Advisory Board on Toxic Substances and Workers Health

Draft Report and Recommendation on Group 2A Carcinogens, April 16, 2021

Background

In 2019 a Working Group of the US DOL Advisory Board on Toxic Substances and Workers Health (ABTSWH)began an evaluation of agents rated as "Probably Carcinogenic in Humans (Group 2A)*" by the International Agency for Research on Cancer (IARC) for potential inclusion in decision-making under the Energy Employees Occupational Illness Compensation Program (EEOICP). Since 2016, IARC has updated 90 chemicals, including 22 agents in Group 2A. Of those 22 agents, 18 were toxic substances that could be encountered in the workplace and those became the focus of this Working Group. A toxic substance could be rated as a probable human carcinogen based upon data from human epidemiological studies, experimental animal data, mechanistic evidence, or a combination thereof. For worker compensation purposes, however, the Working Group determined that linking the toxic substances to specific human cancer sites requires, in most cases, at least limited evidence from human epidemiological studies in support of such linkage.

Questions

The Working Group reviewed these 18 toxic substances to determine the following:

1. Is there human epidemiological support, as cited by IARC or the National Toxicology Program (NTP), for an association between the toxic substance of concern and specific human cancer sites?
2. For the Group 2A toxic substances with limited links to human cancers, are these links identified or listed in the DOL Site Exposure Matrices (SEM)?

Findings

Of the 18 toxic substances rated IARC Group 2A:

- 11 toxic substances had limited evidence of human cancers in specific organs (Table1)
- All of these 11 toxic substances are listed in the SEM, but none are linked in the SEM to the human cancer sites identified in the IARC review
- Of the cancers that are linked to toxic substances in the SEM, , none are linked to the IARC Group 2A toxic substances.
- Breast, Prostate and Testicular cancers were not listed at all in the SEM

Recommendation

The Advisory Board on Toxic Substances and Workers Health recommends that toxic substances that are found to be probable human carcinogens (IARC Group 2A) and that have limited human epidemiological evidence for specific human cancer sites as identified in table 1, should be linked to those cancer sites in the SEM. The SEM should specify that IARC and NTP evaluations have been used in addition to HAZ MAP for the purpose of asserting linkages between toxic substances and human cancer sites. Future IARC Group 2A substance-cancer linkages identified by IARC or NTP should be incorporated

in the SEM. Data from IARC and NTP should be used in addition to HAZ MAP for health effects and linkages of toxic substances to cancers.

Table 1: Group 2A Carcinogens with Limited evidence in humans for cancers

2A Carcinogen	Description	Associated Cancers	SEM Status
Glyphosate ("Roundup")	Herbicide-widely used	Non-Hodgkin Lymphoma	Present in SEM No Diseases (or cancers) listed in Haz-Map
Malathion	Organophosphate insecticide	Non-Hodgkin Lymphoma; Cancer of the Prostate	Present in SEM No associated cancers listed Not listed under Lymphoma, Non-Hodgkin
Diazinon	Organophosphate insecticide, miticide, and nematicide	Non-Hodgkin Lymphoma Leukemia Cancer of the Lung	Present in SEM as Haz-Map name: O,O-Diethyl-O-(2-isopropyl-4-methyl-6-pyrimidinyl) phosphorothioate No associated Cancers listed
Dichloromethane (Methylene Chloride)	Solvent	Biliary-Tract Cancer Non-Hodgkin lymphoma	Present in SEM No associated cancers listed
DDT 4,4'-dichlorodiphenyltrichloro-ethane	Insecticide	Liver Cancer Testicular Cancer Non-Hodgkin Lymphoma	Present in SEM No associated cancer listed Not listed under Liver, Lymphoma-Non-Hodgkin; no testicular
2-Mercaptobenzothiazole	Organosulfur compound used in the sulfur vulcanization of rubber	Urinary bladder cancer	Present in SEM No associated cancer listed Not listed under Bladder Cancer
Hydrazine	Used in polymerization; precursor to pesticides and pharmaceuticals, other reactions	Lung Cancer	Present in SEM No associated cancer listed Not listed under Lung Cancer

N, N-Dimethylformamide	Solvent (used in mfg fo polyacrylonitirele fibers, polyurethane and polamide coatings, electronics, other)	Testicular Cancer	Present in SEM No associated cancer listed
Styrene		Lymphohaematopoietic malignancies (stronger and more consistent for AML and T-cell lymphoma)	Present in SEM No associated Cancer listed Styrene not listed under leukemia, lymphoma, or Lung cancer
Aldrin and its metabolite **dieldrin** [Inadequate evidence for aldrin, but limited evidence for its metabolite dieldrin]	Synthetic organochlorine pesticides	Cancer of the Breast	Present in SEM No associated Cancer listed in Haz-Map Breast Cancer not listed in SEM
Silicon Carbide "Whiskers"	"Silicon carbide whiskers are monocrystalline and homogeneous in form, while fibrous silicon carbide is mostly polycrystalline and heterogeneous in form". Given differences in physiochemical properties-Separate evaluation for "fibers" and "whiskers"	Lung Cancer	Present in SEM No associated Cancer listed Not listed under Lung Cancer

Table 2: Cancers and Group 2A Carcinogens To Be Added to SEM

IARC

CANCER TYPE	2A Carcinogen*
Lung Cancer	Hydrazine Diazinon Silicon Carbide “Whiskers”
Lymphoma, Non Hodgkin	DDT Diazinon Dichloromethane Glyphosate Malathion Styrene
Leukemia	Diazinon
Lymphohaematopoietic	Styrene
Testicular Cancer (need to add)	DDT N, N-Dimethylformamide
Bladder Cancer	2-Mercaptobenzothiazole
Breast Cancer (need to add)	Dieldrin (metabolite of Aldrin)
Liver Cancer	DDT
Biliary Tract Cancer	Dichloromethane

Definitions

Graphic representation: https://monographs.iarc.who.int/wp-content/uploads/2019/07/2019-SR-001-Revised_Preamble.pdf

From IARC Monographs on the Identification of Carcinogenic Hazards to Humans: Questions and Answers (https://monographs.iarc.who.int/wp-content/uploads/2018/07/QA_ENG.pdf)

Group 1: *The agent is carcinogenic to humans*
This category is used when there is sufficient evidence of carcinogenicity in humans. In other words, there is convincing evidence that the agent causes cancer in humans. The evaluation is usually based on the results of epidemiological studies showing development of cancer in exposed humans. Agents can also be classified in Group 1 on the basis of sufficient evidence of carcinogenicity in experimental animals supported by strong evidence in exposed humans that the agent exhibits one or more of the recognized key characteristics of human carcinogens.

Group 2 This category includes agents with a range of evidence for carcinogenicity in humans and in experimental animals. At one extreme of the range are agents with positive but not conclusive evidence in humans. At the other extreme are agents for which evidence in humans is not available but for which there is sufficient evidence of carcinogenicity in experimental animals. There are two subcategories, which indicate different levels of evidence.

Group 2A: *The agent is probably carcinogenic to humans.*
This category is used when there is limited evidence of carcinogenicity in humans and either sufficient evidence of carcinogenicity in experimental animals or strong mechanistic evidence, showing that the agent exhibits key characteristics of human carcinogens. Limited evidence of carcinogenicity means that a positive association has been observed between exposure to the agent and cancer but that other explanations for the observations (technically termed “chance”, “bias”, or “confounding”) could not be ruled out with reasonable confidence. This category may also be used when there is inadequate evidence regarding carcinogenicity in humans but both sufficient evidence of carcinogenicity in experimental animals and strong mechanistic evidence in human cells or tissues.

Group 2B: *The agent is possibly carcinogenic to humans*
This category is generally used when only one of the following evaluations has been made by the Working Group:
- limited evidence of carcinogenicity in humans
- sufficient evidence of carcinogenicity in experimental animals
- strong mechanistic evidence, showing that the agent exhibits key characteristics of human carcinogens.

Group 3: *The agent is not classifiable as to its carcinogenicity to humans*
This category is used most commonly when the evidence of carcinogenicity in humans is inadequate, the evidence of carcinogenicity in experimental animals is limited (or inadequate), and the mechanistic evidence is limited (or inadequate). Limited evidence of carcinogenicity in experimental animals means that the available information suggests a carcinogenic effect but is not conclusive