit. A *Federal Register* notice is also published announcing the NTP's intention to review the nomination and to solicit public comment. The nomination is then formally reviewed by the NIEHS Review Committee for the Report on Carcinogens (RG1). The second step in the process is formal review by the NTP Executive Committee Interagency Working Group for the Report on Carcinogens (RG2). The third step is the external peer review and receipt of public comments by the RoC Subcommittee, both written and oral. This is followed by a third and final *Federal Register* notice requesting final public comments on the nominations. The next step is formal review by the NTP Executive Committee, which is comprised of agency heads or their

alternates from the Federal health research and regulatory agencies. Dr. Linda Rosenstock, Director of NIOSH, is currently chair of this committee. Following that recommendations of all four review groups are provided to Dr. Ken Olden, NTP Director, who makes his decisions on listing/delisting in the final draft of the Report which is submited to the Secretary of DHHS for approval and formal submission to Congress. Dr. Lucier said that we expect the Ninth *Report on Carcinogens* to be submitted to the Secretary sometime during the summer of 1999.

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, RG1 and 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 concluding with motions and votes by Subcommittee members on recommendations to be forwarded to the NTP. Dr. Brown said there had been 35 requests to make formal public statements addressing the 11 nominations to be reviewed at this meeting. In addition, 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 9th *Report on Carcinogens* :

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) – Dr. Scott Masten, NIEHS, presented the nomination and said that TCDD was currently listed in the 8th *Report on Carcinogens* as *reasonably anticipated to be a human carcinogen* , and was nominated by RG1 for upgrade to *known to be a human carcinogen,* based in part on the evaluation by IARC in 1997 that classified TCDD as Group 1, which formally states that "the agent (mixture) is carcinogenic to humans." Dr. Masten noted that this was the second review of this nomination by the Subcommittee. TCDD is primarily a contaminant in various manufacturing and incineration processes, while human exposure is primarily through food. There have been various episodes of much higher exposure in the workplace during production of chlorophenoxy herbicides, in specific segments of the population, and through documented instances of industrial accidental release. Dr. Masten said that over the past 20 years or so, there have been well over a dozen studies conducted on the experimental carcinogenesis of TCDD, all of which have been positive. TCDD causes tumors in multiple organs and tissues, in multiple species and strains of experimental animals, in both sexes, at very low non-acutely toxic doses, and by multiple routes of administration in a dose dependent fashion. TCDD is also a promoter for genotoxic carcinogens. Dr. Masten spoke to the evidence from human studies of TCDD exposure, noting there is a wealth of published epidemiological information, largely from occupationally exposed populations. He summarized the cancer data from six of the most highly exposed cohorts noting the relative risks for the several different types of cancers, and the epidemiology data from the Seveso incident which has been followed up since 1976. Dr. Masten concluded from this wide body of human epidemiology literature, there were significant associations in the highest exposed cohorts between TCDD exposure and elevated cancer mortality for all cancers combined and for specific sites. With regard to mechanism, TCDD binds to the intracellular aryl hydrocarbon (Ah) receptor, a step considered necessary for most if not all of TCDD responses. The function of this receptor is generally similar in humans and animals. Numerous Ah receptor dependent responses have been characterized in experimental systems, and many are relevant to plausible mechanisms of carcinogenesis. Dr. Masten summarized the arguments supporting the proposed upgrading of the listing of TCDD to a *known to be human carcinogen* based on: (1) it is carcinogenic in animals in multiple tissues, by multiple

routes of exposure, in multiple species and strains, and in both sexes; (2) an association between dioxin exposure and all cancers combined, lung cancer and non-Hodgkin's lymphoma in human studies; (3) similarity in Ah receptor function and responses to TCDD and structurally related compounds in humans and animals; and (4) similar responses in humans and animals at comparable dioxin body burdens. Arguments against the proposed upgrading were: (1) low relative risks for cancer mortality in human studies of TCDD-exposed populations; (2) confounding of cancer associations by other chemical exposures cannot be ruled out; and (3) the mechanism of carcinogenicity for TCDD has not been completely elucidated in animals or humans. Dr. Masten reported that RG1 unanimously with 11 votes and RG2 unanimously with eight votes recommended upgrading TCDD in the 9th Report to a *known to be human carcinogen* . Dr. Frederick commented that hormonal dependent sites were decreased and overall cancer incidence in the Seveso follow-up was not significantly elevated. Dr. Masten acknowledged this and responded that there is only a 15 year follow-up in the Seveso population and, further, it was a single exposure and not the continuous high level exposure seen in occupational cohorts.

Dr. Hooper, the primary reviewer, noted that in the previous RoC Subcommittee review of TCDD, he had voted against upgrading to *known to be a human carcinogen,* in part because there was not a known mechanism for TCDD as a human carcinogen. Having evaluated the epidemiology more in depth including the more recent literature, he now believed that the human, animal and mechanistic data supported an upgrade. Dr. Hooper said that in rats and mice, tumorigenic effects are seen at incredibly low doses, levels one might expect to see as a contaminant. With regard to the epidemiology data, he focused on the recent elegant reanalysis of the Boehringer study, the BASF study, and the NIOSH study. In all of these, there were elevated standardized mortality ratios (SMRs) for all sites combined. He stated that the high TCDD body burdens in these three studies suggest prolonged, high-level exposures to TCDD and likely little confounding by the weak or non-carcinogenic chemicals to which workers were concurrently exposed, such as trichlorophenol (TCP). Cigarette smoking was not considered a significant confounder either. Dr. Hooper concluded by commenting on the promoting actions of TCDD in animals and the evidence that the Ah receptor is involved in some part of the carcinogenic process, at least in promotion, and suggested that promotion is involved at many sites in humans.

Dr. Bailer, the secondary reviewer, said that in the previous review he had voted for upgrading. He said that in recently evaluating the epidemiology studies he found some that were not very informative, noting especially the Seveso cohort. He said there was no clear pattern associated with the exposure zones, and he also found the ranch hand cohort not very informative because of some of the potential confounding. Dr. Bailer said the data from the German cohort were the most extensive and convincing. Although he said the animal data were strong, there was a shadow of a doubt on the human data with regard to potential confounders and strength of dose response data to lead him to support TCDD remaining listed in the 9th Report as *reasonably anticipated to be a human carcinogen..*

Public Comments. Mr. Jim Tozzi, Multinational Business Services, Inc., representing the Center for Regulatory Effectiveness, complimented the NTP for listening to the public debate around the previous review of TCDD and agreeing to a rereview. However, he said that not a word had been changed in the background document, and it fails to address why it disagrees with the IARC working group conclusion that the human evidence is "limited" and the recommendation of their own consultant that the listing remain as *reasonably anticipated* . Further, he said that NTP is violating its own criteria for listing as *known to be a human carcinogen*, and, thus, could be subject to judicial review.

Dr. Nathan J. Karch, Karch & Associates Inc., representing the Vinyl Institute, said that he would focus on the use of mechanism by NTP. Dr. Karch stated that the NTP relied on IARC's reasoning that TCDD causes cancer in animals by acting through the Ah receptor with the receptor being highly conserved in mammals, functioning the same way in humans and animals. Dr. Karch presented four lines of evidence that highlighted the inadequacy of receptor binding as a basis for upgrading the classification of TCDD. He concluded that interspecies variability in response to TCDD was striking, with wide variability in half-life, distribution to various organs, and significant differences in toxicity among animal species and humans.

Dr. Raymond Greenberg, Medical University of South Carolina, representing the Chlorine Chemistry Council of the Chemical Manufacturers Association (CMA), began by emphasizing that the IARC panel in 1997 concluded that "there is limited evidence in humans for the carcinogenicity of TCDD". He said the three principal reasons for this conclusion were (1) risk elevations were quite small, (2) the most consistent association across all studies was with all cancers combined, without specific cancers predominating, and (3) confounding could not be excluded. Dr. Greenberg stated that the literature published since 1997 does not alter that conclusion.

Dr. Thomas Starr, representing the American Forest and Paper Association, reiterated the conclusions of the IARC panel, and noted that mechanistic evidence is still insufficient noting that the carcinogenic mechanism is not known in laboratory animals or humans. He also commented on the poor correlation with plausible dosimetrics in the most recent epidemiologic studies reported and referred to by Dr. Hooper. He urged the Subcommittee not to recommend upgrading of the listing for TCDD.

In further discussion, Dr. Frederick said that a problem for him was the lack of a clearly identifiable target organ in humans. Also of concern were the potential confounding effects of other inhaled materials on the incidence of lung cancers in industrial sites. He did not think the evidence was sufficient to drive the proposed listing on the basis of occupation of the Ah receptor. Dr. Frederick suggested that the immunosuppressive properties of TCDD may be changing the susceptibility of exposed individuals analogous to cyclosporin, and providing a plausible mechanism by which TCCD could be increasing human tumor response. Dr. Hooper emphasized the issue of dose, i.e., that microgram or sub-microgram doses produced tumors in rodent, as opposed to chemicals such as TCP which require much higher doses, and the issue of body burden in humans as relating to the long half-life of TCDD. He said there are several potential mechanisms for human cancer causality. Dr. Mirer supported the more recent epidemiology studies, especially the Flesch-Janys studies of one of the German cohorts, as providing clear evidence of carcinogenicity of TCDD in humans. Dr. Kelsey said mechanism is important but if you consider cigarette smoke we don't know the mechanism of cancer causation. Dr. Zahm liked the idea that TCDD acting in some way as a promoter could explain why there is no one cancer site that predominates, and why industrial cohorts seem to have more positive results than the Seveso cohort. She found the epidemiology data where so much of the interpretation relies upon all cancers combined to be very unsatisfying. Dr. Yamasaki commented that tumor promoting activity is usually considered to be tissue/organ specific and not associated with multisite tumors.

Dr. Hooper moved that the current listing of 2,3,7,8-tetrachlorodibenzo-*p* –dioxin (TCDD) be upgraded in the 9th Report to a *known to be human carcinogen* . Dr. Bingham seconded the motion, which was defeated by seven no votes (Bailer, Belinsky, Friedman-Jimenez, Hecht, Medinsky, Russo, Zahm) to five yes votes (Bingham, Frederick, Hooper, Kelsey, Mirer) with one abstention (Henry). Dr. Henry abstained because her employer, the American Petroleum Institute, has gone on public record in commenting on EPA's dioxin assessment.

Isoprene – Dr. Ronald Melnick, NIEHS, presented the nomination and said that isoprene was nominated for listing as *reasonably anticipated to be a human carcinogen* based on evidence that it induces benign and malignant tumors at multiple organ sites in multiple species of animals and because of its close structural relationship to the animal and human carcinogen, 1,3-butadiene. Dr. Melnick reported the environmental release and occurrence and potential occupational exposure, reviewed the target sites for carcinogenicity from the NTP bioassay and an industry study, and noted that no studies of potential carcinogenicity have been identified in humans. He reported that like butadiene, isoprene is metabolized to mono- and diepoxide metabolites, it is not mutagenic in *Salmonella* but the diepoxide is. Isoprene and butadiene both induced sister chromatid exchanges (SCEs) and micronuclei in mice. Lung and Harderian gland tumors in mice exposed to isoprene have a high frequency of unique K-*ras* mutations. Dr. Melnick reported that RG1 voted unanimously with six votes and RG2 voted 6-0 with one abstention to recommend that isoprene be listed in the 9th Report as *reasonably anticipated to be a human carcinogen* .

Dr. Henry, the primary reviewer, agreed with the proposed listing noting also that it belongs to a well defined structurally related class of substances whose members are listed in previous Reports. There are no data available to suggest that tumor induction by isoprene in animals would not also occur in humans. Dr. Henry noted that a comparison of estimated potential occupational exposures from the National Occupational Exposure Surveys from 1972 to 1974 with data from 1981 to 1983 suggest a dramatic reduction in potential exposure which should be pointed out and some explanation given in the document. She recommended that the summary statement include a comparison of isoprene with 1,3-butadiene regarding potency, common genotoxic metabolites, endogenous levels, differences in species response, and how a practical threshold for carcinogenic hazard might be characterized for external exposure.

Dr. Mirer, the secondary reviewer, also agreed with the proposed listing suggesting that the structure activity relationship could push it in the direction of a mechanistic basis for listing it as a *known human carcinogen*. He thought comparison with vinyl chloride was not appropriate because vinyl chloride does not have a conjugated double bond , while furan should have been included in a comparison. Dr. Mirer noted the increase in forestomach tumors with a substance not given by gavage.

Public Comment. Dr. Philip Leber, Goodyear Tire and Rubber Company, representing the International Institute of Synthetic Rubber Producers, Inc. (IISRP), said that he and his group had reviewed the basis for the proposed listing and found it scientifically deficient. Dr. Leber stated that in the NTP bioassay, it is implicit that benign and malignant tumors are interchangeable with no documentation to suggest that the benign tumors in question are known to progress to malignancy in support of the criteria for clear evidence in rats. Secondly, Dr. Leber said the estimated potential exposure of workers to isoprene is greatly overstated in numbers, 350 vs. 3700, and in degree. Industrial hygiene surveys indicate that over 91 % of workers are exposed to less than a part per million on a time weighted average basis.

Dr. Mirer moved that the nomination of isoprene for listing in the 9th *Report* as *reasonably anticipated to be a human carcinogen* be accepted. Dr. Henry seconded the motion, which was accepted unanimously with 13 votes

Alcoholic Beverage Consumption – Dr Bill. Jameson, NIEHS, presented the nomination and said that alcoholic beverage consumption was nominated for listing in the *Report* as a *known to be human carcinogen* based on epidemiologic studies that indicate a causal relationship between consumption of alcoholic beverages and an increased risk of cancer in humans. He reviewed figures on the consumption of the three major classes of alcoholic beverages, wine, beer, and

spirits. Dr. Jameson reported that there are multiple studies reported by IARC and subsequently that provide evidence that consumption is causally related to cancers of the mouth, pharynx, larynx, and esophagus, while other epidemiology studies indicate there may be a causal relationship with cancers of the liver and breast. He identified 59 of the largest case control and cohort studies for consumption of alcoholic beverages and gave relative risks (RRs) for the various target sites. There are no adequate experimental animal studies for alcoholic beverages, and the mechanism by which consumption of alcoholic beverages causes cancer in humans is not established. Dr. Jameson said that RG1 voted 6/1 and RG2 voted unanimously with seven votes both to recommend that alcoholic beverage consumption be listed as a *known to be human carcinogen*.

Dr. Friedman-Jimenez, the primary reviewer, strongly agreed with the proposed listing. He reviewed the epidemiologic data site by site and discussed why he didn't think that the conclusions had changed since the major IARC review in 1988. He noted that the relative risks for heavy drinkers were an order of magnitude larger than the other studies with some over 100. Dr. Friedman-Jimenez addressed the key issue of confounding, especially tobacco smoking since it is a risk factor for all four cancers. He stated that most of the studies for the four major cancer sites were controlled for smoking, i.e., all of the case control and a few of the cohort studies and relative risks remained high with a clear dose response at virtually all sites. He reviewed the evidence for breast cancer in women, and liver cancer. With regard to breast cancer, the inability to rule out confounding by unmeasured risk factors correlated with alcoholic beverage consumption made the statement on possible causal relationship appropriate. With regard to liver cancer, his major concern was that most of the key case control studies of liver cancer in alcoholic beverage consumption seemed to have excluded controls who had a history of alcohol related disease thus under-representing certain groups such as heavy drinkers. The case control studies did not suffer from this methodologic difficulty. Dr. Friedman-Jimenez commented that the summary statement should mention the inconsistency between the possible acetaldehyde mechanism, which suggests a systemic effect, and consistent findings that the strongest associations are with cancers of tissues most directly exposed to alcoholic beverages, suggesting a locally mediated effect.

Dr. Medinsky, the secondary reviewer, did not agree with the proposed listing. She concluded that the strength of the epidemiology studies was derived from the portion of the study groups with high alcohol consumption and these individuals also have additional risk factors or confounders that complicate interpretation. The confounders are common in a lifestyle associated with excess alcohol consumption, including smoking, inadequate nutrient intake, and viral infection. Thus, Dr. Medinsky thought the lifestyle including alcohol could be known to be carcinogenic to humans, while the confounders preclude an attribution of risk to any particular exposure which includes alcohol. With regard to a possible mechanism, she observed that inhalation studies with acetaldehyde demonstrate that it is a carcinogen only at the portal of entry, thus it is unlikely that acetaldehyde generated through metabolism from ethanol would be carcinogenic.

Public Comments. Dr. William Waddell, University of Louisville, representing the Alcohol Beverage Industry, said his comments would address only the association between alcohol drinking and cancers of the oral cavity, pharynx, larynx, and esophagus. He noted that the background document cites the largest case control studies and a review by Longnecker and Tseng as evidence for the proposed classification. Dr. Waddell said that the review states that "the effect of alcohol among lifelong nonsmokers has been clearly demonstrated." However, he stated that references cited clearly contradict or do not agree with the statement. He reported that he had examined the case control studies cited in the document for oral, pharyngeal, laryngeal, and esophageal cancers particularly for nonsmokers and observed inconsistent findings and increases

in cancer incidence only at levels of consumption which are those of an alcoholic and the alcoholic lifestyle. Dr. Waddell concluded that the data do not support labeling alcoholic beverage consumption independently as a known human carcinogen.

Dr. Emanuel Rubin, Jefferson Medical College, spoke to the possible association between alcohol drinking and cancer of the breast and liver. He commented that alcohol *in vitro* inhibits cell proliferation and had never produced an experimental carcinoma. With regard to liver cancer, 85 % of alcoholics do not get cirrhosis and do not develop liver cancer. Prevalence of hepatitis B virus is increased in alcoholics two to four times over the general population, and hepatitis B is the single most common cause of liver cancer in the world. With regard to breast cancer, Dr Rubin concluded that there are so many confounders in life style that it is difficult to determine association, with only heavy alcohol consumption associated with modest increases in breast cancer

In further discussion, Dr. Zahm observed that in the oral-esophageal studies, virtually all are confounded by smoking but this is adjusted for in the evaluation of the data. With regard to diet or other lifestyle factors, excess risks would have to be larger than observed to explain away the alcohol associated excess risk. With regard to mechanism, she said that people who are fast metabolizers of alcohol because of genetic polymorphisms for alcohol dehydrogenase are at much higher risk for oral cancer which lends credibility to alcohol being the carcinogen. Dr. Belinsky proposed that the data describe to him a synergistic interaction between alcohol and tobacco. Dr. Mirer asked whether there are clean studies that show a relative risk for a nonsmoking population. Dr. Matthew Longnecker, NIEHS, who served as a secondary reviewer for the NIEHS Review Group (RG1), responded that there were a few and he interpreted these to show a dose response in nonsmokers. Dr. Bingham alluded to the possible synergistic effects of smoking and alcohol perhaps analogous to smoking and asbestos or alcohol and vinyl chloride. Dr. Zahm noted that with oral cancer at least there is an independent effect of alcohol itself. Dr. Lucier commented that we have to come back to the main issue, and that is whether alcoholic beverage consumption is a known human carcinogen, and to which a significant portion of the U.S. population is exposed.

Dr. Friedman-Jimenez moved that the nomination of alcoholic beverage consumption for listing in the *Report* as a *known to be human carcinogen* be accepted with a proposed change in language of the first sentence of the summary statement. The sentence would be replaced with the following statement: "Consumption of alcoholic beverages is causally related to cancers of the mouth, pharynx, larynx, and esophagus. Cohort and case control studies in a variety of human populations are notable for their consistency in reporting the presence of moderate to strong associations with dose-response relationships for these four sites." Dr . Mirer seconded the motion. Dr. Frederick proposed an amendment to change the second sentence of the first paragraph from "Studies indicate that the risk is most pronounced at the highest levels of consumption" to "Studies indicate that the risk is most pronounced among smokers and at the highest levels of consumption." Dr. Bailer seconded the amendment. Dr. Friedman-Jimenez interjected that he had misspoken and the sentence he wished to replace as part of his motion was actually the first sentence of the second paragraph of the summary statement. Dr. Frederick's amendment was accepted by 11 yes votes to 2 no votes (Medinsky, Russo). Dr. Friedman-Jimenez's corrected motion was then accepted by 9 yes votes to 3 no votes (Belinsky, Medinsky, Russo) with 1 abstention (Bingham). Dr. Bingham said that she had abstained because the issue of synergism of alcoholic beverage consumption and smoking had not been dealt with to her satisfaction.

Environmental Tobacco Smoke – Dr. John Bucher, NIEHS, presented the nomination and said that environmental tobacco smoke was nominated by RG1 for listing in the *Report* as a

known to be human carcinogen based on previous evaluations of the data on passive smoking or environmental tobacco smoke by the IARC, the U.S. Surgeon General, and the National Research Council, all in 1986, by the USEPA published in 1992, and most recently an extensive evaluation of the health effects of environmental tobacco smoke published by the California EPA in 1997. The studies also support association of environmental tobacco smoke with cancers of the nasal sinus. Environmental tobacco smoke (ETS) is a complex mixture of gases and particles comprised of sidestream smoke from the burning cigarette, pipe, or cigar tip, mainstream smoke that is not inhaled by the smoker, and exhaled smoke. Approximately half of ETS by weight is sidestream smoke. Dr. Bucher said it has been estimated that ETS contains over 4,000 chemicals, a number of which are known to be carcinogenic and toxic. There is sufficient evidence that inhalation of tobacco smoke as well as topical application of tobacco smoke condensates cause cancer in experimental animals. Tobacco smoke condensates are mutagenic in a wide variety of *in vitro* mammalian cell and bacterial systems. Dr. Bucher reviewed the primary human studies to date beginning with the 1986 IARC studies of cancers related to spousal smoking where some showed increased risk in relation to the extent of spousal smoking and others did not. However, based on knowledge of the nature of sidestream and mainstream smoke and the materials absorbed, they concluded that passive smoking leads to some risk of cancer. The Surgeon General in his 1986 report concluded that "the absence of a threshold for respiratory carcinogenesis in active smoking, the presence of the same carcinogens in mainstream and sidestream smoke, the demonstrated uptake of tobacco smoke constituents by involuntary smokers, and the demonstration of an increased lung cancer risk in some populations with exposures to ETS, lead to the conclusion that involuntary smoking is a cause of lung cancer." The USEPA in 1992 analyzed data from 27 case-control and 4 cohort studies of lung cancer in nonsmoking women married to smokers or nonsmokers. Pooled relative risks were generated through meta-analysis. The pooled RR of lung cancer was 1.19 with a 90% confidence interval that did not include 1 with the conclusion being that ETS is a group 1 carcinogen. Dr. Bucher said that the California EPA published a report in 1997 that dealt with potential systematic biases in studies of spousal exposure. Between the EPA 1992 report and the 1997 California EPA evaluation, there were three large case control studies published that addressed potential systematic biases to a great degree. These were the Stockwell *et al.*, 1992, study; the Brownson *et al.* , 1992, study; and the Fontham *et al.*, 1994, study, which is considered the best study in the literature at this time. All three gave results compatible with causal association of ETS and risk of lung cancer in nonsmokers. Dr. Bucher reported there have been a number of studies that have published information looking specifically at the issue of lung cancer risk of nonsmokers exposed only in occupational settings. In a recent paper sent to the Subcommittee, five of 14 available studies addressing this issue were found useful and when considered in a meta-analysis gave a pooled odds ratio of 1.39 with a 95% confidence interval that did not include 1. The RG1 with seven yes votes and one abstention and the RG2 by five yes to two no votes , recommended environmental tobacco smoke be listed in the 9th Report as a *known to be human carcinogen* . Dr. Bucher concluded by reporting on a paper by Boffeta *et al.* , which was published since the RG1 and RG2 reviews, and had been provided to the Subcommittee before the meeting. This paper describes a multi-center case control study of exposure and lung cancer in Europe (the IARC multi-center study). Odds ratios reported in this paper were in the same range as those reported in the earlier studies discussed.

Dr. Zahm, the primary reviewer, agreed with the proposed listing. She focused her review on the epidemiologic data primarily on studies looking at nonsmoking spouses of smokers, nonsmokers exposed in the workplace and among persons exposed as children to their parent's smoke. The spousal research and to a lesser extent, the occupational studies, have consistently shown excess lung cancer associated with ETS. The spousal exposure has been consistently associated with increased risks of about 20 to 30%. Although increased risks of 20% are difficult to establish as causal associations in epidemiologic research, Dr. Zahm proposed to examine the criteria for

judging causality of epidemiologic data. First, there is consistency of the findings across numerous studies, particularly if recency of exposure is taken into account. Second, some evidence of dose-response is present in most studies, a critical feature. The next thing would be looking at different biases. She said that selection bias is unlikely to explain away the result, particularly for the recent studies, while likely sources of confounding have been evaluated and not found to account for the association. Finally, the association between ETS and lung cancer is certainly biologically plausible based on animal data and on the well established relationship with direct tobacco smoking.

Dr. Yamasaki, the secondary reviewer, agreed with the proposed listing. He noted that IARC in 1986 did not conclude a causal relationship between passive exposure to tobacco smoke and human lung cancer because the evidence was not conclusive at that time. Since the components of ETS are very similar to mainstream smoke, it is scientifically very plausible that ETS is associated with human cancers.

Public Comments. Dr. Roger A. Jenkins, Oak Ridge National Laboratory, said the views he would present were his own although his appearance was sponsored by the Center for Indoor Air Research. His purpose was to contrast definitive data from their laboratory with assumptions made by EPA in its risk assessment on lung cancer. The data were from a 16 city study of exposure to ETS in the home, away from work, and in the workplace which measured a variety of constituents both in the particle and vapor phases as well as salivary cotinine. Dr. Jenkins contrasted their measured Z-factor data (ratio of ETS exposure to a female living with a smoking spouse vs. that in a female living with a nonsmoking spouse), and misclassification rates for lifetime never smoking females. Dr. Jenkins stated that using their definitive data, rather than EPA estimates, would act to lower estimated relative risk.

Mr. Keith Phillips, Covance Laboratories Ltd., presented data from their 11 city study of office worker's exposure to ETS with measurements of many of the same markers as described by Dr. Jenkins. The concentrations found were converted into potentially inhaled quantities using the estimated amount of air that a person might breathe in over a period of time. He said there was close similarity between their data and those reported by Dr. Jenkins where comparisons were possible

Dr. Chris Coggins, Lorillard Tobacco Company, reported that published negative rat studies for lung tumor induction by ETS submitted for inclusion in section 4 of the background document had not been used. He contended that the contractors had ignored the full body of available evidence in animals and had placed complete reliance on a few recent studies employing a single hypersensitive animal model, the strain A mouse. Dr. Coggins concurred with a quote by the authors of the original strain A mouse study that "the usefulness of our animal model for the study of human tobacco smoke induced lung cancer remains to be established."

Dr. Paul Levy, University of Illinois at Chicago, representing the R.J. Reynolds Tobacco Company, said the work he was presenting was his own and concerned meta-analysis of studies on workplace ETS and lung cancer. He contrasted meta-analyses done by himself and three other investigators on workplace exposure to ETS that found odds ratios very close to unity and not significant, with the recent meta-analysis by Wells, which was statistically significant. He explained the differences by there being different judgments concerning appropriate data points, use of the fixed effects method by Wells rather than the random effects method, and use by Wells of only five of the 16 studies.

Mr. James Repace, Repace Associates, said that he commissioned the EPA study (that was published in 1992) in 1987, and their report was reviewed by an outside science advisory board of 18 independent experts who unanimously endorsed the report, heard the tobacco industry's comments and rejected them. He discussed models used by him and associates to measure nicotine and cotinine in blood and urine, and how they can be used now to assess exposure and improve greatly the assessment of epidemiology. In response to a question from Dr. Medinsky, Dr. Repace said a major flaw in epidemiology studies on ETS is in defining unexposed controls.

Dr. Richard Carchman, Philip Morris U.S.A., said that he would give comments on the IARC multi-center study, one of the largest, well conducted, and most comprehensive epidemiology studies in that it also had a mechanistic component. There was no statistically significant overall increased risk reported for any sources of reported ETS exposure. He said IARC collected data on many sources of bias but did not report an odds ratio adjusted for all of these factors. Dr. Carchman said that if all the adjustments had been made the reported excess risk would have been reduced by at least 50 percent.

Dr. William Butler, Environmental Risk Analysis Inc., representing the R.J. Reynolds Tobacco Company, said he would focus on the two largest U.S. epidemiologic studies included in the background document, those by Brownson and Fontham. The NTP reports these studies as indicating a positive association between ETS and lung cancer, when in fact, he said the data indicate that there is no association. He described the details of their analysis that came to the latter conclusion.

Dr. Gerhard Scherer, Analytisch-biologisches Forschungslabor, ABF, sponsored by the German association of cigarette manufacturers, presented recent results of biomonitoring studies on ETS related exposure to three classes of carcinogens, polycyclic aromatic hydrocarbons (PAH), aromatic amines, and tobacco specific nitrosamines. Conclusions of their findings were that although ETS contains substances classified as carcinogens by different organizations, the exposure of nonsmokers to ETS under realistic conditions does not exceed the background exposure to carcinogens unspecific for tobacco smoke.

Dr. Gio Gori, the Health Policy Center, representing the Brown & Williamson Corporation, stated that mainstream smoke and ETS are not equivalent. Meta-analyses of workplace exposures continue to show practically no elevation of risk. Further, he said, no studies have credibly accounted for misclassification of smokers as nonsmokers, nor controlled for 30 odd risk factors for lung cancer. Thus, ETS is an avoidable irritant but there is no credible evidence that it is a human carcinogen.

Dr. Ronald Marks, University of Florida, sponsored by the R.J. Reynolds Tobacco Company, summarized his comments in two areas. First, he reported on an evaluation of the original and complete data sets in the Brownson study, the Stockwell study, CPS 1 and CPS 2. His findings were that dietary factors are by far the most common and consistent risk factors for lung cancer. The other risk factor was ETS, and the overall conclusion was that there is no evidence that ETS is related to lung cancer development. The second area he researched was the dose-response relationship between ETS and lung cancer, and they found no evidence for a dose-response relationship.

Dr. Maurice LeVois, LeVois Associates, consultant for the Tobacco Institute, discussed issues around recall bias, and publication bias wherein studies not found to be significant are later detected as not having been submitted for publication. Dr. LeVois stated that 90% of the exposure to the substances of interest in ETS are not measured in spousal smoking studies, and could not

possibly have been controlled for in terms of potential confounding due to blue collar lifestyle and lower socioeconomic status which are known to be associated with the smoking habit.

In further discussion by the Subcommittee, Dr. Frederick referred to the recent Boffeta *et al.* paper (*J. Natl. Cancer Inst.*, October 1998) and the accompanying editorial by Blot and McLaughlin in which the authors came to the inescapable scientific conclusion that ETS is a low level human lung carcinogen. The hopeful sign, he thought, was the rather short time frame after cessation of ETS exposure in which the risk of lung cancer was reduced to that of a non-exposed nonsmoker. Referring to the same papers, Dr. Hecht observed that it was not surprising that it is difficult to demonstrate an effect in the epidemiologic studies as the dose is so much lower. One can estimate that carcinogen uptake from ETS is about one percent of what it is from mainstream smoke. Dr. Russo stated that the most important element missing here in these studies is information on the total amount of carcinogen produced in the target tissue and how the target tissue produced and/or repaired the adducts. Dr. Mirer commented that he did not see how we could take into account unpublished data presented the day of the meeting, especially when some of these presentations attack the validity of critical epidemiologic studies. Drs. Bingham and Medinsky commented on how they were more comfortable with the likelihood that the low relative risks would have been higher if truly unexposed control groups could have been obtained.

Dr. Zahm moved that the nomination of environmental tobacco smoke for listing in the 9th Report as a *known to be human carcinogen* be accepted. Dr. Friedman-Jimenez seconded the motion, which was accepted unanimously with 13 votes.

Silica, Crystalline (Respirable Size) – Dr. James Huff, NIEHS, presented the nomination and said that respirable crystalline silica (RCS) was nominated for listing in the *Report* as a *known to be human carcinogen* (currently listed as a *reasonably anticipated to be human carcinogen)* based on findings of increased lung cancer rates in occupational groups exposed to crystalline silica dust, and supporting animal and mechanistic data. Dr. Huff reported that silicon is the second most abundant chemical in the earth's crust, quartz is the most common form of silica in nature, and said the most ancient use was to make glass. Workers are exposed to RCS in a large range of industries and occupations, and the severity of its health effects and widespread exposure has long been recognized. He said that about 121, 000 workers were exposed at or above the NIOSH Recommended Exposure Limit (REL) of 0.05 mg/m^3 RCS, and of these workers, nearly 100,000 were exposed at 2X, 55,000 at 5X, and 25, 000 at 10X the REL. He reviewed adverse health effects of RCS deposited in the lungs, noting the persistence culminating in development of chronic silicosis, emphysema, obstructive airways disease, lymph node fibrosis, and lung cancer. Dr. Huff reviewed the epidemiology literature of which there were 38 cohort studies, 9 case control studies, 24 of individuals with silicosis, and 20 ongoing other studies. The IARC concluded from studies that addressed exposure response associations that "crystalline silica inhaled in the form of quartz or cristobalite from occupational sources is carcinogenic to humans (Group 1)." He focused on recent meta-analysis studies by Steenland and Stayner, and Smith that reported relative risks of lung cancer ranging from 2.1 to 2.4 in people with silicosis. With regard to experimental carcinogenesis, inhalation or intratracheal instillation studies produced adeno- and squamous cell carcinomas of the lung with fibrosis a common feature. Dr. Huff summarized the relevant issues as that RCS was carcinogenic to both sexes of multiple strains and species of rodents and by multiple routes of exposure. There was a concordance of cancer sites between humans and rodents – lung, lung tumors in humans and animals are histogenically and histologically the same, and mechanistic hypotheses indicate that the biological behavior of RCS is qualitatively similar in humans and animals. Dr. Huff said that RG1 voted unanimously (9/0) and RG2 voted five yes to two no votes to recommend that respirable crystalline silica be upgraded to a *known to be human carcinogen* .

Dr. Kelsey, the primary reviewer, agreed with the proposed listing. He said the human data are very complex, and his concern was with potential confounders, especially smoking and asbestos exposure. He thought the human data taken as a whole were remarkably consistent, particularly given the fact that the large number of studies of very different occupational cohorts are not likely to be confounded by the same thing, and particularly given the fact that he didn't believe asbestos could account for the positive risks. Dr. Kelsey said that additionally, there is a plausible mechanism and genotoxicity data are there to suggest that reactive oxygen and DNA damage play a role.

Dr. Belinsky, the secondary reviewer, also agreed with the proposed listing. He said that the fact that a number of studies demonstrate by themselves an association between silica and lung cancer would support its proposed classification. Moreover, the meta-analysis conducted by Smith *et al* ., using 23 of 29 studies demonstrated a pooled relative risk for lung cancer of 2.2 leading to the conclusion that there was an association which was in fact causal between silicosis and lung cancer.

Public Comments. Dr. Robert Glenn, Chemical Manufacturers Association (CMA), representing the Crystalline Silica Panel, pointed out that although the IARC Working Group concluded there was sufficient evidence for the carcinogenicity of RCS, their vote was divided 10 to 7 and qualifications were made that carcinogenicity was not detected in all industrial circumstances. Dr. Glenn described a weight of the evidence review of RCS
which summarized the strength of association as weak, said the exposure reponse relationship was usually absent, and indicated no convincing dose-response relationship with lung cancer where silicosis is a surrogate for exposure.

Dr. William Moll, Sorptive Minerals Institute, stated they believed classifying RCS as a known human carcinogen was not appropriate based on examination of the epidemiological evidence not showing a strong connection between RCS exposure and cancer, on the divided IARC vote, and on the fact that crystalline silica is an extremely complex substance and there are differing biological properties for the various forms, and, thus, some forms are being indicted unfairly.

Dr. David Crawford, Clorox Company, said that after reviewing the available biological and epidemiological evidence he wanted to make three points: (1) certain forms of RCS, in particular unfractured occluded quartz, have not been shown to be a human carcinogen; (2) IARC's recent classification of certain forms of silica applys to occupational and not to nonoccupational exposures; and (3) physiological mechanisms operative in rats exposed to RCS via inhalation are not predictive of human responses. He recommended that unfractured occluded quartz be delisted from the *Report* .

Dr. Kelsey moved that respirable crystalline silica be upgraded in the *Report* to a *known to be human carcinogen.* Dr. Belinsky seconded the motion. Dr. Henry asked for comment about the claims in public comments that there was little dose-response and the problems with the many forms of silica. Dr. Kelsey responded that the meta-analysis comes close to dose response but he was not bothered by that because of the consistency overall of the epidemiology data. He said the best data comes from occupational groups and this is well stated in the first sentence of the summary statement. Dr. Mirer agreed with the consistency of the data and commented that to get a two-fold cancer risk you are dealing with a self limiting population with severe silicosis and other respiratory problems. Dr. Henry moved to amend the motion on the floor to change the first sentence of the summary statement to read: "Occupational exposures to respirable crystalline silica is known to be a human carcinogen based on findings of increased lung cancer rates in

occupational groups exposed to crystalline silica dust..." Dr. Bingham seconded the amendment. Drs. Jameson and Lucier pointed out that this changes the nomination to an exposure circumstance. The current listing in the *Report* is for "Silica, Crystalline (Respirable Size)." Dr. Lucier also reminded the members that this is a hazard identification activity not a dose-response/risk assessment activity. Dr. Frederick commented that occupational exposure involves higher exposure levels of a different material than environmental or domestic exposure. Dr. Bailer spoke against the amendment as being redundant in that the importance of occupational exposure is already stated in the first sentence. Dr. Henry's amendment was defeated by eight no votes (Bailer, Belinsky, Hecht, Hooper, Kelsey, Medinsky, Mirer, Zahm) to four yes votes (Bingham, Frederick, Henry, Russo). Dr. Kelsey's original motion to upgrade the listing of respirable crystalline silica in the *Report* to a *known to be human carcinogen* was then accepted by eleven yes votes to one no vote (Henry). Dr. Friedman-Jimenez was absent.

Ethylene Oxide – Dr. Ronald Melnick, NIEHS, presented the nomination and said that ethylene oxide was nominated for listing in the *Report* as a *known to be human carcinogen* (currently listed as *reasonably anticipated to be a human carcinogen*) based on the 1994 IARC reevaluation that raised the classification from "probably carcinogenic to humans" (Group 2A) to "carcinogenic to humans" (Group 1) based on limited evidence in humans, sufficient evidence in animals , and mechanistic data. He said ethylene oxide was a high production chemical with nearly eight billion pounds produced yearly in the U.S. and is used as a chemical intermediate and sterilant. Much of its human exposure is occupational. The OSHA permissible exposure limit expressed as an eight hour time weighted average is 1 ppm. It is regulated by EPA under a variety of acts, the Clean Air Act, TSCA, FIFRA, and Superfund. Dr. Melnick said that the first reports of ethylene oxide's carcinogenicity in humans were in Swedish (Hogstedt *et al.*) sterilant and production workers where there were associations between exposure and increased leukemia and stomach cancer risk. The largest study in humans (>18,000) was the NIOSH study reported by Steenland with follow-up analysis by Stayner which reported a positive trend between cumulative exposure to ethylene oxide and mortality from cancers of lymphoid cell origin. A recent study found increased breast cancer incidence in sterilant workers, and in the same plant a three fold increase in sister chromatid exchanges had been found earlier. Dr. Melnick reviewed a meta-analysis by Shore encompassing about 28,000 people that was suggestive for non-Hodgkins lymphoma and stomach cancer. With regard to animal studies, an NTP bioassay by inhalation in $B6C3F_1$ mice demonstrated increased incidences of neoplasms of the lung, uterus, Harderian gland, mammary gland, and hematopoietic system (lymphoma). Inhalation bioassays in F344 rats by Union Carbide and NIOSH showed increased incidences of gliomas, mononuclear cell leukemia, and peritoneal mesothelioma. Dr. Melnick went over the rationale for the proposed listing. With regard to the animal data, ethylene oxide induced benign and malignant neoplasms at multiple sites in rats and mice, including lymphatic and hematopoietic cancers. With regard to humans, the data are suggestive, not conclusive but a preponderance relate to mortality associated with lymphatic or hematopoietic cancers, an animal-human correlation. The mechanistic considerations are that: (1) ethylene oxide is a direct acting alkylating agent; (2) it forms DNA adducts; (3) it is mutagenic and clastogenic; and (4) dose-related increases were induced in chromosomal aberrations, SCEs, micronuclei, DNA single strand breaks, and *hprt* mutations in exposed workers. Dr. Melnick said that RG1 voted six to one and RG2 voted unanimously (7/0) to recommend that ethylene oxide be listed in the *Report* as a *known to be human carcinogen* .

Dr. Lucier stated that since mechanistic information was important in support of the proposed listing he wanted to emphasize that a key issue here is the chromosomal aberration data in exposed workers. For the category of *known to be human carcinogen*, the criteria state that there must be sufficient evidence from studies in humans. The NTP's interpretation is that this means not just traditional epidemiology data but all relevant information, including mechanistic mode of action

information from studies in human tissues or cells. Dr. Hooper noted that since mechanistic information is so important, he wondered what other research information would strengthen the argument. Dr. Melnick responded that further follow-up on the NIOSH cohort would be valuable, especially relating to genetic changes.

Dr. Belinsky, the primary reviewer, did not agree with the proposed listing. He said a review of the epidemiology data indicates at best "that only a trend was observed" and this was not evident in many of the studies. He acknowledged that the mechanisms involved in induction of DNA damage occur in both rodents and humans. However, given the low and often imprecise SMRs seen for the epidemiology studies, he found it difficult to justify upgrading the status of this compound.

Dr. Yamasaki, the secondary reviewer, agreed with the proposed listing. He briefly went over the process that IARC uses in evaluating carcinogenicity, including the option to use mechanistic information that must come from exposed humans. In the case of ethylene oxide, mechanistic information from humans was key to raising the category to Group 1. Dr. Lucier agreed that the mechanism can be established in experimental systems but must then be shown to operate in humans exposed to the agent. Dr. Yamasaki stated that in his view, there is strong evidence that ethylene oxide induces relevant genotoxic events in exposed humans.

Public Comments. Dr. Julian Preston, Chemical Industry Institute of Toxicology (CIIT), spoke about the human population monitoring cytogenetic data used by IARC to upgrade ethylene oxide to Group 1. His conclusions were that the assay conducted for measuring chromosomal alterations was not appropriate because these are not necessarily transmissible events. The studies as conducted were not appropriate for detecting long-term ethylene oxide exposures, and the end points that were looked at, even in cases where acute high concentrations of ethylene oxide might induce these particular alterations, were not indicators of subsequent adverse health outcomes, but were indicators of exposure. There was discussion among Dr. Preston and Subcommittee members about whether or not the chromosome aberrations detected in the ethylene oxide human studies were transmissible or non-transmissible. Dr. Preston maintained that fluorescence *in situ* hybridization (FISH) should have been conducted to answer the question. In response to a question from Dr. Melnick, Dr. Preston acknowledged that the human cytogenetic data do not exclude the possibility that ethylene oxide caused transmissible chromosomal alterations. Dr. Kelsey commented that when induced chromosomal aberrations are measured, a small percentage of transmissible alterations always occur.

Dr. M. Jane Teta, Union Carbide Corporation, said they had sponsored the meta-analysis conducted and published by Dr. Roy Shore, and the observation periods were certainly long enough to show any health effects. Dr. Teta commented on the individual studies and concluded that the overall epidemiology evidence remains weak and inconclusive. Both the prior and updated meta-analysis indicate that ethylene oxide does not cause increased risk of cancer overall, brain, stomach, or pancreatic cancer. The evidence for leukemia and non-Hodgkin's lymphoma is weakly suggestive. Dr. Teta said that too much weight is given to human genetic effect studies that fail to adequately control for confounding, and the biomarkers measured are uninterpretable for risk of chronic disease.

Ms. Sara Schotland, counsel for Cleary, Gottlieb, Steen, & Hamilton, representing the Ethylene Oxide Industry Council (EOIC), commented that NTP's process had not allowed a scientific dialogue on key questions related to classification of ethylene oxide. There was insufficient time for a dialogue among Dr. Preston and Subcommittee members on the use and interpretation of human cytogenetic data in cancer classification. Ms. Schotland said the EOIC requests a meeting

to explore novel issues presented by the use of cytogenetic data and asks that a decision on ethylene oxide be deferred.

Mr. Ralph Gingell, Shell Chemical Company, argued that the data presented in the background document does not support an upgrading of ethylene oxide. He said that presentations on new information from cancer epidemiology and cytogenetic monitoring in exposed workers were not available to IARC in 1994, and the EOIC has petitioned IARC to review ethylene oxide's classification in light of the new data. Mr. Gingell said there seemed to be a lack of consistency between the chromosomal changes reported and the largely negative epidemiological data. He concluded that the data presented do not meet NTP's criteria for a *known to be human carcinogen* , and therefore, suggested deferral or keeping the current listing.

Dr. Lucier said he wanted to clarify the extent of the opportunity for receiving public comments. It began with a *Federal Register* announcement in February/March 1998 giving the intent to consider this action on ethylene oxide and asking for information. When the background document was released at the end of October, there was another call for public comment, both written as well as at this meeting. Following the meeting, there will be another *Federal Register* notice seeking and allowing additional public comment, and after that the whole package with comments will be reviewed by the NTP Executive Committee and then the Director, NTP.

Dr. Hooper moved that the decision on the proposed listing of ethylene oxide be deferred. Dr. Bingham seconded the motion. In discussion, Dr. Kelsey spoke against deferral noting that there is an enormous amount of good data already, and there is not likely to be much additional data coming out. He commented again on the consistency of the epidemiology data. Dr. Bucher said that data received early enough are incorporated in the background documents to the extent that the data are published. Dr. Hooper's motion was defeated unanimously with 12 votes.

Dr. Belinsky moved that the listing of ethylene oxide in the *Report* remain as *reasonably anticipated to be a human carcinogen.*. Dr. Medinsky seconded the motion. After much further discussion, the motion was defeated by seven no votes (Bailer, Frederick, Hecht, Hooper, Kelsey, Mirer, Zahm) to five yes votes (Belinsky, Bingham, Henry, Medinsky, Russo). Dr. Hooper moved again that the decision on the proposed listing of ethylene oxide be deferred. Dr. Belinsky seconded the motion. The motion was defeated by six no votes (Bailer, Frederick, Hecht, Kelsey, Mirer, Zahm) to five yes votes (Belinsky, Bingham, Henry, Hooper, Medinsky) with one abstention (Russo).

Dr. Kelsey then moved that the nomination of ethylene oxide for upgrading in the *Report* to a *known to be human carcinogen* be accepted. Dr. Zahm seconded the motion, which was accepted by six yes votes (Bailer, Frederick, Hecht, Kelsey, Mirer, Zahm) to five no votes (Belinsky, Bingham, Henry, Medinsky, Russo) with one abstention (Hooper).

Diesel Exhaust Particulates. – Dr. Freja Kamel, NIEHS, presented the nomination and said that diesel exhaust particulates were nominated for listing in the *Report* by the United Auto Workers international union with the level not specified. In 1989, IARC listed diesel engine exhaust as "probably carcinogenic to humans" (Group 2A). She said that diesel exhaust is a complex mixture of diesel fuel combustion products, consisting of a gas phase, primarily water and carbon dioxide with some low molecular weight hydrocarbons, and a particulate phase, consisting primarily of elemental carbon particles coated with organic compounds and some trace metals, including lead and cadmium. The important fact is that these particles are respirable. Dr. Kamel said that human exposure can be assessed with one of two biomarkers, respirable particles or elemental carbon, with the latter more specific for diesel exhaust. The primary occupational

groups exposed are transportation workers and people who work around motor vehicles with more than 1.35 million workers exposed to diesel exhaust in the U.S. Epidemiologic studies have focused primarily on lung cancer with the majority finding some evidence for an association of diesel exhaust exposure with lung cancer. Nine of 14 cohort and 12 of 17 case control studies found an association with most of the relative risks in the 1.3 to 1.5 range. Some studies found exposure response relationships and some were able to take smoking or asbestos, two major confounders, into account. Dr. Kamel reported that a meta-analysis based on 23 of 29 studies gave a pooled relative risk of 1.33 with a confidence interval excluding 1. The strengths of the epidemiologic literature were consistency across studies, the detection of exposure response relationships in some studies, and the fact that studies able to take either smoking or asbestos exposure into account found an association. Weaknesses were that many studies had low power and many used inadequate methods for exposure assessment. Dr. Kamel stated that inhalation of whole diesel exhaust produced lung tumors in rats and mice, and particulates or solvent extracts of particulates produced tumors by various routes., and a number of studies showed that diesel exhaust particulates were genotoxic. A number of lines of evidence indicated that organic compounds adsorbed to particulates are bioavailable. Dr. Kamel said that RG1 first voted four to five against recommending listing as a *reasonably anticipated to be human carcinogen,* and then voted five to four to recommend listing as a *known to be human carcinogen.* The RG2 voted two to five against recommending listing as a *known to be human carcinogen* , and then voted six to one to recommend listing as a*reasonably anticipated to be human carcinogen* .

Dr. Medinsky, the primary reviewer, said she would support listing as *reasonably anticipated to be a human carcinogen* . She commented that the major difference between the two previous review groups was in the degree to which they judged that increased risk of cancer could be ascribed to diesel exhaust exposure. Dr. Medinsky said that public comments received were noteworthy, one of which noted that the repeated findings of small effects coupled with the absence of quantitative data on historical exposure precluded a causal interpretation. She speculated that some or maybe most of the carcinogenicity of diesel exhaust particulates may be attributed to carbon black. Dr. Medinsky concluded that the epidemiology data does not support classification as *known* .

Dr. Zahm, the secondary reviewer, said that based on the current epidemiology data with relative risks typically under 1.5, she would also support listing as *reasonably anticipated to be a human carcinogen.* She said that although confounding by smoking was adjusted for and did not appear to explain excess risk, there are other strong lung carcinogens not adequately addressed such as asbestos in truck drivers and mechanics, and radon and silica in mining studies. Dr. Zahm observed that there are two studies of heavily exposed underground miners, one in the U.S. and one in Germany, underway that will have detailed information on exposure to diesel exhaust and to potential occupational and non-occupational confounders that may spark a later reevaluation.

Public Comments. Dr. Kenny Crump, ICF Kaiser, said he would comment on the Garschick cohort study considered in many circles to be the single most important study of diesel and lung cancer. His conclusions were that lung cancer mortality was higher among train riders than among clerks and signalmen while it was not higher among shop workers despite the fact that they have the most intense exposure to diesel exhaust. And there is no plausible dose response for cancer in this study. Finally, follow-up was incomplete after 1977, and this must be corrected before obtaining a true picture of any potential exposure response.

Dr. Kathleen Nauss, Health Effects Institute (HEI), stated that she was not here to comment on the proposed listing but rather to focus on some issues not fully developed in the background document. She said the emissions section is particularly in need of updating, noting that many of the references are to 1980s papers. Dr. Nauss said there is about a 90% reduction in emissions of

particulate matter from today's diesel engines compared with those of the 1970s and 1980s, and also a shift in the nature of the particulate matter to smaller particles and fewer polycylic aromatic hydrocarbons (PAHs).

Dr. Joe Mauderly, Lovelace Respiratory Research Institute, pointed out that this nomination is dealing with a changing physical class of materials and not a compound, and some of these changes such as reduced emission of mutagenic material would reduce cancer risk. He said that information from the experimental and genotoxicity sections of the document could be strengthened with uncited publications that indicate the rat lung tumor response would not represent an expected human lung response. Finally, human exposures cited are to material not representative of current emissions materials.

Dr. Jeffrey Terry, Engine Manufacturers Association, said they believe the current state of the science does not support consideration of diesel particulates as a known human carcinogen, and the primary reason is that existing studies do not represent current engines and their exhaust technology. The scientific database of diesel particulate exposures is based on the estimated high level occupational exposures of old technology experienced during the 1950s and 1960s.

Dr. Bill Bunn, Navistar Corporation, reemphasized that the diesel of 1998 is very different from the diesel cited in the NTP studies. He reported that the two ongoing major studies (U.S and Germany) with 60-70,000 exposure measurements will allow a much better characterization of the risk of diesel emissions. Dr. Bunn concluded by commenting on some of the deficiencies or inconsistencies in the cohort and case control studies cited by the NTP.

Dr. Roger McClellan, CIIT, commented that the numerous epidemiological studies suffer from serious limitations in terms of lack of control for confounding factors, the lack of measurements of exposure, and a lack of any characterization data on those exposures which occurred decades ago. He said the latter two points are important because of major improvements made in diesel engine technology and fuel quality. Dr. McClellan opined that the rat lung tumors were a species specific effect and only occurred in the presence of a pulmonary overload phenomenon. In his judgment, diesel exhaust particulates should be classified as *reasonably anticipated to be a human carcinogen.*

In response to a query from Dr. Hooper, Dr. Zahm said that the two large ongoing epidemiology studies are three to four years away from reporting. Dr. Mirer presented data in support of the 10 truck driver studies and 10 railroad worker studies pointing out the consistency across studies and the risk ratios in the 1.3 to 1.5 range. He provided comparisons of diesel exhaust with environmental tobacco smoke data regarding incidence of cancer in rodents. He concluded that the level of evidence should be the same as for environmental tobacco smoke. Dr. Zahm agreed that the consistency across studies was greater than for environmental tobacco smoke but taking dose into account, it doesn't make a lot of sense. Further, in the diesel studies, other than a few studies where smoking was adjusted for, potential confounders were not well controlled, e.g., asbestos. Dr. Mirer said asbestos was not a confounder for many of the workers, only those who assemble or maintain brakes. Dr. Belinsky commented that the confidence intervals on many of the epidemiologic studies were very large, and the rat studies represented a high dose phenomenon with tumors appearing late in life. Dr. Hooper said the discussion pointed out to him the definite need for decision criteria for the epidemiology.

Dr. Medinsky moved that for the nomination of diesel exhaust particulates for listing in the *Report* , the summary review statement of the RG2 be accepted that exposure to diesel exhaust particulates is *reasonably anticipated to be a human carcinogen* based on findings of elevated lung cancer rates in exposed occupational groups. Dr. Zahm seconded the motion, which was accepted by nine yes

votes with three abstentions (Belinsky, Henry, Mirer). Dr. Belinsky said he was perceived as having a conflict of interest because a member of his place of employment (Dr. Mauderly) had provided formal comments. Dr. Henry said she abstained because she had provided public comments on diesel fuel and on the background document, and her employer, the American Petroleum Institute has an interest in the outcome. Dr. Mirer said that members of his organization make engines for trucks so it is perceived that he has an interest in the outcome. Dr. McClellan stated that he was not aware of a Committee policy requiring a member to abstain when a person from his organization provided public comment, and if it is a policy, he wanted to voice a very strong objection to it for the record.

Methyl *tert* –Butyl Ether – Dr. Melnick presented the nomination and said that methyl *tert*-butyl ether (MtBE) was nominated for listing in the *Report* as *reasonably anticipated to be a human carcinogen* based on evidence of benign and malignant tumor induction at multiple organ sites in long-term studies in two animal species. In addition, a recent review by the National Science and Technology Council (NSTC) concluded that MtBE is an animal carcinogen and has carcinogenic potential for humans. He said that U.S. production of MtBE had increased enormously in the past 5 to 10 years and is currently about 24 billion pounds, and it is used primarily as an oxygenate for gasoline. Human exposure is through the air primarily from various types of emissions (industrial, vehicles, and gasoline stations), and from drinking water contaminated by leaking storage tanks. Dr. Melnick said there are no identified studies of potential carcinogenicity in humans. There were inhalation bioassays in CD-1 mice (18-months) and in F344 rats (24-months) which resulted in increased incidences of liver tumors in mice and renal tubule adenoma and carcinomas and interstitial cell adenomas of the testis in male rats. Gavage administration to Sprague-Dawley rats (2 years) resulted in increased interstitial cell adenomas of the testis in males, and lymphomas or lymphomas and leukemia in females. Dr. Melnick listed other information relating to carcinogenesis: MtBE is metabolized to formaldehyde and *t* –butyl alcohol (a renal carcinogen in male rats) in humans and rats, it is not mutagenic in *Salmonella* , mutagenicity in mouse lymphoma cells is sensitive to formaldehyde dehydrogenase, MtBE is metabolized to *t-butyl* –alcohol in humans and rats, and MtBE does not alter serum estrogen levels nor mediate effects through the estrogen receptor. He then discussed arguments for and against listing in the *Report.* Dr. Melnick said that RG1 voted four to three to recommend listing MtBE in the *Report* as *reasonably anticipated to be a human carcinogen* , while RG2 voted four to three against a motion for listing MtBE in the Report as *reasonably anticipated to be a human carcinogen.*

Dr. Bailer, the primary reviewer, agreed with the proposed listing. He said that MtBE induces dose-related increases in renal tumors in male F344 rats with the lower response at the higher exposure level likely due to treatment-related toxicity yielding poor survival in the high dose group. It was also associated with dose-related increases in Leydig cell tumors of the testes in F344 rats, hepatocellular carcinomas in CD-1 male mice, and after gavage studies in Sprague-Dawley rats significant increases in Leydig cell tumors in males and in leukemia/lymphomas combined in females. Dr. Bailer maintained that this all supports the proposed listing.

Dr. Frederick, the secondary reviewer, said that besides the background document he had evaluated the reports of other groups on MtBE, such as EPA and the state of California. He thought a key point in the inhalation study in CD-1 mice and F344 rats was that the top dose, 8,000 ppm, was clearly neurotoxic and these were clearly not normal animals for evaluating cancer effects.. The animals at 3,000 ppm appeared to be normal. He thought the Leydig cell tumors demonstrated a hormonal action of MtBE.. With regard to the kidney tumors in male rats, it appears to be a mixed mechanism, in part due to alpha-2-globulin. Dr. Frederick said that in his opinion, the very limited carcinogenicity data available at appropriate dose levels (essentially male

and female rats) and the available mechanistic information were not sufficient to warrant listing in the *Report* .

Public Comments. Dr. Susan Borghoff, CIIT, said her remarks would be confined to the kidney tumors in male rats. She noted that a number of studies looking at the ability of MtBE to induce alpha-2 nephropathy were not cited in the background document. In her work at CIIT and that of others, there is an increase in numbers of protein droplets in male rats and some of the aspects of the pathological sequence of lesions associated with alpha-2 nephropathy are seen. The response is mild compared with potent inducers of alpha-2 such as d-Limonene. She said there is also increased cell proliferation in male but not female rats which correlates with increases in alpha-2. Dr. Borghoff described studies demonstrating that binding to alpha-2 increased the uptake of MtBE in the male rat kidney.

Dr. Robert Tardiff, the Sapphire Group, representing the Oxygenated Fuels Association, said he wanted to comment on the relevance of the various animal carcinogenicity studies to humans. He said MtBE is clearly an animal carcinogen, but the studies described by Dr. Borghoff lend support to the male rat kidney tumors not being relevant to humans. With regard to female mouse liver tumors, he said there are differences of opinion on the relevance of these tumors and a model that indicates these are not predictive of tumorigenic responses in humans. Dr. Tardiff said there may be other factors involved besides MtBE in the production of Leydig cell tumors. The Italian study he claimed had many limitations.

In further discussion, Dr. Hecht said he did not think that release of formaldehyde was a plausible mechanism for any carcinogenicity of MtBE because there are many drugs and compounds that have an N-methyl group that release formaldehyde upon metabolism and are not carcinogens. Dr. Bailer argued that if the 8,000 ppm top dose in rats is discounted because of neurotoxicity, there is still evidence of trend with increasing level. Dr. Frederick agreed. Dr. Belinsky commented that there is very limited carcinogenicity data in the animal models, and now with the question of the relevance of the kidney tumors, we just don't know enough to list the compound.

Dr. Bailer moved that the nomination of methyl *tert* –butyl ether for listing in the *Report* as a *reasonably anticipated to be human carcinogen* be accepted. Dr. Bingham seconded the motion. Dr. Brown stated that the understanding is that if the motion is voted down, MtBE will not appear in the *Report* . Dr. Mirer noted that the criteria say that we have to have mechanistic reasons to downgrade the tumors observed, not that we have to come up with a new mechanistic basis to support listing. He said that he didn't buy the rationale for alpha-2-globulin, and in humans, there is more kidney disease in males than in females, and certainly in the dry cleaning industry there is excess mortality associated with some of the alpha-2 compounds used there. Dr. Medinsky observed that studies by Dr. Borghoff have shown that MtBE meets EPA criteria for a male rat specific process. Dr. Hooper suggested deferral as there are data from the University of California that will be published that conclude that MtBE is an animal carcinogen with the potential to cause cancer in humans. Dr. Henry said that she would abstain on the vote because there is a perception that the petroleum industry has an interest. She agreed with Dr. Hooper's proposal to defer as over the next five years, there will be a large testing program in animals under the Clean Air Act for MtBE and other oxygenates. Dr. Bailer's motion to list MtBE in the Report was defeated by six no votes (Belinsky, Frederick, Hecht, Kelsey, Medinsky, Zahm) to five yes votes (Bailer, Bingham, Hooper, Mirer, Russo) with one abstention (Henry). Thus, methyl *tert* –butyl ether was not recommended for listing in the 9th *Report.*

Ethyl Acrylate – Dr. Robert Maronpot, NIEHS, presented the nomination and said that a formal petition for delisting ethyl acrylate from the *Report* was received from the Basic Acrylic Monomer

Manufacturers, Inc (BAMM)., based upon mechanistic studies by the NTP and others and the assumption that significant human exposure is unlikely. Ethyl acrylate was first listed in the Fifth *Annual Report on Carcinogens* as *reasonably anticipated to be a human carcinogen* based on an NTP gavage study resulting in dose-related benign and malignant forestomach neoplasms in rats and mice. Dr. Maronpot described the properties of the chemical noting that it is rapidly metabolized by carboxylesterases and by conjugation with glutathione, and has a half-life in the rodent forestomach of 94 minutes. He said the greatest human exposure is going to occur in manufacturing of acrylic resins, and that ethyl acrylate can be found in paint, latex products and industrial coatings. Dr. Maronpot reported that while ethyl acrylate is mutagenic in some *in vitro* tests, it is not genotoxic under *in vivo* physiological conditions perhaps due to its rapid metabolism. He discussed an excellent epidemiologic study reported by Walker *et al.* in 1991 of three occupational cohort studies, one of which demonstrated excess mortality from colon cancer. Dr. Maronpot described the four animal carcinogenicity studies with the NTP study in 1986 the most recent, leading to a conclusion by IARC in 1986 that there was sufficient evidence for the carcinogenicity of ethyl acrylate in experimental animals. He presented a table showing what human exposure would be if one used the TLV or PEL (permissible exposure limit) compared to exposure levels for the rat and mouse inhalation study. Subsequent to the NTP gavage study, a variety of mechanistic studies related to the forestomach tumor response were conducted following the hypothetical line of investigation that irritation and sustained cell proliferation were probably associated. Using the high dose, 200 mg/kg, that produced forestomach tumors in the NTP bioassay, substantial cell proliferation was observed in the forestomach mucosa in days, even hours of gavage dosing. A premise of the petition is that humans would not ingest ethyl acrylate, rather inhalation and dermal would be primary routes of human exposure, and, further, humans do not possess forestomachs. The RG1 voted seven yes to two no votes, and RG2 voted six yes to one no vote, both to recommend delisting of ethyl acrylate from the *Report*

Dr. Mirer, the primary reviewer, said that he did not agree with the proposal to delist ethyl acrylate. He asked for clarification on the mechanism that does not exist in people. Dr. Maronpot responded that in his opinion it was that oral gavage in corn oil does not exist in people and repeated long-term oral exposure to something as irritating as ethyl acrylate does not occur in people. Dr. Mirer reviewed the findings in the NTP bioassay for which there were positive carcinogenicity findings for male and female rats and mice. He said that based on the current levels of evidence used by the NTP, all four groups would have provided clear evidence of carcinogenic activity. He disputed that stomach tumors arise only from gavage dosing, and cited data from a recently peer reviewed NTP bioassay on 2-butoxyethanol by the inhalation route in which some evidence of carcinogenic activity was approved for male and female mice based on forestomach squamous cell papillomas or carcinomas in females and possibly supported by squamous cell papillomas in male mice. With regard to epidemiology, Dr. Mirer noted the significant relative risk for colon cancer in the first of the cohort studies reported by Dr. Maronpot, and commented that the observation of carcinogenicity in the digestive tract in animal studies lends more plausibility to the observation in human studies.

Dr. Hecht, the secondary reviewer, agreed with the proposed delisting. He said this was a clear example of a high dose phenomenon that is irrelevant to human exposure, and in animals, another example of forestomach tumors induced secondary to cell proliferation seen with a number of different non-genotoxic compounds.

Public Comments. Dr. Sandra Murphy, BAMM, summarized the major points of their submission including comments on the NTP gavage bioassay and follow-up mechanistic studies. She noted chronic studies by different exposure regimens failed to elicit a carcinogenic response, and that NTP data show that even using gavage dosing of ethyl acrylate at a concentration

sufficient to cause sustained hyperplasia must continue for six months or more in rodents before the lesions become irreversible and progress to tumors. With regard to the one positive cohort study, they had discussed it with the principal author, and concluded that the etiology of the colon cancers remains unknown. She asked that the recommendations of RG1 and RG2 be accepted.

Dr. Hooper inquired about the earlier drinking water chronic study in Wistar rats as to whether the forestomachs had been examined. Dr. Maronpot replied that the gastrointestinal system was reported to be examined but no further detail was given. Dr. Medinsky commented that with gavage, a bolus dose is introduced into the stomach within a minute or so and it is likely that metabolic detoxification mechanisms are being overwhelmed.

Dr. Mirer moved that ethyl acrylate continue to be listed in the *Report* as *reasonably anticipated to be a human carcinogen* . Dr. Bingham seconded the motion. Dr. Hooper asked for more discussion of the epidemiology data as to whether the second and third cohorts were less sensitive. Dr. Kamel said these cohorts were less sensitive with very few person years of observation. Dr. Zahm said that the first cohort that had the excess risk also had mixed exposures. Dr. Medinsky asked about forestomach tumors produced by other chemicals. Dr. Maronpot explained that strong forestomach carcinogens are always associated with a remarkable hyperplasia and can occur by other routes than gavage. Dr. Mirer's motion was defeated by eight no votes (Bailer, Belinsky, Hecht, Henry, Kelsey, Medinsky, Russo, Zahm) to two yes votes (Bingham, Mirer) with two abstentions (Frederick, Hooper). Dr. Frederick said he abstained because he had done research on ethyl acrylate and reported on it. Dr. Hooper said he abstained because there was unexplained possible genotoxic data that he did not have access to so he felt that he could not make a decision.

Dr. Hecht moved that ethyl acrylate be delisted from the *Report.* Dr. Henry seconded the motion, which was accepted by eight yes votes (Bailer, Belinsky, Hecht, Henry, Kelsey, Medinsky, Russo, Zahm) to two no votes (Hooper, Mirer) with two abstentions (Bingham, Frederick). Dr. Bingham said she abstained because there was important information on cell transformation that she did not have access to. Dr. Frederick abstained for the reason previously cited.

Nickel Compounds. – Dr. Michael Waalkes, NCI at NIEHS, presented the nomination and said that nickel compounds were nominated for listing in the *Report* as a *known to be human carcinogen* (nickel and certain nickel compounds are currently listed as *reasonably anticipated to be human carcinogen* s) based on findings of increased risks of cancers in exposed workers and evidence of malignant tumor formation by multiple routes of exposure at various sites in multiple species of experimental animals. Also, in 1990, an IARC evaluation of nickel and nickel compounds concluded "nickel compounds are carcinogenic to humans." Dr. Waalkes said this listing does not designate the compounds of metallic nickel and/or nickel alloys, which will be reviewed at a later date. He said that nickel exposure can be from occupational and environmental settings, and it has been estimated that about 1.5 million workers are exposed to nickel compounds in the U.S. with current exposure levels in general being much lower than historical levels. He listed several sources of occupational exposure including mining and refining, and sources of environmental exposure. Dr. Waalkes said that both soluble and insoluble nickel compounds are clearly animal carcinogens and cause tumors both at the site of application and at distant sites. Nickel compounds have been shown to be carcinogenic by a variety of routes of administration and in many different species of animals, including rats, mice, hamsters, rabbits, and salamanders. Based on the activity of a wide variety of nickel compounds by various routes at a variety of sites, it was concluded that ionic nickel is the active carcinogenic species. Dr. Waalkes reported that cohort studies of human cancer evaluated by IARC in 1990 provide consistent evidence of elevated lung and nasal cancer risks in people occupationally exposed to nickel compounds with SMRs often in excess of 3 for lung and in excess of 100 for nasal cancers. These cohort studies indicated

that compounds included sulfates, which are soluble, and combinations of sulfides and oxides found in the refining industry which are insoluble and are carcinogenic. More recent cohort studies by Andersen *et al*. in 1996, and Anttila *et al*. in 1998, confirm that occupational nickel exposure is linked to elevated risk of lung and nasal cancers in a dose dependent fashion and confirm carcinogenic potential of soluble nickel compounds. Dr. Waalkes cited possible carcinogenic mechanisms to include that soluble and insoluble nickel compounds can cause chromosomal aberrations in exposed human populations, malignant cellular transformation, mutation, chromosomal damage and chromatin condensation, DNA damage such as strand breaks, redox damage, and methylation changes as well as disrupted DNA repair. The ionic form of nickel is likely the active, genotoxic species. Dr. Waalkes reported that RG1 unanimously (7/0) and RG2 by 4 yes to 3 no votes with 1 abstention voted to support the proposed listing of nickel compounds as a *known to be human carcinogen*. Dr. Hooper asked why three members of RG2 voted against the proposed listing. Dr. Jameson responded that the votes against reflected a concern that the data for soluble nickel compounds was not as strong as that for insoluble compounds. He said that subsequently he and Dr. Waalkes worked to clarify the data for the soluble nickel compounds which is reflected in the current background document.

Dr. Frederick, the primary reviewer, said that he generally supported the proposed listing. He was concerned that there is little information in the document on oral exposure, the most common route of consumer exposure. Dr. Medinsky commented that toxicokinetic studies that she had been involved in showed that gastrointestinal absorption of nickel, even a soluble form, was very low, perhaps 5%. Dr. Frederick said that he found the human studies, especially the more recent studies to be most compelling, and in reading the public comments did not find arguments to counter these studies. He presented data on exposure concentrations for soluble and insoluble nickel from the various epidemiological studies and the NTP inhalation studies that convinced him that toxicity and carcinogenicity of soluble nickel compounds present a problem of a similar magnitude as the insoluble nickel compounds.

Dr. Kelsey, the secondary reviewer, agreed with the proposed listing. He suggested adding to the section on nickel chemistry, noting that the various forms of this metal are complex and thought it would be helpful to even the most knowledgeable reader to expand the chemical description of nickel and its alloys and species.

Public Comment. Dr. Adriana Oller, Nickel Producers Environmental Research Association (NiPERA), stated that in their view, the proposed listing ignores the issue of speciation, which is that different nickel compounds should be evaluated independently, that there is a difference in carcinogenic potential, not just potency. She said it was not just the presence of the nickel ion that will determine carcinogenicity but rather whether the nickel ion would be bioavailable at nuclear sites within target cells. With regard to soluble compounds, she commented that even though two basic epidemiological studies were discussed in the document, there was no effort made to integrate that with the previous body of human data. With regard to the animal data, she said the cancer assessment seemed to be predominately based on intraperitoneal studies, while the well conducted NTP inhalation studies were ignored. Dr. Oller provided a table recommending which nickel compounds should be listed as human carcinogens and which should not be listed at all.

There was some confusion among the members about the current listing of Nickel and Certain Nickel Compounds in the Report as *reasonably anticipated to be human carcinogens.* Dr. Jameson explained that the IARC upgrade of nickel and certain nickel compounds to Category 1, "known human carcinogen", stimulated the NTP to examine the literature and conclude that the data for nickel compounds appeared to meet the criteria for listing in the Report as *known to be human carcinogens* while metallic nickel did not. Metallic nickel will remain in the Ninth *Report*

as *reasonably anticipated to be a human carcinogen.* Dr. Frederick said this was consistent with the IARC evaluation where metallic nickel is rated as Group 2B, "possibly carcinogenic to humans." Dr. Belinsky questioned the strength of the evidence on the soluble compounds. Dr. Waalkes responded that the data on human exposure to soluble nickel is very strong, and there are positive animal data, e.g., transplacental administration which produced rare malignant pituitary tumors. He said the key to carcinogenic activity is solubilization.

Dr. Frederick moved that the nomination of nickel compounds for upgrading in the *Report* to a *known to be human carcinogen* be accepted. Dr. Kelsey seconded the motion, which was accepted unanimously with 12 votes.

Boot and Shoe Manufacture and Repair – Dr. H.B. Matthews, NIEHS, presented the nomination and said that boot and shoe manufacture and repair was nominated for listing in the *Report* by RG1 in response to a commitment to include exposure circumstances known to cause cancer in humans. He said this is the first exposure circumstance to be considered for listing, and currently boot and shoe manufacture and repair appears in Appendix A of the 8th *Report on Carcinogens* as one of 13 "Manufacturing Processes, Occupations, and Occupational Exposure Circumstances" classified by IARC as Category 1, "Known Human Carcinogens." Dr. Matthews reported that the review of the literature was largely limited to those publications describing risks associated with the industry in the U.S., although recent publications from European countries were also considered. It is acknowledged in Appendix A that "the manufacturing processes and occupations reviewed by IARC in their determinations may differ greatly from what has been or is currently used in the United States." Dr. Matthews said there have been several publications in the last 20 to 30 years indicating that workers employed in the U.S. industry have experienced increased incidences of cancer at a number of sites. However, most studies are of poor quality and indicate weak and variable correlations between increased tumor incidences and employment in the industry. He said that all of the studies of the U.S. industry are based on workers who died 20 or more years ago and were exposed quite some time before that, some as much as 40 years before their deaths. Thus, the cohorts surveyed were probably not employed under modern standards of industrial hygiene. Only one study was considered adequate, and that study showed an increased incidence of tumors in the trachea and lungs at an increased incidence of 1.47, which was significant in men but not women. Dr. Matthews said the NTP recommendation is that this exposure circumstance should be included in the *Report* as having been reviewed but not listed due to inadequate data. Boot and shoe manufacture and repair would be moved from Appendix A to a new appendix. He reported that RG1 voted five to two, and RG2 voted six to one in favor of including the nomination as being reviewed but not listed.

In response to questions about how the recommended action would differ from delisting, Dr. Jameson explained that boot and shoe manufacture and repair had never formally been reviewed or listed in the Report, only mentioned previously in the Introduction and now in an appendix. If the recommendation is upheld, it will be contained in an appendix in the 9th Report, as will MtBE. The introduction to the appendix would say that the nomination had been reviewed for possible listing but found not to meet the criteria at this time.

Dr. Bingham, the principal reviewer, said there are statements in the background document that have no references, and some of the agents used in this industry are said to be no longer permitted in the U.S. industry but no information is given as to what agency has banned any of these chemicals. She noted that comprehensive U.S. health and safety standards have eliminated many of the agents, although what they are is not well defined, and benzene has been substituted for in this industry. Besides the epidemiology study cited by Dr. Matthews, Dr. Bingham pointed out a study in leather workers with elevated PCMRs for the stomach of 170 and colon of 140. She also

commented on a study of female shoe workers where there was an SMR for excess of bladder cancer of 2.51 She said that although none of these studies stand alone, taken together they indicate that this exposure circumstance should be considered a likely human carcinogen.

Dr. Hooper, the secondary reviewer, was critical of the document for not giving a better evaluation of the strengths and weaknesses of the epidemiologic studies. He stated that if we are going to say boot and shoe manufacture and repair is not relevant to the U.S., you need to have a clear documentation of U.S. exposures to say the various carcinogenic chemicals are not present. Lacking use of the European data, he would recommend *reasonably anticipated to be a human carcinogen.*.

Public Comment. Mr. Ralph Mosely, Mosely and Associates, Inc., representing the Footwear Industries of America, Inc. (FIA), stated that it seemed to him that the entire concept for listing this exposure circumstance in the *Report* is based on dose-response relationships, and the question that he has relates to dose-response for what substances? He said that wood dust is not a problem in the U.S. nor is benzene, and other chemicals used are within acceptable exposure levels. Mr. Mosely commented that with one exception, all of the epidemiology studies are looking at data that are almost 30 years old. In conclusion, he said FIA could support the NTP proposal. Dr. Mirer asked whether the FIA had conducted any mortality studies. Mr. Mosely replied that they had not as they did not consider there to be a problem.

There was discussion among the members on the difficulty of grappling with exposure circumstances such as this one particularly lacking recent adequate human data. Dr. Lucier said that before the NTP comes forward with this again, the NTP needs to establish some guidelines, perhaps through a working group that defines the issues that need to be addressed.

Dr. Hooper moved that the nomination to include boot and shoe manufacture and repair in the *Report* as having been reviewed but not listed due to inadequate data be deferred. Dr. Henry seconded the motion. Dr. Bingham inquired as to what would happen with this exposure circumstance if deferral was voted. Dr Lucier said that it would stay where it is currently, Appendix A. Dr. Hooper's motion was accepted unanimously with 10 votes.

Dr. Brown thanked the Subcommittee for their hard work and adjourned the meeting.

These Summary Minutes have been read and approved by the Chair of the National Toxicology Program, Board of Scientific Counselors, Technical Reports Review Subcommittee as certified below.

Date: _____

Dr. Arnold Brown
Chair
NTP Board of Scientific Counselors
Report on Carcinogens Subcommittee