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RECOMMENDATION

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Occupational exposure limits for cumene, 2,4-dichlorophenoxy acetic acid, silicon carbide whisker, benzyl alcohol, and methylamine, and carcinogenicity, occupational sensitizer, and reproductive toxicant classifications

The Committee for Recommendation of Occupational Exposure Limits, Japan Society for Occupational Health

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1 | OCCUPATIONAL EXPOSURE LIMITS (OELs) FOR CHEMICAL SUBSTANCES

Cumene [CAS No. 98-82-8] is a colorless liquid (boiling point 152°C, vapor pressure 427 Pa [20°C]) with characteristic odor that reacts violently with acids and strong oxidants with generation of fire or explosion hazard. It is mainly used as a raw material in the manufacture of phenol, acetone, and prooxidant, and is a minor constituent of jet fuel. The OEL-mean of 10 ppm is proposed based on the results of animal experiments. In the 14-week inhalation exposure experiment with Fischer 344 rats (0, 62.5, 125, 250, 500, 1000 ppm), hepatocellular injury and decrease in plasma components for hepatobiliary function were observed in the group of 250 ppm or more together with increase in relative kidney weight.[1] In the 13-week inhalation exposure experiment with Fischer 344 rats, no adverse effect was observed in 100 ppm.[2,3] Slight, local atrophy in olfactory epithelia in the nasal cavity was also observed at concentration of 125 ppm in the results of 105-week inhalation studies of B6C3F1 mice.[1] Skin absorption notation is indicated, and carcinogenicity classification is proposed as Group 2B.

2,4-Dichlorophenoxy acetic acid [2,4-D; CAS No. 94-75-7] is a nonflammable, white crystal or powder (melting point 138-141°C, boiling point 160°C) that reacts with strong oxidants generating fire hazard and forming hazardous gas or vapor such as hydrogen chloride. It is a herbicide of the chlorophenoxy family. In two 104-week oral gavage studies in rodents,[4,5] increase in relative kidney weight was observed in 5 mg/kg/day in female Fischer 344 rats (0, 1, 5, 15, 45 mg/kg/day), and degeneration of renal proximal tubule was observed in 15mg/kg/day in male B6C3F1 mice (0, 1, 15, 45 mg/kg/day). Thus, the Japan Society for Occupational Health (JSOH) proposes 2 mg/m^3 as OEL-M for 2,4-D, by assuming an 8-h-respiratory volume of 10 m^3 for 50-kg body weight and 100% absorption via the lung. Skin absorption notation is indicated, and reproductive toxicant classification is proposed as Group 2 in two-generation or one-generation reproductive studies.

Silicon carbide whisker (SiCW) [CAS No. 409-21-2, 308076-74-6] is a cylindrical-shaped, single-crystal fiber with a width of <3 μm that fulfils the definition of WHO fibers (particles >5 μm with a width of <3 μm and an aspect ratio of >3). The JSOH proposes 0.1 fiber/mL as OEL-M for SiCW based on the observed effect of pulmonary fibrosis by a one-year inhalation study (98 fiber/mL in average) in Wistar male rats.[6] Although SiCW has a carcinogenic potency equivalent to asbestos, fibrosis is deemed to be a precedent health effect to lung cancer and adherence to the proposed OEL-M is expected to prevent from lung cancer. Carcinogenicity classification is proposed as Group 2A based on sufficient evidence from animal carcinogenicity and mechanistic consideration in vitro.

Benzyl alcohol [CAS No. 100-51-6] is a colorless, neutral liquid at room temperature (boiling temperature, 204.7ºC; saturated vapor pressure, 3 Pa 20ºC) that is used as a fixative or stabilizer in perfume or fragrance. The OEL-Ceiling, defined as the reference value to the maximal exposure concentration of the substance during a working day at or below which adverse health effects do not appear in most workers, of 25 mg/m^3 is proposed based on the acute effects on human airway mucosa in a randomized, double-blind, placebo-controlled study,[7] in which four out of five volunteers experienced strong respiratory symptoms with relation to benzyl alcohol exposure (exposed to 3 mL of 9 mg/mL benzyl alcohol solution four times a day for 2 weeks by a nebulizer) by assuming minute ventilation of 7 L during 15-minute nebulization. OEL-C of 25 mg/m^3 is expected to prevent from observed systemic effects in subacute and chronic animal experiments. The skin occupational sensitizer classification is proposed as Group 2 based on human studies.

Methylamine [CAS No. 74-89-5] is a colorless corrosive gas with the ammonia odor (boiling point −6.33°C, vapor pressure 353.3 kPa [25°C]). It is used as production raw materials of pharmaceuticals, agrichemicals, dyes, explosives, and rubber vulcanizing agent. This chemical wa s recommended 10 ppm (13 mg/m^3) for OEL-M in 1979. The JSOH reevaluated the OEL by examining subsequent reports this time, and proposes 5 ppm (6.5 mg/m^3) as OEL-M for methylamine based on the observed light inflammation and epithelial hyperplasia in the transitional epithelium of the respiratory region of the nasal cavity at concentrations ≥15 ppm in a 2-year inhalation study (0, 5, 15, and 45 ppm) in B6D2F1 mice.[8]

For the table of OELs for dusts, notes are added as follows: (a) OLEs for dusts are being set to prevent from category 2 pneumoconiosis, and (b) OEL for "inorganic and organic dusts other than Classes 1 and 2" in class 3 is the reference value to prevent from pneumoconiosis caused by massive exposure to dust that is insoluble or hard to dissolve to water, and has no apparent toxicity and thus no existing applicable OEL in Tables I-1 and I-2. Therefore, even below the OEL value, unknown toxicity may cause health impairment.

2 | CLASSIFICATIONS ON CARCINOGENICITY

SiCW and hydrazine are proposed to be a group 2A carcinogen. Proposed group 2B carcinogens are 2-amino-4-chlorophenol, *o*-chloronitrobenzene, *p*-chloronitrobenzene, cumene, 1,4-dichloro-2-nitrobenzene, 2,4-dichloro-1-nitrobenzene, *N,N*-dimethyl acetamide, 2-ethylhexyl acrylate, furfuryl alcohol, melamine, 2-mercaptobenzothiazole, *p*-methoxynitrobenzene, methyl acrylate, *o*-phenylenediamine and its dihydrochloride, tetrabromobisphenol A, tetrahydrofuran, trimethylolpropane triacrylate (industrial grade). Reference values corresponding to an individual excess lifetime risk of cancer for benzene remains unchanged after reevaluation by examining subsequent reports. Carcinogenicity classification for 2,4-D was excluded from the table of carcinogenicity classification because of insufficient evidence for classification.

3 | OTHER CLASSIFICATIONS

Skin occupational sensitizer classification for benzyl alcohol and 2-hydroxyethyl methacrylate is proposed as Group 2. Reproductive toxicants classification for 2,4-D is proposed as Group 2.

The latest OEL recommendations (2019-2020) will appear in the Environmental and Occupational Health Practice (Volume 1) as an open access. A brief summary of the proposal will be posted at the society's website (https://www.sanei.or.jp/oel-eng) in September.

DISCLOSURE

Approval of the research protocol: N/A. *Informed consent*: N/A. *Registry and the registration no. of the study/trial*: N/A. *Animal studies*: N/A. *Conflict of interest*: None declared.

AUTHOR CONTRIBUTIONS

All the authors contributed to draft preparation and deliberation of the proposals in the committee. The corresponding author (TT) developed and finalized the article based on the comments from all other authors' feedback.

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