Advisory Board for Toxic Substances and Worker Health

Subject: Whether IARC Group 2A carcinogens should be added to SEM, linking them to specific cancers

The Department of Labor requested that the Board assist in evaluating whether the Energy Employees Occupational Illness Compensation Program should incorporate IARC Group 2A carcinogens to the SEM and associate them to specific cancers.

The process IARC uses to review these carcinogens involves multidisciplinary and interdisciplinary expert panels that do more in-depth evaluations than any individual physician could do. This includes a thorough review of the toxicology, epidemiology, exposure assessment, mechanistic science, statistics, and clinical disciplines at world-class levels of expertise.

Presumption of causality:

Review:

The SEM IARC 2A Work Group has reviewed the IARC list of Group 2A agents from 2016-2019 and identified 22 agents in total (please see Excel spreadsheets attached). The following were omitted for the purposes of this analysis: Pioglitazone, Red meat (consumption of), Very hot beverages at above 65 °C (drinking), and Night shift work.

A search query was performed in SEM for the Group 2A agents (please see word document attached).

IARC monographs for the Group 2A agents were downloaded from the IARC website and the Lancet Oncology (please see attached pdfs of the Monographs).

Recommendation:
The Board recommends that the following listed IARC 2A agents be incorporated into the SEM, including their respective associations with cancer based primarily on the IARC monographs as well as other reputable sources (including NTP, ATSDR).

Rationale:

For **polybrominated biphenyls**, IARC upgraded to Group 2A with supporting evidence from other relevant data, namely mechanistic similarity with polychlorinated biphenyls classified in Group 1. PBB mixtures have been manufactured mainly as three homologue groups: hexabromobiphenyls, octabromobiphenyls, and decabromobiphenyls. Production of PBBs generally involves the reaction of biphenyl with bromine and chlorine in a solvent with aluminum chloride as a catalyst. Commercial PBB mixtures were manufactured primarily as flame retardants. PBBs are highly lipophilic, bioconcentrate and bioaccumulate, and are environmental contaminants worldwide. FireMaster FF-1, the most widely used commercial

PBB product, consistently induced benign and malignant hepatocellular tumours in rats and mice, and cholangiocarcinomas in rats. PBBs, like their chlorinated analogues, are ligands to several cellular and nuclear receptors, including AhR. They are efficacious inducers of hepatic drug metabolism, accelerating the biotransformation of both endogenous and exogenous compounds.

For **1,3-Propane sultone**, IARC's overall evaluation upgraded this agent from Group 2B to Group 2A with supporting evidence in lab and animal studies that it is a strong, direct-acting alkylating agent that reacts with DNA and proteins and is thus genotoxic. 1,3-Propane sultone has been used as a chemical intermediate in the production of fungicides, insecticides, cation-exchange resins, dyes, vulcanization accelerators, and variety of other chemicals. The routes of potential human exposure to 1,3-propane sultone are ingestion, inhalation, and dermal contact. Based on one study of cancer in humans exposed to 1,3 propane sultone (Bolt & Golka, 2012): out of 55 employees at a factory in Germany that manufactured 1,3-propane sultone between 1952–1963: as of 2010 - cancer had been observed in 20 of the exposed workers. Among the 24 tumors identified in these 20 workers: one duodenal cancer, one malignant Schwannoma, two glioblastomas, and two cancers of skin (one basal cell, the other type unspecified) were also observed. There is sufficient evidence in experimental animals for the carcinogenicity of 1,3-propane sultone.

For the herbicide **glyphosate,** there was limited evidence of carcinogenicity in humans for non-Hodgkin lymphoma. The evidence in humans is from studies of exposures, mostly agricultural, in the USA, Canada, and Sweden published since 2001. In addition, there is convincing evidence that glyphosate also can cause cancer in laboratory animals. On the basis of tumours in mice, the United States Environmental Protection Agency (US EPA) originally classified glyphosate as possibly carcinogenic to humans (Group C) in 1985. After a re-evaluation of that mouse study, the US EPA changed its classification to evidence of non-carcinogenicity in humans (Group E) in 1991. The US EPA Scientific Advisory Panel noted that the re-evaluated glyphosate results were still significant using two statistical tests recommended in the IARC Preamble. The IARC Working Group that conducted the evaluation considered the significant findings from the US EPA report and several more recent positive results in concluding that there is sufficient evidence of carcinogenicity in experimental animals. Glyphosate also caused DNA and chromosomal damage in human cells, although it gave negative results in tests using bacteria. One study in community residents reported increases in blood markers of chromosomal damage (micronuclei) after glyphosate formulations were sprayed nearby.

For **tetrafluoroethylene**, IARC's overall evaluation in 2017 recommended upgrade to Group 2A on the basis of sufficient evidence in experimental animals with a striking and atypical pattern of tumors. The main use of tetrafluoroethylene is in the manufacture of polytetrafluoroethylene that is used as nonstick coatings on cookware, membranes for clothing that are both waterproof and breathable, electrical-wire casing, fire- and chemical-resistant tubing, and plumbing thread seal tape. Occupational exposure occurs in the primary manufacture of tetrafluoroethylene and during the subsequent polymerization process. Only one cohort study analyzing cancer risk in relation to exposure to tetrafluoroethylene was

available to the Working Group. Consonni et al. (2013) studied mortality from cancer and from selected non-malignant diseases in a cohort including workers in six polytetrafluoroethylene-production sites. Elevated risks were seen for all cancer sites of a-priori interest: liver, 1.27 (95% CI, 0.55–2.51); kidney, 1.44 (95% CI, 0.69–2.65); and leukemia, 1.48 (95% CI, 0.77–2.59).

For the insecticide **malathion,** there is limited evidence of carcinogenicity in humans for non-Hodgkin lymphoma and prostate cancer. The evidence in humans is from studies of exposures, mostly agricultural, in the USA, Canada, and Sweden published since 2001. Malathion also caused tumors in rodent studies. Malathion caused DNA and chromosomal damage and also disrupted hormone pathways. There is no conclusive proof that **malathion** causes **cancer** in humans, although some studies have found increased **incidence** of some **cancers** in people who are regularly exposed to pesticides, such as farmers and pesticide applicators. Animal studies also fail to provide conclusive evidence of carcinogenicity (ATSDR).

For the insecticide **diazinon,** there was limited evidence of carcinogenicity in humans for non-Hodgkin lymphoma and lung cancer. The evidence in humans is from studies of agricultural exposures in the USA and Canada published since 2001. The classification of diazinon in Group 2A was also based on strong evidence that diazinon induced DNA or chromosomal damage.

For **silicon carbide whiskers**, animal studies have shown significant increase in the incidence of mesothelioma in rats. The few available studies in experimental animals do not provide any insight into the carcinogenesis. Mechanistic studies on silicon carbide materials in humans are lacking but there have been occupational studies. Exposure to silicon carbide whiskers may occur during the manufacture of the whiskers or during the production, machining, and finishing of composite materials. Silicon carbide in fibrous and non-fibrous forms has been detected in occupational environments. With respect to cancer in humans, only a few studies that refer directly to exposure to silicon carbide fibers have been published. The workers studied had been engaged in the production of silicon carbide using the Acheson production process (the dominant method of producing silicon carbide). In Bugge et al. (2012), the standardized incidence ratio (SIR) for lung cancer in long-term workers (≥ 3 years of employment) was 1.6 (95% CI, 1.3–2.1). IARC has concluded that there is sufficient evidence in humans for the carcinogenicity of occupational exposures associated with the Acheson process. Occupational exposures associated with the Acheson process cause cancer of the lung. There is limited evidence in humans for the carcinogenicity of fibrous silicon carbide. Positive associations have been observed between exposure to fibrous silicon carbide and lung cancer.

Dichloromethane (Methylene chloride) was first prepared in 1840 by the chlorination of methyl chloride in sunlight. In chemical processing, dichloromethane is used in the manufacture of polycarbonate plastic, the manufacture of photoresist coatings, and as a solvent carrier for the manufacture of insecticides and herbicides. Dichloromethane is a major ingredient of cleaning solvent used to remove printer ink during the offset printing process. With respect to exposure to dichloromethane and carcinogenicity: IARC identified two cohort studies of workers exposed to dichloromethane in the U.S. reported findings for cancers of the liver and biliary tract (based on small numbers). In a case series of biliary tract cancer among printing workers in Japan, most

of the cases were exposed to dichloromethane. Two additional cohort studies and three case–control studies in several countries evaluated non-Hodgkin lymphoma, with all except one cohort study reported increased risks among workers exposed to dichloromethane. Thus, IARC found limited evidence in humans for the carcinogenicity of dichloromethane, but positive associations have been observed between exposure to dichloromethane and cancer of the biliary tract and non-Hodgkin lymphoma. The overall determination of IARC to classify dichloromethane as Group 2A agent was based on sufficient evidence in experimental animals and limited evidence in humans. Additional, Group 2A evaluation was recommended because there was sufficient evidence in experimental animals. Lastly, there was strong evidence that the metabolism of dichloromethane can lead to toxic byproducts and the formation of reactive metabolites.

The insecticide **DDT** (otherwise known as (4,4'-dichlorodiphenyltrichloroethane) was classified as probably carcinogenic to humans (Group 2A), based on sufficient evidence that DDT causes cancer in experimental animals and limited evidence of its carcinogenicity in humans. Epidemiological studies found positive associations between exposure to DDT and NHL, testicular cancer, and liver cancer. There was also strong experimental evidence that DDT can suppress the immune system and disrupt sex hormones. Overall, there was no association between breast cancer and DDT levels measured in samples of blood or fat.

The chemical **2-Mercaptobenzothiazole** is principally used as a reactant in the manufacture of rubber products. It is also used as a corrosion inhibitor in oils, grease, and cooling fluids. It is added to polyether polymers as a stabilizer to resist damage by air and ozone. Due to its use as an accelerant in rubber vulcanization, 2-mercaptobenzothiazole can be found as a contaminant in rubber products. A series of studies of workers at a chemical production plant in north Wales, United Kingdom focused on morbidity and mortality from bladder cancer. Out of 2160 male production workers employed for at least 6 months during the period 1955–84, 363 were exposed to 2 -mercaptobenzothiazole. In this cohort, there was an excess in mortality (8 deaths; standardized mortality ratio [SMR], 3.74; 95% CI, 1.62–7.37) and incidence (12 cases; standardized relative risk [SRR], 2.53; 95% CI, 1.31–4.41) as compared with national rates of bladder cancer (Sorahan & Pope, 1993; Sorahan et al., 2000; Sorahan, 2008, 2009). There were also excess cancers identified of the large intestine and lung as well as multiple myeloma (Sorahan, 2009). Among a cohort of 1059 male chemical-production workers in Nitro, West Virginia: 511 had worked exclusively with 2-mercaptobenzothiazole and among these 511 individuals, there were five deaths from bladder cancer. The standardized mortality ratios (SMRs) for bladder cancer in this cohort also showed a significantly-increasing trend when workers had increased cumulative exposure to 2-mercaptobenzothiazole. Based on this human data, IARC found that there is limited evidence in humans for the carcinogenicity of 2-mercaptobenzothiazole and that there is sufficient evidence in experimental animals for the carcinogenicity of 2-mercaptobenzothiazole. They concluded that 2-Mercaptobenzothiazole is probably carcinogenic to humans (Group 2A).

With reference to **hydrazine**: it is used primarily as a reagent for the treatment of nuclear reactor waste. An occupational cancer study was conducted: a cohort of 6107 male workers

who worked at the Santa Susana Field Laboratory rocket testing facility (Rocketdyne) near Los Angeles, California were included. Selection: the workers had to have been employed before 1980 and worked at least 2 years, and not to have been exposed to radiation groups. Relative risks for cancer of the lung for high exposure with a 15-year lag were 1.93 (95% CI, 1.27–2.93) or 2.10 (95% CI, 1.36–3.25) for high exposure. Cancer mortality analyses of all rocket- testing workers compared with California population rates were unremarkable and not significantly different from the null for any specific type of cancer analyzed, including lung. Cancer mortality analyses of all rocket-testing workers compared with California population rates were unremarkable and not significantly different for any specific type of cancer analyzed, including lung. There is limited evidence in humans for the carcinogenicity of hydrazine. A positive association has been observed between exposure to hydrazine and cancer of the lung. IARC concluded that There is limited evidence in humans for the carcinogenicity of hydrazine. A positive association has been observed between exposure to hydrazine and lung cancer. There has been sufficient evidence in experimental animals for the carcinogenicity of hydrazine. Thus, IARC recommended that hydrazine be classified as a Group 2A carcinogen.

N,N-Dimethylformamide was used predominantly as a solvent in the manufacture of polyacrylonitrile fibers, and trends in its production parallel those of the polyacrylic fiber industry. With respect to human carcinogenicity, IARC has accumulated human studies demonstrating strong evidence that N,N-dimethylformamide is metabolically activated, induces oxidative stress, and alters cell proliferation. in exposed humans. Its link to cancer came with an investigation of a cluster of three cases of testicular germ cell cancer that occurred between 1981 and 1983 among military aircraft repair workers. These Repair workers who were sent to naval air rework facilities were exposed to surface coatings and associated emulsifiers and surfactants (including “Teflon” paints and dyes, solvents, and metals) (Ducatman et al., 1986). There is limited evidence in humans for the carcinogenicity of N,N-dimethylformamide, with a , positive association observed between exposure to N,N-dimethylformamide and testicular cancer. When incorporate animal data (sufficient evidence in experimental animals for the carcinogenicity of N,N-dimethylformamide), IARC classified this chemical as probably carcinogenic to humans (Group 2A).

The production process for **tetrabromobisphenol A** involves the bromination of bisphenol A in the presence of a solvent. Approximately 58% of tetrabromobisphenol A is used as a reactive brominated flame retardant in epoxy, polycarbonate, and phenolic resins in printed circuit boards. Occupational health studies have not identified a clear association between workplace exposures and cancer. However, there is strong in-vitro and animal evidence that tetrabromobisphenol A can cause modulation of receptor-mediated cellular effects, induction of oxidative stress, and initiation of immunosuppression. These reasons were the main rationale for IARC to declare terabromobisphenol a Group 2A carcinogen.

Styrene is one of the most important monomers for polymers and copolymers that are used in an increasingly wide range of applications. The major uses for styrene are in plastics, latex paints and coatings, synthetic rubbers, polyesters, and styrene-alkyd coatings. Retrospective cohort studies of

styrene have been conducted. In a European multinational cohort study of workers in the glass fiber-reinforced plastics industry, there was no excess mortality from lymphatic and hematopoietic neoplasms in the entire cohort as compared with the general population. Another study of cancer incidence in the reinforced-plastics industry found a significant excess of leukemia among workers employed before 1971 (the period with the highest styrene exposures) as well as in a follow-up study of workers 10 years since first exposure to styrene (among workers who worked less than 1 year). However, another large study of workers exposed to styrene in the reinforced-plastics industry in the U.S. found no overall excess of lymphatic nor hematopoietic neoplasms. Additional studies of chemical workers in the U.S. and the United Kingdom involved in the production of styrene and styrene derivatives found a weak association between exposure to styrene and lymphatic and hematopoietic cancers. occurred. A small excess of leukemia mortality has been reported in studies of styrene–butadiene workers in the U.S. A small exposure study among Finnish workers with exposures to styrene during the 1970s and early 1980s did not show any increase in risk for lymphatic nor hematopoietic neoplasms. Thus, there is *limited evidence* for carcinogenicity and this is solely based on positive associations with primarily lymphohematopoietic malignancies. There was a noted small increase in the incidence of sinonasal adenocarcinoma in one large cohort but since the numbers were so few, it is difficult to be certain that this is a real phenomenon. In experimental animals, there has been sufficient evidence to demonstrate the carcinogenicity of styrene. Styrene had been classified as a Group 2B carcinogen previously (because the epidemiological studies provided limited evidence for its carcinogenicity). But after more in-depth analysis of its metabolite styrene-7,8-oxide (see next paragraph), IARC decided that it would grant independent support of the classification of styrene as probably carcinogenic to humans (Group 2A).

Styrene-7,8-oxide is primarily used to produce epoxy resins. Human exposure has been identified to occur during the manufacture of styrene-7,8-oxide, or during the production or use of epoxy In humans. There was also sufficient evidence of carcinogenicity for styrene-7,8-oxide mainly because styrene-7,8-oxide is an electrophile and reacts directly with DNA, thus making it genotoxic. There is sufficient evidence of carcinogenicity for styrene-7,8-oxide in animal and in vitro studies. In humans, there has been inadequate evidence to establish carcinogenicity of styrene-7,8-oxide. IARC's overall evaluation of styrene-7,8-oxide as probably carcinogenic to humans (Group 2A) took into account the mechanistic data pertinent to the key characteristics of carcinogens (Smith et al., 2016).

3,3',4,4'-Tetrachloroazobenzene (TCAB) is a contaminant generated in the production of several commonly used herbicides (such as propanil, linuron, diuron, and neburon). There was *sufficient evidence* in experimental animals for the carcinogenicity of TCAB to be established. TCAB was assigned to Group 2A because mechanistically it behaves like a carcinogen in vitro.: Specifically, TCAB activates the aryl hydrocarbon receptor and causes a multitude of downstream effects. Any agent that activates this receptor include dioxin, polychlorinated biphenyls, and polybrominated biphenyls.

Aldrin and its metabolite dieldrin are organochlorine pesticides that were widely used through the 1970s to control soil insects, termites, and ants. Their use has been severely restricted over the last 40 years. For aldrin, there was sufficient evidence for cancer in experimental animals, but epidemiological data on aldrin were inadequate. However, since aldrin rapidly converts to dieldrin in the body, exposure to aldrin inevitably entails internal exposure to dieldrin. For dieldrin, there was limited evidence for cancer in humans and sufficient evidence for cancer in experimental animals. Given the quality of the evidence, both aldrin and dieldrin have been classified as probably carcinogenic to humans (Group 2A).

Glycidyl methacrylate is mainly used in the production of epoxy polymers and vinyl and acrylic resins. These polymers are subsequently used in dental sealants, composites and adhesives, bone composite materials, powder coatings, hydrogel lenses, and food contact material. Potential short-term exposure might occur during the preparation of dental or bone composite materials, but no exposure data is currently available from these occupational settings. There is strong evidence that glycidyl methacrylate belongs to a class of reactive glycidyl epoxides, for which one member (glycidol) has been classified as probably carcinogenic to humans. There is also strong evidence that glycidyl methacrylate exhibits key characteristics of carcinogens in human primary cells. Moreover, there has been sufficient evidence in experimental animals to demonstrate the carcinogenicity of glycidyl methacrylate, These studies revealed an increased incidence of malignant neoplasms in both sexes of two species exposed by inhalation. Glycidyl methacrylate induced nasal cavity haemangiosarcoma in both male and female mice, bronchioloalveolar carcinoma and uterine histiocytic sarcoma in female mice, nasal cavity squamous cell carcinoma in both male and female rats, rare nasal cavity neuroepithelial carcinoma and peritoneal mesothelioma in male rats, and uterine endometrial stromal sarcoma in female rats. Glycidyl methacrylate has thus been classified as probably carcinogenic to humans (Group 2A).