

Advisory Board on Toxic Substances and Workers Health
Probable Human Carcinogens (2A) Analysis
4/22/2021

Query: Which if any of the 18 IARC 2A relevant toxic substances have at least limited human epidemiological evidence of increased risk of cancers in specific sites?

Review Sources: IARC Monographs; NTP

Polybrominated biphenyls

- IARC monograph #107 (updated 2 August 2018) (<https://monographs.iarc.who.int/wp-content/uploads/2018/06/mono107-002.pdf>)
- “Polybrominated biphenyls” or “polybromobiphenyls” (PBBs) is a group of halogenated hydrocarbons (HC’s) formed by substituting hydrogen with bromine on a biphenyl ring—209 possible structural congeners—but only a few have been synthesized and used commonly- classified by positions of bromine on the double benzene rings (ortho, meta and para) and number of bromines-same numbers are called *homologue* – 3 common mfg’ed: hexa, octa, deca. Example: “Firemaster” is a mixture of mostly hexabromobiphenyl and heptabromobiphenyl and smaller amounts of lesser brominated; sometimes present, contaminants or impurities (eg. toluene, naphthalene...). Commercial PBB mixtures created primarily to use as flame retardants—contain numerous congeners. Also used in acrylonitrile-butadiene-styrene (ABS) plastics. Environmental contamination when Firemaster mixed up with NutriMaster -animal feed supplement. Worker exposures-production PBB, PBB plastics, PBB fire retardants or processing e-waste.
- IARC summary of human carcinogenicity
“Most data from follow-up of resident exposure to contaminated food following industrial accident in Michigan-nested case-control analysis, positive findings for lymphoma and cancers of the digestive system combined (liver, stomach esophagus, and pancreas). Cohort was unique, but small and risk estimates are imprecise.”
- IARC Evaluation
 - Cancer in humans:
Inadequate evidence for carcinogenicity of polybrominated biphenyls
 - Cancer in experimental animals:
Sufficient evidence for carcinogenicity of Firemaster FF-1
Limited evidence for PBB -153
inadequate for PBB-169, Firemaster BP-6
 - Overall evaluation: PBB are *probably carcinogenic to humans (Group 2A)* on basis mostly of mechanistic similarities to PCB’s., also animal data
- NTP:
“Polybrominated biphenyls (PBBs) are reasonably anticipated to be human carcinogens based on sufficient evidence of carcinogenicity from studies in experimental animals”
Mention is made of the Hoque et al 1998 case-control student of exposure-level related increased in lymphoma and digestive-system cancers. Noted that other studies were uninformative.
- SEM: Present in SEM, no link to cancers

- Since rated as “*inadequate evidence*” for Cancer in Humans, not included in list of 2A with limited evidence.

1,3-Propane sultone

- IARC monograph (<https://monographs.iarc.who.int/wp-content/uploads/2018/06/mono110-05.pdf>) 2018 update
- Although the industrial use of 1,3-propane sultone was largely discontinued in the 1960s, it has been used more recently in the manufacture of lithium batteries, and for chemical synthesis in the laboratory. Workers involved in the formulation of compounds made from 1,3-propane sultone are at the greatest risk of potential exposure.
- Human carcinogenicity data:
Only one case series among 55 employees at a factory in Germany that manufactured 1,3-Propane sultone in 1952-1963—number of expected cancers not presented, precluded interpretation of this study
- IARC Evaluation:
 - *Inadequate evidence* in humans for carcinogenicity
 - *Sufficient evidence* in experimental animals
 - *Probably carcinogenic to humans* (Group 2A)
Rationale -mechanistic in that 1,3 propane sultone is a strong, direct-acting alkylating agent that reacts with DNA and proteins, + genotoxic, and +experimental animal
- SEM: present, but no links to Cancer
- Since rated as “*inadequate evidence*” for Cancer in Humans, not included in list of 2A with limited evidence.

Glyphosate

- IARC monograph 112 (2015) <https://publications.iarc.fr/549>
- Herbicide widely used
- IARC: Evaluation
 - *Limited evidence* in humans - + associations for non-Hodgkin Lymphoma
The evidence in humans is from studies of exposures, mostly agricultural, in the USA, Canada, and Sweden published since 2001. ARC Working group summarized the epidemiological data: case–control studies in the USA, Canada, and Sweden reported increased risks for NHL associated with exposure to glyphosate. The increased risk persisted in the studies that adjusted for exposure to other pesticides. The AHS cohort did not show an excess of NHL. The Working Group noted that there were excesses reported for multiple myeloma in three studies; however, they did not weight this evidence as strongly as that of NHL because of the possibility that chance could not be excluded; none of the risk estimates were statistically significant nor were they adjusted for other pesticide exposures." They also noted that there were no other significant associations with other cancers and exposure to glyphosate.
 - *Sufficient evidence* in experimental animals

- *Probably carcinogenic in humans* (Group 2A) – because of strong evidence of genotoxicity in human invitro studies, experimental animals; also chromosomal damage in blood cells in a study of individuals exposed to glyphosate formulations
- SEM: Present, but no links to cancer;
- Not listed under health effects: Lymphoma, Non-Hodgkin
- Include in list of 2A carcinogens with limited evidence in humans for specific cancer: non-Hodgkin Lymphoma

Tetrafluoroethylene

- IARC monograph 110-02, update 6/2018 <https://monographs.iarc.who.int/wp-content/uploads/2018/06/mono110-02.pdf>
- Occupational exposures to workers during primary manufacturing and later polymerization process
- IARC: Evaluation
 - *Inadequate evidence* in humans for carcinogenicity
 - *Sufficient evidence* in experimental animals
 - *Probably carcinogenic in humans* (Group 2A) -absence of adequate data on cancer in humans or adequate mechanistic data, upgrade to 2A was based upon “unusual results” in animals: Tetrafluoroethylene induced neoplasms at multiple sites—cells of differing embryological origin, and also increase in rare liver haemangiosarcoma in mice even at lowest doses tested—implication that it is a potent carcinogen
- SEM: present in SEM, and no links to Cancer
- Since rated as “*inadequate evidence*” for Cancer in Humans, not included in list of 2A with limited evidence.

Malathion

- IARC monograph 112, meeting 2015, publication 2017 (<https://publications.iarc.fr/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Some-Organophosphate-Insecticides-And-Herbicides-2017>)
- Organophosphate insecticide – worker exposures during formulation, application
- IARC:evaluation
 - *Limited evidence in humans* -positive associations observed with non-Hodgkin lymphoma and cancer of the prostate
Note: The evidence in humans is from studies of exposures, mostly agricultural, in the USA, Canada, and Sweden published since 2001. The IARC working group summarized the human epidemiological data: “ four case–control analyses found excesses of non-Hodgkin lymphoma associated with exposure to malathion in the USA, Canada, and Sweden, but no association with number of days of use was observed. In the Cross-Canada Case–control Study, there was an association with malathion, but in a pooled analysis of case–control studies in the USA there was little evidence of an association. No excess occurred in the Agricultural Health Study cohort.
 - *Sufficient evidence* in experimental animals
 - *Probably carcinogenic in humans* (Group 2) -based on mechanistic and other relevant data—strong evidence of several key characteristics of human carcinogen—genotoxic on studies in

humans, in experimental animals, and in human and animal cells in vitro; also disrupted hormonal pathways; induces oxidative stress and other inflammation; other mechanisms

- SEM: In SEM, no mention cancer health effects
- Not listed under health effects: Lymphoma, Non-Hodgkin
- Include in list of 2A carcinogens with limited evidence in humans for specific cancer: Lymphoma, Non-Hodgkin

Diazinon

- IARC monograph, 112 (<https://www.ncbi.nlm.nih.gov/books/NBK436774/>)
- Diazinon is a wide-ranging organophosphate non-systemic insecticide, miticide, and nematocide. US- Currently used to control fire ants, and “plague infected fleas on squirrels -Used more in the past
- IARC evaluation
 - *Limited evidence in humans* – positive associations for non-Hodgkin lymphoma, leukemia, and cancer of the lung
Note: IARC identified 9 reports from 3 cohort studies, and 14 reports on 6 case–control studies, that reported on associations between cancer and exposure to diazinon specifically. The IARC working group noted positive associations and exposure–response trends were noted for NHL, leukaemia, and cancer of the lung. Although studies reported on other cancers, IARC did not report increased risks for those cancers.
 - *Limited evidence* in experimental animals
 - *Probably carcinogenic in humans* (Group 2) -two key characteristics of human carcinogens: genotoxic from studies in experimental animals in vivo, and animal cell lines; human cell lines in vitro show chromosomal damage; positive results in study of small number volunteers; also can act to induce oxidative stress
- SEM: In SEM under different name: O,O-Diethyl-O-(2-isopropyl-4-methyl-6-pyrimidinyl) phosphorothioate. No mention of any cancers.
- Diazinon not mentioned under health effects for Lymphoma, non-Hodgkin, cancer of the lung or leukemia
- Include in list of 2A carcinogens with limited evidence in humans for specific cancers: Lymphoma, Non-Hodgkin, cancer of the lung, and leukemia

Silicon carbide whiskers

- IARC monograph, 111 (<https://www.ncbi.nlm.nih.gov/books/NBK436610/>)
- Silicon carbide appears in two different crystalline forms: hexagonal α -silicon carbide is the main product, while cubic β -silicon carbide is formed at lower temperatures. 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. Various forms of silicon carbide can comply with the WHO definition of a fibre (i.e. a particle longer than 5 μm with a diameter of less than 3 μm and an aspect ratio of more than 3). “silicon carbide whiskers” specifically refers to monocrystalline forms produced at high cost for targeted high technology use.

- Inhalation is the primary route of exposure to fibrous silicon carbide in occupational settings. Exposures to both these respirable manufactured silicon carbide whiskers and silicon carbide fibres may occur during their production and the manufacturing, machining, finishing use of composite materials.
- Based on very limited evidence of fibrous 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). Supported as well by evidence of similar structure to asbestos, known human carcinogen. However, working group considered fibers should be considered separately from whiskers
- No data on cancer in humans exposed to silicon carbide whiskers was available for the IARC monograph 111. However, based on structural similarity to asbestos, a known human carcinogen, this structure was deemed a probable carcinogen in humans. In addition, available mechanistic studies were consistent with this conclusion.
- IARC working group considered fibers should be considered separately from whiskers
- Related chemical found in SEM, "Silicon Carbide Cas 409-21-2", but not associated with lung cancer in the SEM
- Include in list of 2A carcinogens with limited evidence in humans for specific cancers: Cancer of the lung

Dichloromethane

- IARC monograph, 110 (<https://www.ncbi.nlm.nih.gov/books/NBK436263/>)
- Dichloromethane is used for a variety of purposes and products including the making of polycarbonate plastics, paint stripping, metal cleaning, aerosol propellants, and synthetic fibres.
- Dichloromethane was classified as probably carcinogenic to humans (Group 2A) on the basis of limited evidence that it causes biliary-tract cancer and non-Hodgkin lymphoma in humans; coupled with strong evidence that the genotoxicity is mediated by GSTT1 metabolism that does occur in humans.
- These findings of carcinogenicity were corroborated with experimental animal model findings in rodents (mice)
- Chemical found in SEM, but no cancers associated in the SEM.
- Include in list of 2A carcinogens with limited evidence in humans for specific cancers: biliary-tract cancer and Non-Hodgkin lymphoma

DDT (otherwise known as (4,4'-dichlorodiphenyltrichloroethane)

- IARC monograph, 113 (<https://www.ncbi.nlm.nih.gov/books/NBK507424/>)
- DDT has been widely used as an insecticide, use was banned in the 1970s, but due to persistence in the environment exposures still occur mostly via dietary routes.
- Associations between cancer and exposure to DDT have been investigated in more than 100 cohort and case-control studies from diverse countries. Those associated include liver, testicular and NHL, but not breast.
- These findings of carcinogenicity were corroborated with experimental animal model findings in rodents (mice, rat and hamster)
- Chemical found in SEM, but no cancers associated in the SEM.

- Include in list of 2A carcinogens with limited evidence in humans for specific cancers: liver cancer, testicular cancer, Non-Hodgkin Lymphoma

2-Mercaptobenzothiazole

- IARC monograph, 115 (<https://www.ncbi.nlm.nih.gov/books/NBK506754/>)
- 2-Mercaptobenzothiazole is principally used as a reactant in the manufacture of rubber products, but is also used as a corrosion inhibitor in oils, greases and cooling fluids. It is added to polyether polymers as a stabilizer to resist damage by air and ozone. 2-mercaptobenzothiazole can be found as a contaminant in rubber products.
- An English/Welsh population and USA chemical plant study found significant association for incidence or mortality from bladder cancer.
- These findings of carcinogenicity were supported with experimental animal model findings in rodents (mice and rat)
- Chemical found in SEM, but no cancers associated in the SEM.
- Include in list of 2A carcinogens with limited evidence in humans for specific cancers: bladder cancer

Hydrazine

- IARC monograph, 115 (<https://www.ncbi.nlm.nih.gov/books/NBK506754/>)
- Hydrazine is utilized as rocket propellant and aircraft fuel. In its hydrated form, hydrazine (solutions with concentrations ranging from 0.01% to 100%) serve as a reagent for the treatment of nuclear reactor wastes.
- Two studies on overlapping cohort, outcome of incidence or mortality found association with lung cancer among workers based on facility history. Further humans rapidly absorb and metabolize hydrazine
- These findings of carcinogenicity were supported with experimental animal model findings in rodents (mice, rat and hamster). Mechanistic studies support these conclusions as well via evidence of oxidative stress, genotoxicity, and altered nutrient supply.
- Chemical found in SEM, but no cancers associated in the SEM.
- Include in list of 2A carcinogens with limited evidence in humans for specific cancers: cancer of the lung

N,N-Dimethylformamide

- IARC monograph, 115 (<https://www.ncbi.nlm.nih.gov/books/NBK506754/>)
- N,N-Dimethylformamide is used predominantly as an aprotic solvent in the manufacture of polyacrylonitrile fibres, and trends in its production parallel those of the polyacrylic fibre industry.
- Two studies in specific aircraft repair workers and one with leather workers found increased incidence of testicular cancer. It is readily absorbed in humans.
- These findings of carcinogenicity were supported with experimental animal model findings in rodents (mice and rat). Mechanistic studies show N,N-Dimethylformamide induced oxidative

stress and induces formation of adducts of the valine and lysine amino acids in human globin and in other contexts with cytosine.

- Chemical found in SEM, but no cancers associated in the SEM.
- Include in list of 2A carcinogens with limited evidence in humans for specific cancers: testicular cancer

Tetrabromobisphenol A

- IARC Monograph 115.
- It is a flame retardant reviewed
- No human epidemiologic data were available to IARC in 2016 on carcinogenicity of TBBPA. It was classified as 2A probably carcinogenic in humans based on strong evidence that tetrabromobisphenol A demonstrates 3 “key” mechanistic characteristics of human carcinogens (Guyton et al, 2018), that it modulates receptor-mediated effects, induces oxidative stress and is immunosuppressive. There is sufficient evidence in experimental animals (male mice and female rats) for the carcinogenicity of tetrabromobisphenol A.
- Since rated as “*inadequate evidence*” for Cancer in Humans, not included in list of 2A with limited evidence.

Styrene

- Reviewed IARC Monograph 121
- Finds limited evidence in human epidemiologic studies of increased risk of lymphohaematopoietic malignancies. Evidence was stronger and more consistent for AML and T-cell lymphoma, weaker and less consistent for other leukemia and lymphoma subtypes because case numbers were limited and effect estimates were small with low precision (wide confidence intervals). Evidence for lung cancer and other solid tumors was judged not convincing. Epidemiologic evidence was summarized as credible for lymphohaematopoietic malignancies, but co-exposure to 1,3 butadiene, and confounding, bias and chance could not be ruled out as alternative explanations. Evidence for carcinogenicity in animal studies was judged sufficient with tumors of lung and mammary gland most commonly reported. Some of the mechanistic evidence for carcinogenicity was judged strong, including genotoxicity in human cell culture, however specific mechanistic events for lung tumor induction in mice were not considered established.
- Chemical found in SEM but not associated cancers.
- Styrene not listed under leukemia, lymphoma.
- *Limited evidence in humans* for lymphohaematopoietic malignancies
- Include in list of 2A carcinogens with limited evidence in humans for lymphohaematopoietic malignancies

Styrene-7,8-oxide

- Reviewed IARC Monograph 121
- The chemical is closely related to, and a human metabolite of, Styrene. IARC considered evidence of human carcinogenicity of styrene-7,8-oxide to be inadequate. They classified styrene-7,8-oxide as “probably carcinogenic to humans” (Group 2A) based on sufficient evidence of carcinogenicity in experimental animals and strong evidence that styrene-7,8-oxide, an electrophile, forms DNA adducts and is genotoxic, a mechanism that also operates in humans.
- Since rated as “*inadequate evidence*” for Cancer in Humans, not included in list of 2A with limited evidence.
- SEM, no list of any cancers

3,3',4,4'-Tetrachloroazobenzene (TCAB)

- Reviewed in IARC Monograph 117
- They did not identify any human epidemiologic studies of carcinogenicity of TCAB. TCAB was classified as 2A because of sufficient evidence of carcinogenicity at multiple sites in animals, and mechanistic considerations. It belongs to a class of agents that activate the Aryl Hydrocarbon Receptor AhR, and some members of this class have previously been evaluated as Group 1 or Group 2A carcinogens.
- SEM: not listed
- Since rated as “*inadequate evidence*” for Cancer in Humans, not included in list of 2A with limited evidence.

Aldrin and its metabolite dieldrin

- Reviewed in IARC Monograph 117.
- Aldrin is a synthetic organochlorine pesticide that rapidly metabolized in humans to dieldrin, which is sequestered in fat and slowly excreted. One epidemiologic study of dieldrin in Denmark reported increased risk of breast cancer with a dose response. A similar but smaller study in Norway did not find a significant increase. Associations of breast cancer risk with dieldrin exposure were reported wives of men who had used dieldrin in a US agricultural study, and in the highest exposure category of a case control study in Long Island. Evidence of breast carcinogenicity in humans was considered limited. Evidence for non-Hodgkin lymphoma and other cancers in humans was considered insufficient. Evidence of hepatocellular carcinogenicity in animals was considered sufficient and mechanistic studies provided moderate evidence for multiple key characteristics of carcinogens. So dieldrin is classified as 2A with breast as the best supported cancer site. Human epidemiologic data on carcinogenicity of aldrin were considered insufficient in the 2016 IARC review, mechanistic evidence was sparse, however evidence of carcinogenicity of aldrin in animal studies was considered sufficient.
- IARC summary evaluation:
 - There is *inadequate evidence* in humans for the carcinogenicity of aldrin.
 - There is *limited evidence* in humans for the carcinogenicity of dieldrin.
A positive association has been observed between dieldrin and cancer of the breast
 - There is *sufficient evidence* in experimental animals for the carcinogenicity of aldrin and dieldrin
- IARC: Because aldrin is rapidly metabolized to dieldrin in humans and experimental animals, exposure to aldrin always leads to internal exposure to dieldrin
- SEM: both are present, but no link to breast cancer
- Breast cancer is not listed in SEM at all
- Include Dieldrin (and necessarily aldrin which metabolizes to dieldrin in list of 2A carcinogens with limited evidence in humans for specific cancers: Cancer of the breast

Glycidyl methacrylate

- Reviewed in IARC Monograph 125
- Glycidyl methacrylate is an intermediate used in production of epoxy polymers and vinyl and acrylic resins.

- Human epidemiologic evidence of carcinogenicity was considered inadequate. Evidence of carcinogenicity in animal studies was considered sufficient. Mechanistic evidence was considered strong because “glycidyl methacrylate belongs to a class of compounds (reactive glycidyl epoxides), a member of which (glycidol) has been classified as “probably carcinogenic to humans”. This determination was based on structural similarity to other glycidyl epoxides and the close concordance to glycidol with respect to the genotoxicity profile and the tumour-site profile in chronic animal bioassays.” (IARC, Lancet Oncology, 2019) Glycidyl methacrylate was classified as 2A primarily on this basis.
- SEM: not listed in the SEM
- Since rated as “*inadequate evidence*” for Cancer in Humans, not included in list of 2A with limited evidence.