

RECOMMENDATION

Occupational exposure limits for acetaldehyde, 2-bromopropane, glyphosate, manganese and inorganic manganese compounds, and zinc oxide nanoparticle, and the biological exposure indices for cadmium and cadmium compounds and ethylbenzene, 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 FOR CHEMICAL SUBSTANCES

Acetaldehyde [CAS No. 75-07-0] is an irritating colorless liquid (boiling point 20.2°C, vapor pressure 101 kPa (20°C)) that is used as an intermediate raw material in the manufacture of chemical materials, preservatives, organic solvents, reducing agents, and glues as a substitute of formaldehyde. The occupational exposure limit-Ceiling (OEL-C) was recommended at 50 ppm (90 mg/m³) for acetaldehyde in 1990, and acetaldehyde was assigned to carcinogenicity Group 2B in 1991. The Japanese Society for Occupational Health (JSOH) re-evaluated the OEL-C, and proposes 10 ppm as the OEL-C for acetaldehyde based on observed eye irritation in human at concentrations of 50 ppm for 15 min and 4 hours¹ and the possibility of slight impairment of mucociliary transport in upper respiratory tract in rats² at the concentrations of 150 ppm for 6 hours/day, 5 days/week for up to 65 exposure days (13 exposure weeks; No-observed-adverse-effect-level

(NOAEL) 50 ppm). As the new OEL-C, 10 ppm is expected to prevent the observed effects on the eyes and upper respiratory tract in consideration of the higher sensitivity due to the lower metabolic rate for acetaldehyde on in approx. 40% of the Japanese population, which has the ALDH2*2 genotype.³ The carcinogenicity group remains the same.

Glyphosate [CAS No. 1071-83-6] is a white crystalline powder (melting point 184.5°C, vapor pressure 1.31×10⁻⁵ Pa (25°C)) that is used as liquid, powder, or mist pesticide for weeding. The JSOH proposes 1.5 mg/m³ as OEL-Mean (OEL-M) for glyphosate based on the results of animal experiment. The NOAEL in male and female rats was considered 10 mg/kg body weight per day based on observed pathological changes: an increased incidence of pronounced cellular alterations of parotid and mandibular glands at or above 100 mg/kg body weight per day in 104 weeks.⁴ Uncertainty factors for species and absorption rates were applied and weight, respiratory volume, and working hours were adjusted in the assessment. The proposed carcinogenicity classification for glyphosate is

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Group 2B based on limited epidemiological and insufficient experimental carcinogenicity evidence.

Zinc oxide nanoparticle [CAS No. 1314–13–2] is a white crystalline powder with particle size of 1–100 nm. It is used as a material in the manufacture of cosmetics, pharmaceuticals, household and sporting goods, paint, and ink. The JSOH proposed 0.5 mg/m³ as the OEL-M for zinc oxide nanoparticle based on the results of animal experiment. The NOAEL in male mice was considered 3.5 mg/m³ based on the absence of increases in inflammatory markers in the lung, e.g., neutrophils and cytokines other than macrophages in bronchoalveolar lavage fluid in a 13-week inhalation study.⁵ Uncertainty factors for species and exposure duration were applied in the assessment.

2-Bromopropane [CAS No. 75–26–3] is a nonflammable colorless liquid (melting point –90°C, boiling point 59.4°C, vapor pressure 315 hPa (25°C)). It is used as solvents and intermediates for pharmaceuticals, pesticides, and photosensitizers. The recommended OEL-M for this chemical is 1 ppm (5mg/m³), and a skin absorption notation was indicated in 1999. 2-Bromopropane was classified in Group 1 as a reproductive toxicant in 2014. The JSOH re-evaluated the chemical's OEL by examining subsequent reports. The JSOH now proposes 0.5 ppm (2.5 mg/m³) as the OEL-M for 2-bromopropane based on epidemiological and animal experimental studies. Hematological indices might be adversely suppressed in female workers exposed to approx. 6.5 ppm.⁶ The low-observed-adverse-effect-level (LOAEL) in male rats was considered 67 ppm based on the significant increase in the incidence of ear canal carcinoma,⁷ despite its rarity in humans. Uncertainty factors for species and absorption rates were applied and body weight, respiratory volume, and working hours were adjusted in the assessment. The proposed carcinogenicity classification is Group 2B based on the lack of epidemiological and sufficient experimental carcinogenicity evidence. The skin absorption notation and the classification as a reproductive toxicant (Group 1) remain the same.

Manganese and its compounds (as Mn except for organic manganese compounds) [CAS No. 7439–96–5] is a red-gray or silver metal (melting point 1,245°C, boiling point 2,150°C, specific gravity 7.43), and is an essential trace element contained in water, soil, and food. Manganese is used as raw material for manganese-containing alloys, reagents, fungicides, bleach, gunpowder, and pharmaceuticals. The recommended OEL-M was set at 0.2 mg/m³ in 2008, and manganese and its compounds were categorized in Group 2 as a reproductive toxicant in 2014. The JSOH re-evaluated the OEL and reproductive toxicant class by examining subsequent reports, and proposed the OEL-M values of 0.1 mg/m³ and 0.02 mg/m³ for the total and respirable particulate matters for manganese and its compounds, respectively, based on

the results of epidemiological studies in which the cumulative exposure concentrations were converted to annual average concentrations for 25 years. The LOAELs for total particulate matters were 0.143 mg/m³,⁸ 0.225 mg/m³,⁹ and 0.301 mg/m³.¹⁰ A dose-dependent functional decrease on the finger-tapping test was observed in three groups of workers exposed to 0.031, 0.137, and 0.423 mg/m³ of total particulate matters, respectively, and the functional decrease among workers exposed to 0.423 mg/m³ was significantly low compared to that in workers exposed to 0.031 mg/m³.¹¹ The NOAEL has been set at 0.060 mg/m³¹² of total particulate matters based on several neurobehavioral tests. The LOAELs of respirable particulate matters were 0.029 mg/m³,⁸ 0.035 mg/m³,⁹ 0.036 mg/m³,¹⁰ and 0.01–0.04 mg/m³,¹³ and the NOAEL was set at 0.021 mg/m³ based on observed effects on the nervous system.¹² The class of reproductive toxicant (Group 2) remains the same.

Ethylbenzene [CAS No. 100–41–4] is a colorless liquid (boiling point 136.2 °C, vapor pressure 1.27 kPa (25 °C)) that is used as a raw material in the manufacture of styrene monomer, plastic, and rubber, and it is a component of mixed xylene. The JSOH proposed 150 mg/g·creatinine (Cr) of mandelic acid (MA) at the end of a work shift, 200 mg/g·Cr of MA plus phenylglyoxylic acid (PGA) at the end of the shift at the end of a work-week, and 15 µg/l of ethylbenzene at the end of a work shift in the urine for ethylbenzene as OEL based on biological monitoring (OEL-B) obtained in human studies. The estimated values of MA, MA+PGA, and ethylbenzene were 152 mg/g·Cr,^{14–17} 205 mg/g·Cr,^{14,17} and 13 µg/l^{15,18} in urine corresponding to the OEL-M of 20 ppm for ethylbenzene.

Cadmium and its compounds [CAS No. 7440–43–9] are a soft bluish silver white metal (melting point 321°C, boiling point 765°C) that are used as raw materials for cadmium-containing alloys, pigments, and batteries. The LOAELs were 10 µg/l in blood and 10 µg/g·Cr in urine based on renal tubular effects in human study,¹⁹ and no effects were observed in workers whose cadmium concentrations were less than 5 µg/l in blood and 5 µg/g·Cr in urine.²⁰ The OEL-Bs of 5 µg/l in blood and 5 µg/g·Cr in urine of cadmium are expected to prevent critical effects on renal function.

2 | CARCINOGENICITY CLASSIFICATIONS

Both ultraviolet (UV) radiation from welding and welding fumes are proposed to be group 1 carcinogens. Proposed group 2B carcinogens are 2-bromopropane, CI direct blue 218, crotonaldehyde, glyphosate, and *N*-nitroso-*N*-phenylhydroxylamine ammonium salt (cupferron).

3 | OTHER CLASSIFICATIONS

Group 1 is proposed as the respiratory and skin occupational sensitizer classifications for ortho-phthalaldehyde. Group 2 is proposed as the skin occupational sensitizer classification for ethylene glycol dimethacrylate and 1,6-hexanediol diacrylate. Group 3 is proposed as the reproductive toxicants classification for glyphosate.

4 | DATA AVAILABILITY STATEMENT

Data openly available in a public repository that issues datasets with DOIs.

5 | MEMBERS OF THE COMMITTEE FOR RECOMMENDATION OF OCCUPATIONAL EXPOSURE LIMITS, JAPAN SOCIETY FOR OCCUPATIONAL HEALTH

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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: The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

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

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