

**Advisory Board on Toxic Substances and Worker Health**

April 30, 2021

Mr. Marty Walsh  
Secretary of Labor  
Department of Labor  
200 Constitution Ave.  
Washington, DC NW 20210

Honorable Secretary Walsh:

On behalf of the Department of Labor Advisory Board on Toxic Substances and Worker Health, I submit the attached Advisory Board Recommendation that was adopted unanimously at the Board's meeting on April 22-23, 2021.

We sincerely hope that our advice is useful to the Department. We thank you for the opportunity to serve as Board members and wish the Program continued success in meeting the needs of the United States energy employees. Please let us know if there are questions.

Sincerely,



Steven Markowitz MD, DrPH  
Chair

Advisory Board on Toxic Substances  
and Worker Health

## **Advisory Board on Toxic Substances and Workers Health**

### **Recommendation on Including Probable Human Carcinogens in the Site Exposure Matrices**

The Advisory Board on Toxic Substances and Workers Health recommends that:

1. Toxic substances that are found to be probable human carcinogens (International Agency for Research on Cancer - 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 Site Exposure Matrices (SEM).
2. The SEM should specify that IARC and National Toxicology Program (NTP) evaluations have been used in addition to HAZ MAP for the purpose of asserting linkages between toxic substances and human cancer sites.
3. Data from IARC and NTP should be used in addition to HAZ MAP for health effects and linkages of toxic substances to cancers. At least on a yearly basis going forward, future IARC Group 2A (as well as Group 1) substance-human cancer site linkages identified by IARC or NTP should be updated in the SEM.

### **Report on Group 2A Carcinogens**

#### **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

## Rationale

Review Sources: IARC Monographs; NTP Report on Carcinogens

### 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 study 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 nematicide. 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  $\alpha$ -silicon carbide is the main product, while cubic  $\beta$ -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  $\mu\text{m}$  with a diameter of less than 3  $\mu\text{m}$  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 ( $\geq 3$  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.

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

<b>2A Carcinogen</b>	<b>Description</b>	<b>Associated Cancers</b>	<b>SEM Status</b>
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 nematocide	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

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

2A Carcinogen	Description	Associated Cancers	SEM Status
N, N-Dimethylformamide	Solvent (used in mfg fo polyacrylonitrile fibers, polyurethane and polyamide coatings, electronics, other)	Testicular Cancer	Present in SEM No associated cancer listed
Styrene		Lymphohematopoie- tic 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**

<b>CANCER TYPE</b>	<b>2A Carcinogen*</b>
Lung Cancer	Hydrazine Diazinon Silicon Carbide “Whiskers”
Lymphoma, Non Hodgkin	DDT Diazinon Dichloromethane Glyphosate Malathion Styrene
Leukemia	Diazinon
Lymphohematopoietic	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

## **Advisory Board on Toxic Substances and Workers Health**

### **Recommendation on COVID-19 as a Consequential Condition in EEOICP**

The Board recommends that any chronic health condition or risk factor that is listed by the US Centers for Disease Control and Prevention (CDC) as being associated with severe COVID-19 disease by meta-analysis, systematic reviews, cohort studies, case control studies, cross sectional studies, case cases/series or mixed evidence be considered to be presumed to be more likely to lead to symptomatic COVID -19 disease. That is, the diagnosis of symptomatic COVID-19 disease is a consequence of those chronic health conditions when it follows or coincides with the onset of those conditions. The Board recognizes the need to periodically review (at a minimum, annually) and update this recommendation based on the evolving scientific and medical knowledge on this topic.

### **Rationale**

The Department of Labor requested that the Board provide guidance on the types of medical conditions that may be accepted as claims under the Energy Employees Occupational Illness Compensation Program (EEOICP) that may, as a matter of consequence, increase the likelihood or severity of COVID-19 disease.

The US Centers for Disease Control has assembled and evaluated the published evidence on what chronic medical conditions may impact the risk of severe COVID-19 disease. This list and the supportive evidence were updated and published on the CDC website on March 29, 2021, making it very timely. See <https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/underlying-evidence-table.html>

The CDC-listed conditions most relevant to EEOICP claims include: cancer, cerebrovascular disease, chronic kidney disease chronic obstructive pulmonary disease (COPD), asthma, other chronic lung disease (including interstitial lung disease, pulmonary fibrosis, pulmonary hypertension), neurologic conditions, heart disease, use of corticosteroids or other immunosuppressive medications, hypertension, liver disease, hypertension and diabetes. Details about specific type of diseases and the studies supporting their COVID-19 associations are provided by the CDC. The CDC lists additional health conditions (such as cystic fibrosis, Type 1 diabetes, and sickle cell disorders) as related to severe COVID-19 disease, but these conditions are not or are unlikely to be the subject of successful EEOICP claims.

The cited health conditions increase the severity of COVID-19 disease. That is, studies of people with severe COVID-19 disease (usually defined as hospitalization or death) find a statistically significant high proportion or rate with one or more of the above-listed chronic diseases or conditions. The Board is unable to identify a similar scientific literature that examines the risk of mild COVID-19 disease (treated as an outpatient or not needing treatment) with relation to underlying medical conditions. However, the Board deems the existing literature about severe COVID-19 disease, to the extent that it has been studied, to be well-supported and believes that it is likely that the aforementioned chronic medical conditions increase the symptomatic expression of SARS CoV-2 infection at any level of symptoms. Or, to use an example that addresses the issue more directly, a person with COPD who becomes infected with the SARS CoV-2 virus will be more likely to have symptoms and require medical attention, even if the disease is mild, than a comparable person without COPD. Most of the chronic medical conditions

that are associated with severe COVID-19 disease are cardiopulmonary diseases or their risk factors, so it is highly plausible, as in the case of COPD, that persons with such conditions are more likely to be ill if they acquire the SARS CoV-2 infection and thereby miss work or incur medical expenses, raising issues relevant to EEOICP claims.

The Board recognizes that knowledge about COVID-19 disease is substantial but incomplete and that much will be learned in the coming years about this disease. We therefore recognize the need to periodically review and update this recommendation based on the evolving scientific and medical knowledge on this topic.

The Board recommends that symptomatic COVID-19 disease be recognized as a consequence of relevant EEOICP-claimed conditions that correspond to the CDC-supported list of such conditions provided above.



## Advisory Board on Toxic Substances and Workers Health

### Recommendation on Asbestos Presumptions

The Advisory Board on Toxic Substances and Workers Health recommends that:

1. The Department of Labor and contractor Paragon Technical Services (PTS) should re-evaluate the job titles of Chemical Engineers, Industrial, Health, & Safety Engineers, and Mechanical Engineers and add these titles to the list of occupations presumptively exposed to the asbestos under EEOICP.
2. We request access to the Generic Profiles, including the Asbestos Generic profile, as cited in the PTS report.
3. We recommend that DOL clarify how DOE jobs that correspond to the job title “Maintenance and Repair, General Helper” are classified within the SEM and whether they are linked to asbestos exposure.

### Rationale

These comments reflect the continued discussion between the Board and the Department of Labor concerning the use of asbestos presumptions by the EEOICP.

1. We are pleased that Paragon Technical Services, Inc. (PTS) agrees that four important job titles should be added to Exhibit 15-4 of DEEOICP PM 4.3 (p. iii).
2. We agree with the opinion of PTS that three selected job titles have no relevance to DOE (p. iii).
3. We note that the PTS report refers to Generic Profiles (p. 2). We request access to these profiles.
4. We note that there is an Asbestos Generic Profile (cited on p. 2 of PTS report) that addresses asbestos exposure of certain work processes associated with job titles, including Janitorial activities, Laundry, Power/Communication line maintenance. These job titles are not listed in Exhibit 15-4 of DEEOICP PM 4.3. We request the Asbestos Generic profile in order to understand how asbestos exposure is addressed for these work processes/job.
5. The PTS report argues against presumptive asbestos exposure for some occupations identified in **the** National Occupational Mortality Surveillance (NOMS) as having excess mesothelioma risk on various rationales: 1) asbestos does not appear for the occupation in the SEM; b) some job titles in NOMS encompass work in diverse industries that may have limited and uncertain relevance to work at DOE sites; c) some job titles may not have widespread exposure to asbestos across many job settings; or d) the occupations are infrequent at DOE. These points make sense,

subject to the caveats discussed below. PTS suggests that DOL review the death certificates from the NOMS for these job categories, which may be challenging due to data privacy issues and is unlikely, in the instances when the numbers of deaths are limited, to provide definitive answers. We do not recommend pursuing the review of NOMS death certificates.

Malignant mesothelioma (MM) is a very uncommon cause of death, even in industries and occupations where asbestos was routinely used. The notion that asbestos exposure in a limited subpopulation of a Standard Occupational Classification (SOC) occupational category confined to one or a small number of industries where the specific SOC is active is responsible for an elevated mesothelioma Proportionate Mortality Ratio (PMR) becomes less tenable when a) the Proportionate Mortality Ratio (PMR) is substantially elevated ( $PMR \geq 250$ ), and/or b) the numbers of deaths are considerable ( $\geq 30$ ). Reviewing the NOMS PMR output provided in Table 3 of our recommendation, occupations meeting these criteria include: Chemical Engineers (PMR = 449; # MM deaths = 30); Industrial, Health, & Safety Engineers (PMR = 259; # MM deaths = 30) and Mechanical Engineers (PMR = 250; # MM deaths = 50). We believe that PTS should re-consider the issue of presumptive asbestos exposure for these three occupations.

One of the reasons that PTS cites for not linking asbestos exposure to certain job categories is the failure of asbestos to appear in the SEM as a potential exposure for those occupations. It is uncertain if the SEM routinely recognizes bystander exposures, raising the question about whether the SEM can be expected to reliably link asbestos exposure to occupations whose only exposure was bystander in nature. This may well apply to the 3 job categories cited above: chemical and mechanical engineers and health and safety engineers. It seems quite likely that documentation provided by the DOE and, thus, the SEM, would not address bystander exposures.

We recommend that PTS re-examine the issue of presumptive asbestos exposure for Chemical Engineers, Industrial, Health, & Safety Engineers, and Mechanical Engineers.

6. The logic behind the rejection of "Maintenance and Repair, General Helper" as presumptively asbestos-exposed is unclear, since most maintenance workers and repair workers whom the general helpers assist will now be covered in the enlarged list of Exhibit 15-4. The SEM doesn't appear to have this job title at many DOE sites. Are they considered by claims examiners as part of the maintenance workers and repair workers whom they assist? Or are they placed in a general category of "laborer"? If the latter, are they included in Exhibit 15-4?

## Advisory Board on Toxic Substances and Workers Health

### Recommendation on the Use of the Six Minute Walk Test in Impairment Evaluations

The Advisory Board on Toxic Substances and Workers Health recommends the following:

1. The Board advises that the 6MWT is an entirely acceptable to measure the VO<sub>2</sub>max for the purposes of impairment assessment.
2. The best valid and available method to estimate a value of VO<sub>2</sub>max from the 6MWD for application in Table 5-12 of the AMA Impairment Guide is to use the equation derived by Ross et al (2010):

$$\text{Peak VO}_2 \text{ (ml / kg /min)} = 4.948 + 0.023 * 6\text{MWD (meters)}$$

### Rationale

The Department of Labor has requested assistance in answering the following questions:

1. What are the permissible testing methodologies that a physician may use in assigning a VO<sub>2</sub>max for application in Table 5-12 of the *Guides*?
2. If the 6MWT is a valid methodology for assigning a VO<sub>2</sub>max for application in Table 5-12, should the evidence document that the test conforms with any particular medical standard in validating the test outcome, and what are acceptable methods for calculating the VO<sub>2</sub>max from a validated 6MWT result?

We revised the questions very slightly and provide the following responses.

- 1. What are the permissible testing methodologies that a physician may use in assigning a VO<sub>2</sub>max for application in Table 5-12 of the Guides?**

In the opinion of the Board, the permissible testing methodologies that a physician may use to assign a VO<sub>2</sub>max to an individual patient for application in Table 5-12 of the Guides include two types:

- a. Direct measurement of  $VO_2\text{max}$  or  $VO_2\text{peak}$ , a satisfactory estimate of  $VO_2\text{max}$ , in a pulmonary function laboratory that is experienced in performing Cardio-Pulmonary Exercise Tests (CPET) using a treadmill or cycle ergometer.
- b. The 6 Minute Walk Test (6MWT) along with a regression equation to estimate  $VO_2\text{peak}$  for application in Table 5-12 of the Guides.

#### A. CPET

Direct measurement of  $VO_2\text{max}$ , or in many cases  $VO_2\text{peak}$ , is the preferred method if the following conditions are met: a) an appropriately equipped and experienced exercise testing laboratory is readily available, b) the patient meets the pre-CPET medical clearance requirements (i.e., is well enough to undergo such testing and there are no medical contraindications), c) payment for the CPET (which is expensive) is covered. These conditions may or may not be achievable in practice.

CPET-based measurement of  $VO_2\text{max}$  is considered the “gold standard” of aerobic capacity and cardiorespiratory and pulmonary fitness assessment (American Thoracic Society; American College of Chest Physicians, 2003). The direct measurement of  $VO_2\text{max}$  by CPET has also been proposed as a gold standard for measurement of impairment due to pulmonary disorders (Sood, 2014) and for that purpose, it is complementary to, but better than, at-rest pulmonary function testing including DLCO. In his review, Sood noted that resting PFTs and CPET for evaluating impairment due to occupational lung diseases often yield discrepant results. One of the classic textbooks of exercise testing, Wasserman and Whipp’s Principles of Exercise Testing and Interpretation, 6<sup>th</sup> edition (Sietsema, 2021) concurs with this and provides more details, emphasizing the high frequency of indeterminate and inaccurate impairment decisions based on PFTs alone. In a study of 348 asbestos-exposed shipyard workers (Oren, 1987), the combination of history, physical examination, chest X-ray, resting electrocardiogram, and resting PFTs (including DLCO), performed poorly in predicting dichotomous work capacity status (impaired vs not impaired) using those variables plus CPET. The initial work capacity determination without CPET was indeterminate in 134/348 subjects, 39% of the total group. Among the remaining 214 subjects, it was erroneous for 22/66 (33%) of cases initially classified as impaired and for 44/148 (30%) of cases who were initially classified as not impaired. Of the indeterminate group, 49/134 (37%) were ultimately found to be impaired by CPET, and 81/134 (60%) were unimpaired. Only 5 (1.4%) of the total group remained as indeterminate impairment status after the CPET. The authors concluded that exercise testing was advantageous for accurate assessment of work capacity in impairment evaluations.

In that study, impairment was due to cardiovascular disease in 69% of those found to be impaired, though the assessment of cardiovascular disease was not confirmed by measurements of ejection fraction or other additional cardiovascular testing. This explains some of the inaccuracy of the PFTs in predicting impairment since some of the subjects with impairment due to cardiovascular disease would have had normal PFTs. It does not explain the high frequency of indeterminate impairment status based on PFTs, especially the 60% of the indeterminate group found to be unimpaired by CPET. It is important to note that the CPET, ideally a maximal effort test, would yield a  $VO_2\text{peak}$  rather than a  $VO_2\text{max}$  in most or all patients with significant lung disease since they can rarely achieve the maximal anaerobic level of exertion needed to generate a true  $VO_2\text{max}$ .

Measuring  $VO_2\text{max}$  requires achieving a plateau in oxygen intake vs work rate graph, i.e., a maximal anaerobic level of effort beyond which even with a further increase in power output the

muscles cannot metabolize more oxygen and rely on anaerobic ATP-based metabolism. This is often clinically contraindicated or unachievable in patients with lung disease or other comorbidities like heart disease. In these common situations,  $VO_2$ peak measurement has been shown to be a valid index of  $VO_2$ max (Day, 2003) and is often used interchangeably (Singh, 2014).

The CPET laboratory requires personnel trained specifically in CPET, which is beyond the routine training of pulmonary function laboratory technicians. The American College of Sports Medicine (ACSM) lists cognitive skills required of personnel supervising the test as well as medical contraindications to the CPET and conditions requiring physician supervision. It is recommended by the ACSM that the person doing the test has performed at least 50 (Rodgers, 2000) tests in the past, and more recently recommended 200 tests in the past (Myers, 2014) and continues to perform 25 to 50 tests per year to maintain competency (Liguri (ACSM), 2021, p. 115-117). It is our impression, without hard data, that many otherwise available PFT laboratories near where claimants live may not meet these minimal criteria, and, therefore, CPET may not be accessible for some claimants. Therefore, there is a need for a second line test to estimate  $VO_2$ max for the purpose of classifying impairment in patients with lung disease.

#### B. Six Minute Walk Test

If CPET is not available or feasible for a given claimant, in the opinion of the Board, the Six Minute Walk Test (6MWT) would be the best available method for estimating  $VO_2$ max in patients with medical impairment due to pulmonary disease, such as those applying for compensation. The 6MWT has been well studied for patients with a variety of lung disorders and is reported to have acceptable repeatability, reproducibility, safety and precision to predict mean  $VO_2$ max of a group (Singh, 2014; Sood, 2014; Ross, 2010; Cahalin, 1995). The evidence was systematically reviewed by the European Respiratory Society / American Thoracic Society (ERS/ATS) in 2014 (Singh 2014). These same Societies also published an official Technical Standard on how the 6MWT should be performed in patients with chronic respiratory disease (Holland 2014).

The ERS/ATS systematic review concluded that the 6MWT is a valid, reliable, and “robust test of functional exercise capacity in adults with chronic respiratory disease.” The review also concluded that the relationship between 6MWD and either  $VO_2$ peak or peak work on a progressive incremental Cardiopulmonary Exercise Testing (CPET) was moderate to strong and was consistent across patient groups with chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD). Seven out of eight studies of patients with COPD or ILD compared the  $VO_2$  peak as estimated by the 6MWT versus the CPET and found no significant differences between the two testing techniques. Review of 35 studies of people with chronic lung disease showed a consistent association between results of the 6MWT and mortality and hospitalization. 6MWT results are associated with oxygen desaturation in many patients, and several studies showed that it was more sensitive than CPET in detecting such exercise-associated desaturation. The authors conclude that “The 6MWT has historically been considered to be a test of submaximal exercise capacity, however, direct comparisons of the physiological demands of the 6MWT and CPET reveal that, in patients with chronic respiratory disease, measures of peak exercise performance are similar between the tests.” (Singh, 2014, p. 1469).

The 6MWT measures peak  $VO_2$  ( $VO_2$ peak), which provides acceptable estimates of  $VO_2$ max when  $VO_2$ max is not clinically advisable or achievable. As for the CPET, the 6MWT would generally yield a  $VO_2$ peak rather than a  $VO_2$ max in most or all of these patients since individuals with significant lung disease can rarely achieve the maximal anaerobic level of exertion needed to generate a true  $VO_2$ max.

Dale and colleagues studied the 6MWT versus the incremental cycle test in 25 people with asbestos-related pleural disease and found that 6MWD correlated with peak work rate ( $r=0.58$ ,  $p=0.002$ ). They concluded that “6MWT may be a useful surrogate measure of peak exercise capacity and physical activity levels in the absence of cardiopulmonary exercise testing” (Dale, 2013).

The 6MWT is a field test that is widely available, does not require specialized equipment, and can be performed safely in a typical medical office setting by most patients with pulmonary or cardiac compromise. The accuracy of estimation of  $VO_2$ max provided by the  $VO_2$ peak from the 6MWT is adequate for the determination of medical impairment. It is important to note that both the 6MWT and the CPET reflect a number of different functional domains, including respiratory, cardiac, peripheral vascular, neurologic and musculoskeletal functionality. For this reason, determination of whether impairment is due to chronic respiratory disease versus other causes requires a clinical decision by the examining physician that impairment is not due to significant disease of other organ systems.

Eaton et al tested 30 people with pulmonary fibrosis with the 6MWT and incremental exercise treadmill testing and found an excellent and highly significant (“striking”) correlation ( $r=0.78$ ,  $p<0.0001$ ) between treadmill  $VO_2$ max and results of the 6MWT (Eaton, 2005). Within-subject-reproducibility on repeat testing was far better for the 6MWT distance ( $r=0.98$ ,  $SD/mean=0.042$ ) than for the  $VO_2$ max ( $r=0.88$ ,  $SD/mean=.105$ ). They concluded that the 6MWT is superior to maximal exercise testing based on the former’s higher reproducibility.

The ERS/ATS Technical Standard published by Holland et al. (2014) provides standardized instructions and quality assurance procedures for 3 field walking tests in chronic respiratory diseases, the 6MWT, the Incremental Shuttle Walk Test (ISWT) and the Endurance Shuttle Walk test (ESWT). All 3 tests produce results similar to those from the CPET; however, in the view of the Board, the 6MWT is more feasible to perform in typical medical settings than the other field walking tests reviewed. The ESWT requires the ISWT as a prerequisite and the ISWT requires much more detailed monitoring and technician training during the test than the 6MWT. As discussed in the next section, a reasonable equation is available to estimate  $VO_2$ peak from the 6MWT but not from the ISWT or ESWT.

So, in the opinion of the Board, if the CPET is not available, affordable or suitable, the 6MWT as described in the ERS/ATS official technical standard (Holland, 2014) is a permissible testing methodology that a physician may use in assigning a  $VO_2$ max for application in Table 5-12 of the Guides.

**2. If the 6MWT is a valid methodology for assigning a  $VO_2$ max for application in Table 5-12, should the evidence document that the test conforms with any particular medical standard in validating the test outcome? Also, what are acceptable methods for calculating the  $VO_2$ max from a validated 6MWT result?**

In the opinion of the Board, yes, the evidence should document that the 6MWT was performed according to the ERS/ATS official Technical Standard (Holland, 2014). The authors of that standard reported that the 6MWT demonstrates good construct validity as a test of functional exercise performance, has good test-retest reliability with evidence of a learning effect between first and second test, elicits a  $VO_2$ peak that is similar to that produced by a CPET, and has similar precautions and contraindications to the CPET. They note that the test is sensitive to variations in methodology including use of encouragement, provision of supplemental oxygen, changes in track layout and length, and use of wheeled walkers and recommended strict adherence to the recommended protocol for performing the 6MWT. They also recommended that clinically significant heart disease and musculoskeletal limitations

be factored into the results of the 6MWT for assessment of respiratory status. The recommendation to perform two 6MWT because of the learning effect is for use of the test in serial assessment of change over time, for example, to assess progress during a program of pulmonary rehabilitation. On p. 1431, Holland et al state, however, that, "Where the 6MWD is used as a one-off measure to stage disease or assess risk (e.g. likelihood of hospitalization or mortality), the magnitude of the learning effect may be less important and one test may be sufficient." Performing the test twice would require sequential 6MWT tests on different days and, given the statement in the Holland review, may not be necessary for a one time use of the 6MWT to assess impairment after maximal medical improvement.

To estimate VO<sub>2</sub>max from the 6MWT requires a statistical methodology derived from study of a large number of subjects. In the opinion of the Board, the best available method which is medically acceptable is to use the equation published by Ross et al in 2010 to estimate the VO<sub>2</sub>peak in an individual patient. This equation is stated in the article as:

$$\text{Peak VO}_2 \text{ (ml / kg /min)} = 4.948 + 0.023 * \text{Mean 6MWD (meters)}$$

This regression equation was derived from pooled data taken from 11 studies conducted between 1996 and 2006 including a total of 1,083 patients with diverse cardiopulmonary disorders. The equation is presented to calculate the mean VO<sub>2</sub>peak in a group from the mean 6MWD in that group. Although the structure of the equation is the same as would be used to calculate the VO<sub>2</sub>peak for an individual from that individual's 6MWD, the authors reported that the Standard Error of the Estimate (SEE) for the individual calculation was 3.82 ml/kg/min and that is too large, i.e., would produce an estimate with wide confidence intervals for an individual. Examining the plots of the regression equations for the whole data set and several of the component sub-studies, we have not found evidence that using the equation for individual patients would systematically over- or under-estimate the VO<sub>2</sub>peak values calculated from the 6MWD values for those patients. So we do not expect that the point estimates of VO<sub>2</sub>peak produced by using this equation would be biased, just that the confidence intervals would be larger than we would like. This is the largest pooled dataset available to derive such a regression equation.

In contrast, the ACSM regression equation provided by DOL is not as good a candidate for use in this setting. That equation, intended for use in sports medicine, appears unchanged in the ACSM text from the 6<sup>th</sup> edition through the current 11<sup>th</sup> edition (issued this month). Its derivation has limited documentation but appears to be based on just two older studies of 3 and 10 young (<45 years old) athletic (VO<sub>2</sub>max 35-58 ml kg<sup>-1</sup> min<sup>-1</sup>) subjects (Dill, 1965; Nagle, 1971). One of the 3 subjects in the first study was a world class marathon runner, the other 2 were healthy athletes. In contrast, the Ross study combined data points from a total of 1,083 subjects with pulmonary and cardiac disease in the 11 studies to derive the equation given above. So in the opinion of the Board, if the 6MWT is used, the VO<sub>2</sub>peak should be calculated from the 6MWD using an equation derived from that in Ross et al:

$$\text{VO}_2\text{peak (ml per minute per kg)} = 4.948 + 0.023 * \text{6MWD (meters)}$$

#### Conclusion and Board recommendations

In conclusion, the preferred method of assigning VO<sub>2</sub>max to an individual claimant with pulmonary disease for application in Table 5-12 of the Guides is direct measurement of VO<sub>2</sub>max or, more likely, VO<sub>2</sub>peak using the CPET. If CPET is not available, the 6MWT is the next best method and is entirely acceptable. For this purpose, it is more reliable, less likely to generate indeterminate results,

and more likely to accurately classify impairment than PFTs alone. It is important to confirm the respiratory disease diagnosis using PFTs and/or other clinical information. A clinical judgment will be required to rule out or properly apportion the contribution of cardiac, musculoskeletal or neurologic causes of impairment as determined with either the CPET or 6MWT. The valid methods of performing the 6MWT are those described in the ERS/ATS standard paper (Holland, 2014). The equation derived by Ross et al (Ross, 2010), although less precise for use in individual claimants than we would like, does not appear to systematically overstate or understate the level of impairment and is far better supported with research data than the ACSM equation for estimating the VO<sub>2</sub>max from the 6MWT in people with respiratory disease.

## References

1. American Thoracic Society; American College of Chest Physicians. ATS/ACCP Statement on Cardiopulmonary Exercise Testing. *Am J Respir Crit Care Med*. 2003;167(2):211-77.
2. Sood A. Performing a lung disability evaluation: how, when, and why? *J Occup Environ Med*. 2014 Oct;56 Suppl 10(0 10):S23-9.
3. Sietsema KE, Sue DY, Stringer WW, Ward SA. Wasserman and Whipp's Principles of Exercise Testing and Interpretation, 6<sup>th</sup> edition. Wolters Kluwer, 2021.
4. Oren A, Sue DY, Hansen JE, Torrance DJ, Wasserman K. The role of exercise testing in impairment evaluation. *Am Rev Resp Dis*. 1987;135:230-35.
5. Day JR, Rossiter HB, Coats EM, et al. The maximally attainable VO<sub>2</sub> during exercise in humans: the peak vs. maximum issue. *J Appl Physiol*. 2003;95:1901–1907.
6. Singh S, Puhan M, Andrianopoulos V, et al. An official systematic review of the European Respiratory Society/American Thoracic Society: measurement properties of field walking tests in chronic respiratory disease. *Eur Respir J*. 2014;44:1447–1478.
7. Rodgers GP, Ayanian JZ, Balady G, et al. American College of Cardiology/American Heart Association Clinical Competence statement on stress testing. A report of the American College of Cardiology/American Heart Association/American College of Physicians–American Society of Internal Medicine Task Force on Clinical Competence. *Circulation*. 2000;102(14):1726–38.
8. Myers J, Forman DE, Balady GJ, et al. Supervision of exercise testing by nonphysicians: a scientific statement from the American Heart Association. *Circulation*. 2014;130(12):1014–27.
9. Liguori G (ed). American College of Sports Medicine's Guidelines for Exercise Testing and Prescription, 11<sup>th</sup> edition. 2021, Wolters Kluwer. p. 115-117.
10. Ross R, Murthy J, Wollak I, Jackson A. The six-minute walk test accurately estimates mean peak oxygen uptake. *BMC Pulmonary Medicine*. 2010;10:31.
11. Cahalin L, Pappagianopoulos P, Prevost S, Wain J, Ginns L. The relationship of the 6-min walk test to maximal oxygen consumption in transplant candidates with end-stage lung disease. *Chest*. 1995 Aug;108(2):452-9.
11. Holland AE, Spruit MA, Troosters T, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. *Eur Respir J*. 2014;44(6):1428-46.
12. Dale M, McKeough Z, Munoz P, et al. Functional exercise capacity and health-related quality of life in people with asbestos related pleural disease: an observational study. *BMC Pulmonary Medicine*. 2013;3:1.
13. Eaton T, Young P, Milne D, Wells A. Six-Minute Walk, Maximal Exercise Tests Reproducibility in Fibrotic Interstitial Pneumonia. *Am J Respir Crit Care Med*. 2005;171:1150–1157.



14. Dill MK. A workshop medical program. The physician's role. *Rehabil Rec.* 1965 Sep-Oct;6(5):8 passim. PMID: 5830825 VERSUS
15. Dill DB Marathoner DeMar: physiological studies. *J Natl Cancer Inst.* 1965 Jul;35(1):185-91. doi: 10.1093/jnci/35.1.185. PMID: 5825455
16. Nagle F, Balke B, Baptista G, Alleyia J, Howley E. Compatibility of progressive treadmill, bicycle and step tests based on oxygen uptake responses. *Med Sci Sports.* 1971 Winter;3(4):149-54.