Summary of all agents

Lead and lead compounds

Although the occurrence of lead in the environment has greatly decreased due to the elimination of most leaded gasoline, substantial occupational exposures continue primarily via lead in the battery industry and lead pigments in paints. IARC Monograph 87 in 2006 classified inorganic lead compounds are probably carcinogenic to humans based on sufficient evidence in animals and limited evidence in humans. IARC based its conclusions regarding humans primarily on six cohorts exposed to inorganic lead. Stomach cancer was consistently

elevated (30-50%) in four of the five cohorts where stomach cancers were reported. Lung, kidney, and brain cancer showed elevation in some studies but were not consistent. There have been four new epidemiologic studies since the 2006 monograph, which have been of limited importance and do not change the overall picture. Future work which could advance knowledge include new large cohorts with documented lead exposure such as the NIOSH ABLES lead surveillance cohort which include 50,000 workers with lead exposure over 25 mg/dl, and which is currently under study. Further followup of the existing lead cohorts would also be useful. This study could be strengthened by the addition of two components: 1) measurement of a sample of subjects for bone lead to determine the correlation of the blood lead measurements with cumulative exposure as measured by bone lead, and 2) assessment of whether *Helicobacter pylori* infection has been more common among those with higher blood leads. If so such infection could either be a mechanism by which lead caused higher rates of stomach cancer, although it could also be a confounder. In addition, given positive results from some studies (Keteleslegers et al., 2008, Rajaraman et al., 2006) it would be good if that future epidemiological studies of relationships between lead exposures and cancer should include evaluation of genetic susceptibility factors, such as the ALAD gene. Finally, further experimental research studies are needed to evaluate the complex mechanisms by which lead may cause cancer with particular emphasis on the roles of oxidative stress / apoptosis and the roles of cellular defense mechanisms, signaling pathways and intracellular lead binding patterns in mediating these processes.

Indium phosphide

Indium phosphide was evaluated as probably carcinogenic to humans (Group 2A) in Monograph 86, based on its carcinogenicity at very low doses in numerous animal studies (IARC 2006). The monograph considered indium phosphide alone; since then, use of other indium compounds [e.g., indium tin oxide (ITO), copper indium gallium diselenide (CIGS)] has burgeoned. More than 300,000 workers are employed worldwide in the semiconductor industry, but over 80% of indium is now used as ITO in flat panel displays, with a large number of workers employed either in display manufacture or in the production and reclamation of indium materials used to manufacture of the displays.

No epidemiologic studies to date have specifically evaluated indium compounds. Several studies of semiconductor industry workers have been conducted (e.g., Beall et al., 2005) and more are underway, including a large study of U.S. semiconductor workers sponsored by an industry trade association and a NIOSH study of circuit board manufacturing workers. While these studies are attempting to characterize risk associated with work in specific departments or operations, they are unlikely to inform on cancer risk of indium compounds, because: 1) little indium exposure likely occurred in past circuit board manufacturing, although its use may be growing; 2) wafer fabrication workers (those most likely to have indium phosphide exposure) are typically exposed to a wide variety of other carcinogens, including arsenic, trichloroacetic acid, tetrachloroacetic acid, and more than 20 others (Cullen et al., 2001); 3) little historical exposure monitoring information is likely available to provide estimates of exposure to indium phosphide or other potential carcinogens, which would be necessary to evaluate the contribution of indium to any observed carcinogenicity among wafer fabrication workers.

A better approach may be to conduct (if feasible) epidemiologic studies (e.g., retrospective cohort studies) of workers involved in primary (e.g., zinc smelting) or secondary refining industries. Most primary indium refining occurs in Asia. There are two large secondary refineries in the U.S. and several elsewhere. Studies in secondary refineries may be more informative because of the presence of cadmium in zinc smelting. Also, the focus of secondary refineries on indium production suggests that exposures to other carcinogenic substances may be lower than those to indium. Analogy exists to Group 1 carcinogenic metals (e.g., nickel, cadmium, beryllium), for which the most informative studies have generally been conducted among the refiners and production facilities for these metals and metal compounds (Straif et al., 2009). Recent reports have indicated that pulmonary effects may be occurring in indium workers in Asia (Chonan et al., 2007, Hamaguchi et al., 2008). Studies of current exposure and biomarkers of genetic damage (using the metrics described below) of such indium-exposed workers may be informative in identifying early precursors of cancer.

Further experimental research is needed into mechanisms of indium-compound-induced toxicity and carcinogenesis with particular focus on formation of oxidative stress, inhibition of protective protein synthetic mechanisms and DNA damage. DNA damage from indium exposures could be evaluated by measurement of validated biomarkers of genetic damage such as chromosomal aberrations in accessible cells (e.g., nasal epithelium, buccal cells, shed urinary cells, or circulating lymphocytes).

Cobalt with tungsten carbide

The evidence for carcinogenicity of cobalt with tungsten carbide in humans comes from two studies of workers in the hard-metal industry in France and Sweden. We understand that a study is about to begin or has recently begun at the University of Pittsburgh.
There is good experimental evidence that cobalt and cobalt with tungsten carbide produce cellular toxicity via formation of reactive oxygen species (ROS). This triggers a number of cellular regulatory pathways which may lead to cancer. This general mechanism is mediated by a number of protective cellular mechanisms which may define subpopulations at special risk. These factors include but are not limited to cellular anti-oxidant systems, the stress protein response, DNA excision and repair enzymes and genetic polymorphisms in the processes which maintain these protective systems. There is growing evidence of cobalt with tungsten carbide being formulated into nanomaterials. These have potential health consequences irrespective of chemical make-up.

We recommend that consideration be given to updating the French and Swedish studies in identifying other plants where hard-metal manufacturing is carried out in order that additional cohort studies might be established. Further studies of cobalt metal without tungsten carbide and soluble cobalt (II) salts would also be useful. The epidemiological studies could usefully include molecular biomarkers of early cellular effects. We also recommend additional research is needed to further understand the genetic factors which regulate the above cellular protective systems in order to better protect sensitive human sub-populations exposed to cobalt with tungsten carbide. Further research is needed into the potential health effects of cobalt with tungsten carbide as nanomaterials.

Titanium dioxide

Worldwide, over 5 million metric tons/year of bulk titanium dioxide (TiO2) is manufactured each year. The percentage of TiO2 manufactured as nanoparticles has been estimated as 2.5% in 2009 and about 10% by 2015. User industries include paints and pigment; plastics; paper; cosmetics, catalysts, ceramics, printing inks, roofing granules, glass, and welding fluxes (Robichaud et al., 2009). In 2006, IARC classified TiO2 as possibly carcinogenic to humans (Group 2B) based on sufficient evidence in experimental animals and inadequate evidence from epidemiological studies (Monograph 93, in press).

Since 2006, one new epidemiological study has been published – a re-evaluation of two previously conducted case-control studies found no association with lung cancer (Ramanakumar et al., 2008). There have been no new chronic studies in animals. New subchronic studies in rats (intratracheal instillation) confirm earlier findings that ultrafine TiO2 (nanometer particle diameter) was more potent in causing pulmonary inflammation and cytotoxicity than fine TiO2 (micrometer particle diameter) on a mass basis, whereas both particle sizes showed a consistent dose-response relationship when dose was expressed as particle surface area (Sager et al., 2008; Sager and Castranova 2009). Recent studies have shown that the crystal structure and coatings can also influence the pulmonary responses (pulmonary inflammation, cytotoxicy, and cell proliferation) to TiO2 (Warheit et al., 2006a,b; 2007). These recent studies are consistent with the mechanistic evidence that inhaled TiO2 and other poorly-soluble particles can be carcinogenic through a secondary genotoxic mechanism involving chronic inflammation and oxidative stress; although possible direct genotoxicity by nanoscale TiO2 cannot be ruled out (Schins and Knaapen 2007).

Epidemiological studies with well-characterized exposures and adequate follow-up are needed, especially for workers producing or using nanoscale TiO2. Exposure data should include information on particle size, crystal structure, and surface properties. A possible cohort for epidemiologic studies would include workers in industries using TiO2, particularly the ultrafine (nanoscale) TiO2 now used extensively in the cosmetics industry. Workers handling or mixing TiO2 powders with other ingredients would probably be at the greatest exposure. NIOSH is currently conducting exposure studies of TiO2 users and identifying possible cohorts.

Experimental studies are needed to elucidate the biological mechanisms between particle-induced inflammation and lung cancer. A study examining the relationship between TiO2 exposure in workers and validated markers of oxidative stress, with quantitative comparison in rodent studies, could provide data on interpretation of the animal studies for predicting lung cancer risk in humans. The observation of inhaled discrete nanoscale TiO2 particles inside rat alveolar epithelial cell organelles including the nucleus (Geiser et al., 2005) suggests that possible direct genotoxic mechanisms for lung cancer should be examined. Given the increasing applications of nano-TiO2 in consumer products (e.g., food or food packaging and skin care products), there is a need to develop better techniques to detect TiO2 in tissues and to examine possible carcinogenicity of nano-TiO2 by other routes of exposure (oral, dermal).

Welding fumes

Epidemiologic studies indicate an increased risk of lung cancer among welders in the order of 20% to 40% (Ambroise et al., 2006; Siew et al., 2008). Experimental studies are suggestive but not conclusive of lung carcinogenicity of welding fume exposure (Antonini 2003; Zeidler-Erderly et al., 2008). Genotoxicity of various types of welding fumes has been shown in many *in vitro* and in human *in vivo* studies (Antonini et al., 2003). Pulmonary effects consistent with oxidative stress and inflammatory responses have been observed in experimental animals. Research needs include re-examination of existing cohorts and new cohorts, or appropriate case-control datasets, with improved exposure assessment and smoking data. Experimental studies are needed using inhalation exposure to different types of welding fumes, and studies on ultrafine/nano-sized particles, epigenetic mechanisms, gene expression pathways, and functional level changes related to welding fume exposure (Ayers et al., 2008; Rim et al., 2007). In addition, the recent finding that welders have an increased risk of ocular melanoma (El Ghissassi et al., 2009, Lancet Oncology 10:751-752) should be pursued to determine whether this is due to ultraviolet or other forms of radiation, or to metal and chemical fumes.

Refractory ceramic fibres

Refractory ceramic fibers (RCF) are fibers used for high-temperature insulation. Their production and use is relatively rare compared to low-temperature insulation materials such as glass wool and rock wool. NIOSH has estimated that there were about 30,000 U.S. workers exposed to ceramic fibers in the 1980s, in both production and use. The general public is not usually exposed. Exposures to RCF are of concern because they are relatively more biopersistent than other fibers like low-temperature insulation wools. However exposures to RCF have been lower than historical levels of asbestos fibers which are known to cause cancer in humans. IARC last evaluated ceramic fibers in 2002 in Vol 81, and determined that evidence for cancer in humans was inadequate, while evidence in animals was sufficient, leading to an overall classification of 2B (possible carcinogenic in humans). Human epidemiology for cancer is confined to a single small U.S. cohort (n=942) which at time of last followup had only 9 lung cancer deaths. There were no mesotheliomas found in a review of 35% of the death certificates, although there has been an exposure-related excess of pleural plaques after controlling for past asbestos exposure. There is also a small English cohort (n=774) which showed some cross-sectional association between fiber exposure and lung function, but which has not been followed for cancer. Research needs in experimental animals include a study of the combination effects of RCF and granular, low biosoluble particles. The presence of granular dust retained in lungs could significantly aggravate effects of inhaled fibres. The impact of fibre length on carcinogenicity should be investigated. Fibres longer than 20 μm are supposed to be more carcinogenic than fibres in the range between 5 and 10 μm. Furthermore, the validity of dose response data in rats after inhalational exposure is potentially questionable as there are indications that the sensitivity of this assay is relatively low. More sensitive models for investigating carcinogenicity of man-made fibres should be developed. Regarding epidemiology, further followup of the U.S. cohort is recommended; more mortality follow-up is currently planned. Incidence follow-up would be useful. However it is unlikely that this small cohort will yield important results until many more

years of followup. Mortality to date is 13% for this relatively young cohort. Follow-up for cancer mortality or incidence in the European cohort would also be useful.

Diesel exhaust

In 1989, IARC classified diesel exhaust (DE) as probably carcinogenic to humans (Group 2A) because of limited evidence of carcinogenicity in humans coupled with sufficient evidence of the carcinogenicity of whole engine exhaust in experimental animals. Environmental exposure to DE is ubiquitous in urban areas and occupational exposure to DE is widespread, affecting 1.4 million workers in the United States and 3 million workers in the European Union. Because of the ubiquitous nature of environmental exposure to DE, it is difficult to measure environmental DE exposure for risk estimation in epidemiologic studies. In contrast, DE exposure is potentially quantifiable among the several DE-exposed occupational groups. With regard to lung cancer, much relevant research on the relation between DE exposure and risk of dying has been published since the last Monograph. Two meta-analyses have estimated the summary risk to range from 1.33 (95%CI = 1.24-1.44) (Bhatia et al., 1998) to 1.47 (95%CI=1.29-1.67) (Lipsett and Campleman, 1999). Although each meta-analysis was based on about 30 studies, most of the studies inferred DE exposure based on job title rather than from data on individual exposure, which may have led to misclassification of exposure and estimates of risk biased towards the null. A small number of studies in the past 20 years have included a retrospective assessment of DE exposure. Studies in miners and truck drivers are among the most informative in this regard (Neumeyer-Gromen et al., 2009; Steenland et al., 1990; Garshick et al., 2008). Epidemiologic evidence to date suggests that the relation between DE exposure and lung cancer risk may be causal, but the dose-response curve in humans remains unknown. To establish causality will require well-designed epidemiologic studies of large cohorts of DE-exposed workers with (a) quantitative estimates of DE exposure for individual study subjects, (b) with adequate latent period for the development of lung cancer, and (c) with information on potential confounders. Two ongoing studies satisfy these criteria and will estimate risk for a wide range of DE exposure: 1) a cohort and nested case-control study of lung cancer in U.S. nonmetal miners with heavy DE exposure (NCI/NIOSH, 1997); 2) additional retrospective exposure assessment in the truck driver cohort with light-to-moderate DE exposure (Garshick, personal communication). If these ongoing epidemiologic studies of nonmetal miners and/or truck drivers yield significant, positive exposure-response relationships, it will be important to conduct research into the underlying mechanisms of DE-induced carcinogenesis. Cross-sectional molecular epidemiological studies in DE-exposed human populations will be needed to evaluate the relationship between DE exposure and biomarkers of inflammation, genotoxicity, and other relevant early biological effects, and to study potential sources of genetic susceptibility. Such studies may help us identify the components of DE that are most biologically active in humans. In the long-term, the design and implementation of technologies for population surveillance of DE exposure coupled with biomarkers of effect merit consideration.

With the increased use of biodiesel in recent years, the potential carcinogenicity of biodiesel warrants future evaluation. Although several biodiesel fuels derived from rapeseed oil or rapeseed methyl ester have been found to be highly mutagenic (Bunger et al., 2007), the soy-oil-based biodiesel emissions are less mutagenic. It is premature to conduct epidemiologic

studies of biodiesel because the latent period for the development of solid tumors is currently inadequate. However, experimental laboratory studies of biodiesel should be a priority in view of the increasing prevalence of use of biodiesel in the United States and European populations.

Carbon black

Carbon black is a powdered form of elemental carbon that is used in rubber products, paints, plastics, and inks. In 2006, IARC affirmed its 1995 evaluation of carbon black as possibly carcinogenic to humans (Group 2B) based on sufficient evidence in experimental animals and inadequate evidence from epidemiological studies.

Sorahan and Harrington (2007) reported elevated lung cancer in an update of the U.K. carbon worker cohort with an additional eight years of mortality follow-up (SMR 146; 95% CI 113-185). Elevated lung cancer risk was limited to workers employed in the most recent 15 years and a significant trend was seen with increasing cumulative carbon black exposure during that time ("lugged" analysis), suggesting that carbon black may be a late-stage carcinogen. SMRs also tended to decrease with time period since leaving employment. In two re-analyses of the German carbon black worker cohort, Morfeld and McCunney (2007; 2009) found no evidence that the risk of lung cancer declined following cessation of employment, or that recent carbon black exposure was related to lung cancer risk.

There have been no new chronic studies of carbon black exposure in animals. Several recent subchronic studies in rats or mice (intratracheal instillation of carbon black) have strengthened the evidence that particle size and surface area influence the dose-response relationships of early biological events considered to be important in particle-induced lung cancer (Schins and Knaapen 2007). These studies showed that ultrafine carbon black was more potent in causing pulmonary inflammation and cell damage than fine carbon black on a mass basis, whereas both particles sized showed a consistent dose-response relationship when dose was expressed as particle surface area (Stoeger et al., 2006; Duffin et al., 2007; Sager and Castranova 2009). In human alveolar or bronchial epithelial cell lines, carbon black particle surface area was associated with the generation of reactive oxygen species and with oxidative stress (Hussain et al., 2009); and ultrafine carbon black caused single-strand DNA breaks, whereas fine carbon black did not at the same mass dose (100 µg/ml) (Mroz et al., 2008).

Worker exposure data in relation to particle size and surface area are needed to better examine possible exposure-response relationships. The possible influence of worker age at exposure to carbon black as an effect modifier of lung cancer mortality should also be investigated. Basic work history data are needed in the study of U.S. carbon black production workers, which would permit further investigation of the hypothesis that carbon black is a late-stage carcinogen. There is also a need to confirm that the lung cancer SMR in this U.S. study is not artefactually depressed by incorrect allocation of person-years-at-risk. In addition, it would be worthwhile to identify other carbon black production facility workers for study. Experimental studies are needed that improve our understanding of the mechanisms of particle-elicited lung cancer. A study examining the relationship between occupational

exposure to carbon black and validated biomarkers of oxidative stress may provide information on the early biological responses relevant to particle-induced lung cancer mechanisms. These exposure-response relationships should be quantitatively compared in humans and rodents, and the role of particle size should also be examined.

Styrene-7,8-oxide and styrene

Styrene is a large volume industrial chemical, with over 50 billion pounds (23 billion kilograms) produced annually worldwide. Styrene is a key component in the manufacture of synthetic rubbers, many plastics, resins and fiberglass and as such is in a wide array of consumer products. Exposure is ubiquitous. For the general population, food packaging residues appear to be the largest source of exposure, followed by indoor air. Smokers are most exposed through tobacco smoke. Concentrations measured in occupational settings are orders of magnitude higher than environmental concentrations.

In 2002, IARC classified styrene as possibly carcinogenic to humans (Group 2B) with limited evidence in humans and experimental animals for the carcinogenicity. The styrene metabolite styrene-7,8-oxidewas classified in 1994 as probably carcinogenic to humans (Group 2A) with inadequate evidence in humans, sufficient evidence in experimental animals, and the following supporting evidence: (i) forms covalent adducts with DNA in humans, rats and mice; (ii) induces gene mutation in bacteria and rodent cells in vitro; (iii) induces chromosomal aberrations, micronuclei, and sister chromatid exchange in human cells in vitro; and (iv) induces chromosomal aberrations and sister chromatid exchange in mice in vivo.

In 2008 National Toxicology Program expert panel reviewed styrene and also found limited evidence in humans, but sufficient evidence of carcinogenic activity in animals from multiple studies in mice by multiple routes. A consistent finding across studies is the occurrence of lung neoplasia in mice. Genotoxicity of the styrene-7,8-oxide metabolite, evidence for styrene-related DNA adducts and cytogenetic effects in styrene-exposed workers were also afforded weight.

The two main epidemiological studies published since the 2002 IARC monograph did not conclusively address certain critical questions such as: why cancer risk is concentrated in cohorts apparently less exposed to styrene, the effect of potentially confounding exposures, the different types of hematolymphopoietic cancers found in different cohorts, and the potential for other than increases in non-hematolymphopoietic (e.g., pancreatic) cancers sometimes observed. Thus at this point the human evidence remains limited.

At least 70 research publications released since the styrene monograph explore various mechanistic aspects of potential carcinogenicity in humans and rodents, such as variability in enzymes involved in activation and detoxification, the possible role of enzymes besides the 7,8-oxide, potential for human extrahepatic metabolism to styrene oxide and other mutagenic metabolites, and dose response relationships between styrene exposure and DNA damage. Overall, the recent mechanistic research point support to all of carcinogenicity, but also leave questions unanswered. The evidence that has been generated since the last monograph together with the evidence in the monograph may support a re-evaluation of styrene.

Recommendations for new research are to: perform a pooled analysis of human studies on chromosome aberrations and other genotoxic effects, as well as the cancer studies; update the existing studies, while clarifying classification of hematolymphopoietic cancers and addressing the questions mentioned above; recruit new cohorts; for the largest cohorts, promote case-control studies of hematolymphopoietic, bladder, kidney and pancreatic cancers; further explore the extrahepatic metabolism of styrene by mammary, hematolymphopoietic, human lung and other tissue/cells; study the formation of other possible genotoxic metabolites such as the 2,3- and 3,4- oxides, their genotoxicity; further study the pharmacokinetic basis for inter-individual differences in susceptibility; and further explore the relationship between styrene exposure, potential increases in prolactin, and the potential for mammary carcinogenesis.

Propylene oxide

Propylene oxide (PO) (CAS 75-56-9) is used primarily as a chemical intermediate for glycols and glycol ethers and to a lesser extent as a fumigant, food additive, and in production of hydroxypropyl starch ethers. Occupational exposure can occur during production of PO and its derivatives. In 1994, IARC classified PO in group 2B. Only one case-control study was available at the time resulting in inadequate evidence in humans for the carcinogenicity of propylene oxide, while there is sufficient evidence in experimental animals for the carcinogenicity of propylene oxide.

Recent exposure and biomarkers studies have shown that PO form chemically stable adducts with the N-terminal valine of hemoglobin (Hb); N-(3-hydroxypropyl)valine (HOPrVal) adducts. Concentration of HOPrVal (Hb) is linearly related to air concentrations of PO (Boogaard et al., 1999). Hb-adducts are sensitive, not subject to repairs, and therefore a cumulative exposure dose over the past 120 days is achieved. The origin of minor background levels of OHPrVal measured in non-occupational control subjects is unknown; but a likely source is propene found in tobacco smoke or automobile exhaust, metabolically converted to PO in the body. Czene et al. (2002) analyzed the levels of specific DNA (1-hydroxypropyl-adenine) and hemoglobin adducts and sister chromatic exchanges in workers occupationally exposed to propylene oxide and in controls. All these outcomes were significantly increased in the exposed group.

Since the last IARC monograph, only one epidemiological study (Olsen et al., 1997) of PO manufacturing workers (USA) has been reported. This occupational mortality study did not show an increased mortality rate due to cancer by duration with or without latency or cancer risk by process (PO versus EO). To further understand the cancer risk of PO, a future prospective occupational biomarker epidemiology study using DNA and Hb-adducts as biomarker would be beneficial particularly in reference to dose-response and adduct appearance/disappearance kinetics. Possible cohorts for future epidemiological studies have been identified: PO manufacturing workers in the United States (Olsen et al., 1997), in France and the Netherlands (Jones et al., 2005), in China (Czene et al., 2008), processing workers where PO is used as a starting material in polyurethane polyols (NTP 11th RoC), surfactants for textiles (Schettgen et al., 2002) and glycol/glycol ether manufacturing (Boogaard et al.,

1999), and manufacturing of polyethylene (PE), which metabolizes to PO. Women should be included in the study as PO might be mammary carcinogen (Rudel et al., 2007). PO is also used in paint and automotive fluids. Workers of these manufacturing sites have never been assessed either for exposure or included in epidemiological studies. Generally, it is recommended that research be conducted to enhance the mechanistic evidence base in human hemoglobin and DNA adducts and cytogenetic changes.

Formaldehyde

Formaldehyde is a major industrial compound with many uses and is a ubiquitous indoor and outdoor air pollutant. At its last review in 2006 it was classified as a Group 1 carcinogen based upon sufficient animal and human evidence of nasal carcinogenesis. However the Working Group noted that the epidemiologic evidence provided "strong but not sufficient evidence for a causal association between leukaemia and occupational exposure to formaldehyde". Further, after reviewing the toxicological and mechanistic data available, the Group concluded that 'Based on the data available at this time, it was not possible to identify a mechanism for the induction of myeloid leukemia in humans'.

Only one new report from an original epidemiology study in relation to leukemia induction by formaldehyde has been published since the last review. The NCI group has published a recent update of one of their studies, with an additional 10 years of follow-up, and it continues to suggest a possible link between formaldehyde exposure and mortality due to lymphohematopoietic malignancies, particularly myeloid leukemia (Beane Freeman et al., 2009). A recent meta-analysis using a "highest exposure" category to evaluate leukemia risk from formaldehyde exposure (Zhang et al., 2009) provides additional evidence of an association between formaldehyde exposure and human leukemia, especially for myeloid leukemia. Questions have been raised about the highest peak exposure metric used in the NCI studies which otherwise did not show a statistically significant association of hematological cancers with more standard dose metrics (Marsh and Youk 2004),

Reevaluation of previously published animal data has led to an additional focus on lymphoid as well as myeloid malignancies. Mechanism models for formaldehyde leukemogenesis have been proposed (Zhang et al., 2008) while other reviews have questioned the plausibility of formaldehyde as a cause of hematological diseases (Goldstein, 2009)

Particularly valuable in providing additional insight into whether formaldehyde is a cause of hematological neoplasms would be additional studies examining the genotoxic and the pancytopenic effects of formaldehyde in epidemiological studies or in laboratory animals, including assessment of biological markers of internal dose. Further evaluation of hematological effects reported in Chinese studies of formaldehyde-exposed workers is needed. Reassessment of the peak exposure dose metric associated with hematological neoplasms would be useful, as would understanding its implications to the toxicological mechanism of action and to risk considerations. Particular emphasis should be placed on clarifying whether formaldehyde fits into the pattern observed with other known myeloleukemogens, including why the formaldehyde latency period appears longer. The nose as a potential site of

formaldehyde leukemogenesis warrants exploration as do pathways by which inhaled formaldehyde or a formaldehyde derived intermediate can reach bone marrow or lymphatic tissue. Additional mechanistic studies should include evaluation of the interaction of formaldehyde or formaldehyde-derived intermediates on blood stem cells. Studies examining the role of FANC/BRCA repair pathway, or of other mouse models of susceptibility are needed. Closer evaluation of the hematological findings and tumor incidence in existing animal studies is warranted.

Acetaldehyde

Acetaldehyde is primarily used as an intermediate in the manufacturing of acetic acid, flavorings, aniline dyes, plastics and synthetic rubber, in some fuel compounds and in the manufacture of numerous other products. Acetaldehyde is also a ubiquitous air and water pollutant. Acetaldehyde is also an endogenous metabolite produced from ethanol. At its last review in Monograph 71 (1999), it was classified as *possibly carcinogenic to humans (Group 2B)* because of *inadequate evidence* of carcinogenicity in humans and *sufficient evidence* of carcinogenicity in experimental animals. Acetaldehyde binds to DNA, forming stable DNA adducts, and acetaldehyde DNA adducts have been found in alcohol consumers.

Epidemiologic studies of cancer in populations occupationally-exposed to acetaldehyde published after Monograph 71 were not identified. The most compelling evidence of the carcinogenicity of acetaldehyde is provided by studies of alcohol drinkers. Acetaldehyde is the first metabolite of ethanol oxidation. The conversion from ethanol to acetaldehyde is catalyzed by the enzyme alcohol dehydrogenase (ADH), and the subsequent oxidation from acetaldehyde to acetate is catalyzed by the enzyme aldehyde dehydrogenase (ALDH). The genes that code for these enzymes are polymorphic and result in low or fast metabolism of ethanol.

Numerous epidemiologic studies in alcohol drinkers with ALDH2 deficiency or low ADH1B activity strongly suggest that acetaldehyde derived from the metabolism of ethanol contributes towards causing upper digestive tract cancers. This notion is also supported by two meta-analyses that used a Mendelian randomization approach and a recent large-scale case-control study that reported a multiplicative combined risk for esophageal cancer among alcohol and tobacco consumers, who were low ADH1B and ALDH2-deficient carriers.

An epidemiologic study that evaluates the association between acetaldehyde exposure and upper digestive tract cancer will require evaluation of all potential sources of exposure to acetaldehyde, to address their contribution to the overall risk. Prospective studies could be designed to assess all sources of exposure using a combination of questionnaires and environmental and biological monitoring, as well as genotyping to identify individuals with ALDH2, ADH1C, and ADH1B deficiencies. However, given the long induction and latency of most cancers, such a study may not be feasible. Retrospective studies, conversely, have the limitation that exposures have to be evaluated retrospectively, increasing the potential for misclassification. Alternatively, acetaldehyde-derived DNA adducts could be used as biomarkers of exposure to acetaldehyde.

The IARC Working Group that evaluated the carcinogenicity of alcoholic beverages (2007, Monograph 96) concluded that “acetaldehyde derived from the metabolism of ethanol in

alcoholic beverages contributes to causing malignant esophageal tumors". Furthermore, recent risk assessments that consider individual sources of exposure have concluded that the lifetime cancer risks for many of these sources of exposure greatly exceed the usual limits for cancer risks from the environment ($1:10^4$-$1:10^6$). Acetaldehyde exposure is cumulative and in some cases synergistic (as occurs with alcohol exposure and smoking). Exposure scenarios that consider multiple sources of exposure and genetic deficiencies in alcohol metabolism convey increased risks. It was thus recommended that the IARC classification of acetaldehyde be reviewed in a Monograph meeting.

Chlorinated solvents

Trichloroethylene (TCE), tetrachloroethylene (perchloroethylene, Perc), and dichloromethane (methylene chloride, DCM) are used worldwide as degreasers, cleaning solvents for metals and fabrics, and as chemical intermediates. In 1998, the U.S., Europe, and Japan used 318,000 metric tons of TCE; 345,000 metric tons of Perc, and 506,000 metric tons of DCM (Chemical Economics Handbook Program 1999; Leder et al., 1999). TCE and Perc both were evaluated by IARC as probably carcinogenic to humans (Group 2A) (International Agency for Research on Cancer, 1995) and DCM was evaluated as possibly carcinogenic to humans (Group 2B) (International Agency for Research on Cancer, 1999).

Several common issues arise in consideration of research needs for TCE, Perc, and DCM. Each has widespread exposures (often as co-exposures), similar tissue targets observed in human and animal studies, and common epidemiological and mode of action (MOA) issues. The body of knowledge is more comprehensive for TCE than Perc and DCM, and is informative for identifying data gaps and research needs for the other solvents. The meta-analysis approaches of human epidemiological studies on TCE (Scott and Chiu, 2006) (see TCE, below) can be useful not only for future study of TCE, but also to help give a clearer signal and identify new targets of toxicity for Perc and DCM.

Each solvent has been associated with increased risk of lymphohematopoietic cancer (LHC). The evaluation of LHC has been limited by the use of mortality studies, changes in ICD codes over time and changes in the understanding of the biology of these cancers over time. For each of these solvents, studies on LHC should evaluate incidence data and if possible use improved diagnoses, such as biological markers to measure disease. Immunologic mechanism may be involved in lymphomagenesis from solvents (Vineis et al., 2007) and this should also be an area of future research. Brain tumor is also a potential target for DCM and Perc and has not been adequately studied for TCE. The working group is aware of several large brain case-control studies (NCI, NIOSH, Interphone), which will be analyzed in the next year or two for an association between exposure to chlorinated solvents and risk of brain cancer (Inskip et al., 2001; Ruder et al., 2006; Cardis et al., 2007).

Mechanistic data gaps for Perc and DCM include the (1) identification and role of metabolic pathways involved in carcinogenicity, (2) identification of modes of actions from the numerous toxicologically active metabolites of the solvents, and (3) development of physiologically based pharmacokinetic (PBPK) modeling. Similar to TCE, Perc and DCM are metabolized by both the cytochrome P450 (CYP) pathway to oxidative metabolites and by the glutathione (GSH) conjugation pathway to genotoxic metabolites. Genetic susceptibility

studies evaluating cancer risk from exposure to chlorinated solvents among individuals with polymorphisms in relevant metabolisms genes (GST and CYP2E1) as well as other genes in the disease pathway are needed. Since the GSH pathway is not active in glutathione S-transferase (GST)-null individuals, it can be hypothesized that cancer risk will be lower among GST-null individuals. Studies should also be conducted using entire genome scans to identify new susceptibility genes. As shown for TCE, multiple MOAs (Caldwell et al., 2008) from multiple metabolites can contribute to toxicity and make comparisons between chlorinated solvents difficult to study. These can account for differences in exposures and pharmacokinetic and pharmacodynamic characteristics of exposed populations contributing to variable responses in a number of studies. Issues and research needs for specific compounds are discussed below.

Chloroform

Human exposure to the trihalomethane (THM) chloroform is primarily from drinking water, where it is a predominant disinfection by-product (DBP). IARC monograph Vol. 73, 1999 evaluated chloroform as having inadequate evidence for carcinogenicity in humans but sufficient evidence for carcinogenicity in experimental animals; thus, it was classified as Group 2B, possibly carcinogenic to humans.

Since Vol. 73, several epidemiological studies have been published on the association between exposure to DBPs and risk of bladder cancer, with two being a pooled analysis of previous case-control studies and a new case-control study from Spain. Both studies found that the risk of bladder cancer in men, but not in women, increased with increasing THM level. In Spain, a dose response was found both for exposure via ingestion and via shower/bath/pools, and this was found only in persons having GSTT1-1.

Two reports of 2-year rodent studies of chloroform were considered in Vol 73, and two more have been published since. Four studies in rats showed that chloroform induced kidney tumors by gavage, kidney tumors by drinking water in one study but no tumors in another study, no tumors in two studies by inhalation, and kidney tumors by a combined drinking water/inhalation exposure. Three studies in mice showed that chloroform induced liver tumors by gavage, liver and kidney tumors by inhalation, and no tumors by drinking water. Thus, chloroform induced kidney tumors in three studies in rat, liver tumors in two studies in mouse, and kidney tumors in one study in mouse.

Chloroform is an anomaly among the THMs in that it is not mutagenic, whereas the other THMs (i.e., the brominated THMs) are activated to mutagens by GSTT1-1. A model has been proposed by which the bladder cancer associated with drinking water results from the dermal/inhalation exposure to the brominated THMs (not chloroform), followed by systemic distribution that largely bypasses the liver, and activation by GSTT1-1 to mutagens in the bladder. In contrast, oral consumption of the THMs (including chloroform) would result in inactivation by CYP2E1 in the liver. A postulated mechanism for chloroform carcinogenicity involves oxidative metabolism by CYP2E1 to produce cytotoxic metabolites, especially phosgene, which would injure and kill cells, resulting in regenerative cell proliferation.

Additional events, such as epigenetic changes and selection of mutations, could then result in tumors.

Future IARC evaluations should address the entire group of DBPs in drinking water, and chloroform. Other THMs/DBPs should be evaluated for biological effects in rodents via the dermal route. Additional epidemiology studies are needed that have information on route of exposure and detailed DBP exposure assessment. A large New England bladder cancer case-control study is currently underway. Also ongoing are pooled analyses of bladder cancer case-control studies from Spain, France, and Finland, as well as of colorectal cancer case-control studies from Spain and Italy. Epidemiological studies are warranted of high-exposure groups such as competitive swimmers and indoor pool attendants/lifeguards. There should be follow up of cohorts of nurses and doctors exposed to chloroform when chloroform was used as an anesthetic gas.

Polychlorinated biphenyls

Polychlorinated biphenyls (PCBs) were widely used from the 1930's through the 1980's and later, with an estimated total production of about 1.2- 2 million metric tons. Exposure continues from leaks from transformers and capacitors, volatilization of PCBs in cites, in buildings, from sewage, landfills and waste sites, and combustion of materials containing PCBs. PCBs were evaluated as probable human carcinogens in Supplement 7 (1987).

Among the most important research since the last IARC evaluation: Considerable new data have been generated about mechanisms of toxicity, and routes of exposure, especially inhalation of airborne PCBs, which are more volatile, lower chlorinated and better substrates for xenobiotic metabolism/activation than commercial PCBs. Several studies confirm that in rodents, PCBs are complete carcinogens, initiating, promoting and progressing tumors (reviewed in Ludewig et al., 2008). In vitro genotoxic endpoints varied widely and were highly structure-dependent (Zettner et al., 2007). In vivo lesions (GC-TA transversions (Lehmann et al., 2007)) may arise from direct adduction of DNA bases or reactive oxygen species. Biomarkers of oxidative DNA damage have been described recently (Jeong et al., 2008). An updated expanded cohort study of 15,000 workers found a strong relationship between estimated cumulative PCB exposure and risk of prostate cancer mortality (Prince et al., 2006); a case-control study of testicular germ-cell cancer, nested in the U.S. military cohort, found a significant decreasing risk of disease with increasing prediagnostic serum PCB levels (McGlynn et al., 2009).

Gaps related to PCB sources and exposures include distribution of airborne PCBs, identification of sources, and mechanisms for human environmental exposure. Potential risks of such exposures are unknown, as are mechanisms of toxicity, protective strategies, and predictions about possible susceptibility factors and/or interactions with other compounds. Airborne PCB profiles differ from those of commercial PCB mixtures. Appropriate biomarkers of exposure/ effect/susceptibility for airborne PCB exposure need to be identified. Mechanisms that deserve study include inhalation, volatilization from paint, child consumption of paint chips and other building materials, accumulation in food, and possible occupational exposures, for example, during building demolition. Contaminated sites and

multiple chemical exposures often are found in poor neighborhoods, with medically underserved and nutritionally deficient children. Issues of in utero exposures, and developmental impacts are all unknown. Understanding and, if needed, ameliorating the risks is a matter of environmental justice and social responsibility. Reasonably accurate inventories of stored PCBs (in transformers and capacitors) are needed. Human exposure to PCB degradation products and metabolites is not well studied.

Research needs related to mechanisms of action/toxicity include investigation of the metabolic fate of lower chlorinated PCBs. What are the reaction products? Are they mutagenic? Could any serve as biomarkers of exposure/effect? Can we prevent or abrogate negative impacts of exposure? The fate of these residues, whether excreted, converted to toxic metabolites, or bound covalently to tissues, is unknown. The roles of metabolism of OH-PCBs (e.g., further oxidation, sulfation, and other metabolic reactions) in the disposition and toxicity represent a significant gap in our knowledge about mechanisms for carcinogenesis. Many mechanisms of genotoxicity/carcinogenicity for PCBs appear to involve reactive oxygen species, oxidative stress, oxidative DNA damage, and formation of DNA adducts. More research is needed with this mode of action and with cell proliferation, as the two could drive the induction of mutations and subsequent carcinogenicity. Specific attention needs to focus on dose-response. There has been only limited information available on PCB effects on metastasis formation. Clinical, epidemiological, and basic research studies are needed to address possible prometastatic effects of PCBs on tumor cells or how PCBs can alter the vascular endothelium to increase transendothelial migration of tumor cells and the development of metastases.

The existing occupational epidemiologic literature, most of it produced since the last review of PCBs in 1987, may suffice for a re-evaluation of the carcinogenicity by an IARC working group.

Possible studies include cancer incidence within the large (>27,000 workers) NIOSH cohort, which is under way. Nested case-control studies in this cohort and/or those in Sweden and Italy, obtaining and evaluating current PCB blood levels in cases and controls, might be informative. A useful study population might be residents of Aniston, Alabama, around the former PCB manufacturing facility, who received high levels of exposure through various routes.

Di(2-ethylhexyl) phthalate

Although extensive human exposure occurs to di(2-ethylhexyl)phthalate (DEHP) through its use as a plasticizer of polyvinyl chloride (PVC), definitive epidemiologic studies are not available due to the difficulty in identifying highly exposed workers in retrospective cohort or case-control studies. Since the previous Monograph review concluded that liver cancer observed in animals resulted from PPAR-*a* induction and peroxisome proliferation activation was not relevant to humans, several lines of evidence suggest that DEHP may have multiple mechanisms of carcinogenesis, some of which might be relevant to humans. A study of DEHP-induced tumorigenesis in wild-type and *Pparα*-null mice found that the incidence of liver tumors in *Pparα*-null mice exposed to 0.05% DEHP (25.8%) was higher than in

similarly exposed wild-type mice (10.0%). Microarray profile studies find that patterns of up- or down-regulated genes are quite different in hepatocellular adenoma tissues of wild-type mice and *Pparα*-null exposed to DEHP. Animal studies also suggest additional target organs in rats (pancreatic acinar-cell adenoma and testicular leydig cell tumors). Future studies in mouse models, using hPPARα^{TetOff}, which expresses the human receptor only in liver, or hPPARα^{PAC}, which expresses the human receptor not only in liver but also in kidney, heart, intestine and brown adipose tissues, may elucidate the role of human PPARα in DEHP carcinogenesis. Further characterization of DEHP exposures in industry is needed and could be done in established cohorts in the PVC-processing factories using DEHP metabolites, mono(2-ethylhexyl)phthalate and mono(5-carboxy-2-ethylpentyl) phthalate, as a sensitive biomarker of DEHP exposure.

Atrazine

Atrazine is a widely used herbicide to which populations are exposed occupationally, through drift, and in surface and ground water. In 1999, an IARC Working Group determined that atrazine was not classifiable as to its carcinogenicity to humans (Group 3), with inadequate evidence in humans and sufficient evidence in experimental animals. The Working Group concluded that the mammary tumors among Sprague-Dawley rats associated with exposure to atrazine involve a non-DNA-reactive, hormonally mediated mechanism that is not relevant to humans. Atrazine causes accelerated aging within the brain-pituitary-ovarian axis (i.e., constant estrus), thereby establishing the hormonal environment conducive to the development of mammary gland tumors in rats. Recent epidemiologic investigations include updated data from a manufacturing cohort study and U.S. non-Hodgkin lymphoma (NHL) case-control studies, a new case-control study of ovarian cancer, analyses from the prospective U.S. Agricultural Health Study (AHS), and several ecological studies of environmental exposure. The manufacturing cohort demonstrated a nonsignificant excess of prostate cancer incidence (MacLennan et al., 2002), which may have been due to the plant's intensive prostate cancer screening program (Hessel et al., 2004). The cohort also had a nonsignificant excess of deaths due to NHL (N=4) (MacLennan et al., 2003). A significant association of NHL with agricultural exposure was observed in pooled data from three population-based case-control studies in the Midwestern U.S. (de Roos et al., 2003), which controlled for potential confounding by other pesticides. Using archival biopsies from a case-control study, atrazine was associated with risk of NHL among t(14;18) cases only (Schroeder et al., 2001) Rusiecki et al. (2004), reported on cancer incidence among 36,513 applicators in the AHS who ever used atrazine, based on follow-up through 2001. There were suggestive, nonsignificant excess risks for lung cancer, bladder cancer, NHL, and multiple myeloma. New studies of general population exposure did not provide convincing evidence of risk (Young et al., 2005; Hopenhayn-Rich et al., 2002; Muir et al., 2004; Mills et al., 2006; Van Leeuwen et al., 1999).

The finding that atrazine is carcinogenic at a single organ, sex, strain, and species of rodent makes it unlikely that atrazine is a human carcinogen, considering that most IARC Group 1 carcinogens are trans-species carcinogens. Nonetheless, clear mechanistic data are lacking to show that atrazine does or does not alter the secretion of luteinizing hormone and prolactin in humans. Thus, further studies are needed to characterize the ability of atrazine to interfere with the hypothalamic-pituitary-ovarian axis in women and to clarify whether atrazine is a

mammary carcinogen in women. Further analysis of the AHS biomarker study among male corn farmers (Vermuelen et al., 2005; Bakke et al., 2008) and expansion of similar efforts to include women could shed light on atrazine's effects on hormonally-related cancers. Of critical importance is the need to analyze the extended follow-up data of the AHS through 2006, which is expected to have over 65% more cases than the last follow-up. Finally, more extensive microarray and proteomic studies in rodents and humans would also help to characterize the pathways disrupted by atrazine. There is also a need to explore atrazine's ability to alter immune function and aromatase in species relevant to humans as well as in human molecular epidemiology studies.

Shift work

Based on the theory that electric light at night might explain part of the international differences in breast cancer incidence, it was predicted in the late 1980s that women working at night would have elevated risk. Evidence has accumulated to the point where the IARC has classified 'shift work' as a probable human carcinogen (2A) based on limited epidemiology and sufficient animal data. Between 5 and 20% of people in the modern world work a non-day shift, so the possibility is important. Research needs in this area are: 1) better definition of what is meant by 'shift work', 2) studies of markers of circadian disruption in non-day workers, 3) better description of controls and their exposure to light-at-night, and 4) investigation of the impact of variations in expression of circadian genes on cancer in shift workers. An emerging area is the relative toxicity of occupational exposure to toxic chemicals depending on time of day of that exposure. There are marked circadian variations in cell division and DNA repair over the daily cycle, and these are changes are controlled by the circadian genes. Therefore, non-day workers may have very different sensitivity to occupational exposures.