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*Opinion/Recommendation*

# Occupational Exposure Limits of lead, dimethylamine, n-butyl-2,3-epoxypropyl ether, and 2-ethyl-1-hexanol and carcinogenicity and occupational sensitizer classification

The Committee for Recommendation of Occupational Exposure Limits, Japan Society for Occupational Health
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The Committee for the Recommendation of Occupational Exposure Limits (OELs) of the Japan Society for Occupational Health (JSOH) proposed provisional OELs as reference values for preventing adverse health effects in workers caused by occupational exposure to chemical and physical agents at the 89th Academic Conference on May 25, 2016 held in Fukushima.

Lead (CAS No. 7439-92-1) is a blue-gray or silver-gray soft metal that is present in the electrodes of lead batteries, alloys, leaded glass, anticorrosive pigments, bullets, sound-proofing sheets, radiation shielding, and fine arts and crafts materials. JSOH proposes 0.03 mg/m$^3$ as the OEL-Mean (OEL-M) for lead, corresponding to the revised OEL Based on Biological Monitoring (OEL-B) of 15 μg/100 m*l* (blood lead), according to two recent epidemiological studies on the relationship between lead present in the air and in blood among workers exposed to relatively low levels[1,2]. Further revisions will be considered if reproductive toxicity below OEL-B is noticed. The carcinogenicity classification is maintained as group 2B because of insufficient animal evidence, although the International Agency for Research on Cancer (IARC) upgraded lead to group 2A. Oral administration of lead to rodents caused renal cancer, but no carcinogenicity was

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observed in an inhalation study.

n-Butyl-2,3-epoxypropyl ether [synonym: n-butyl glycidyl ether (BGE); CAS No.2426-08-6] is an odiferous, colorless liquid at room temperature (boiling temperature, 164℃; saturated vapor pressure, 0.43 kPa 25℃) that is used as a major reactive diluent for industrial epoxy or alkyd resins, a stabilizer for chlorinated solvents, a dye dispersing agent, a cotton or wool surface modifier, and a dye enhancing agent. It is inflammable and may form an explosive peroxide if exposed to air. JSOH proposes 0.25 ppm as OEL-M for BGE according to toxicity testing results. No-observed-adverse-effect level (NOAEL) in mice was considered to be 5 ppm according to pathological changes, such as necrosis or metaplasia of respiratory epithelial cells and atrophy of the olfactory epithelium at concentrations ≥25 ppm in a 13-week inhalation study (12.5-200 ppm)[3], as well as an increased incidence of angioma in the nasal cavity at concentrations ≥15 ppm according to the findings of a 2-year inhalation study (5, 15, and 45 ppm)[4]. Uncertainty factors of 2 for interspecies differences and 10 for severity of the carcinogenic effects on animal were applied. The carcinogenicity classification is proposed as group 2B, reproductive toxicant as group 3, and skin occupational sensitizer as group 2.

Dimethylamine (CAS No.124-40-3) is a colorless gas with an ammonia-like irritating odor at room temperature that forms toxic fumes, such as nitrogen oxides, when burning and is corrosive at acidic pH. It is mainly used as precursor for *N,N*-dimethylformamide, as well as a raw material for manufacture of rubber accelerators, insecticides, microbicides, antihistamines, surfactants, and solvents. In 1979, 10 ppm (18 mg/m$^3$) was designated as OEL-M. JSOH proposes 2 ppm (3.7 mg/m$^3$) as the revised OEL-M, according to dose-dependent pathological changes in respiratory and olfactory epithelia in the nasal cavity at concentrations ≥10 ppm, according to the results of 2-year inhalation studies (10-175 ppm)[5,6]. An uncertainty factor of 5 was applied that accounts for lowest-observed-adverse-effect level (LOAEL) to NOAEL conversion, and interspecies difference in toxicodynamics was applied. The skin occupational sensitizer classification is proposed as group 3.

2-Ethyl-1-hexanol (CAS No.104-76-7) is an odiferous, colorless liquid that is poorly soluble in water, although it is soluble in many organic solvents (boiling temperature, 184.34℃; saturated vapor pressure, 0.36 mmHg 20℃). It is used as a raw material for producing plasticizers for polyvinyl chlorides, such as bis (2-ethylhexyl) phthalate, bis (2-ethylhexyl) adipate, and 2-ethylhexyl acrylate, as well as in the manufacture of adhesives, paint, food additives, and cosmetic fragrances. JSOH proposes 1 ppm (5.4 mg/m$^3$) as OEL-M according to the results of 4-h inhalation experiments using human volunteers. In these experiments, eye irritation occurred under fluctuating exposure with peak concentrations of 20 ppm[7]. Further, intranasal irritation and annoyance were observed at time-weighted average concentrations as low as 10 ppm[8]. An uncertainty factor of 10 was applied to account for LOAEL to NOAEL conversion. Irritation of the nasal cavity and throat or headache was observed at 1 mg/m$^3$ (0.19 ppm) in 2-h human inhalation experiments[9]. This OEL-M is expected to prevent degeneration of the nasal olfactory epithelium, which was observed at 20 ppm in an inhalation study of mice[10]. Reproductive toxicant classification is under consideration. OEL-M for vinyl chloride is currently under review.

For revised carcinogenicity classifications, beryllium and its compounds, o-toluidine, and polychlorinated biphenyls (PCB) are proposed as group 1 carcinogens. Proposed group 2A carcinogens are the polycyclic aromatic hydrocarbons (PAHs), cyclopenta[c,d]pyrene, dibenz[a,h]anthracene, dibenz[a,j]acridine, dibenzo[a,l]pyrene, and 1-nitropyrene, 6-nitrochrysene, and cobalt metal with tungsten carbide. Proposed group 2B carcinogens are benzoyl chloride and PAHs (benz[a]anthracene, benz[j]aceanthrylene, benzo[b]fluoranthene, benzo[c]phenanthrene, benzo[j]fluoranthene, benzo[k]fluoranthene, chrysene, dibenz[a,h]acridine, dibenz[c,h]acridine, dibenzo[a,h]pyrene, dibenzo[a,i]pyrene, 7H-dibenzo[c,g]carbazole, 1,3-dinitropyrene, 1,6-dinitropyrene, 1,8-dinitropyrene, 5-methylchrysene, 3-nitrobenzanthrone, and 4-nitropyrene). Beryllium and its compounds are upgraded from group 2A to group 1 carcinogens. Evidence acquired from studies on humans and animals is considered sufficient, according to the significant increased risk of lung cancer in cohort studies and in an inhalation study of rats. o-Toluidine has also been upgraded from group 2A to group 1 according to sufficient epidemiological evidence of increased risk of bladder cancer in humans. An increased incidence of tumors in multiple organs, such as spleen, liver, and bladder, was observed in experimental animals. Note that OEL-M for o-toluidine remains as 1 ppm (4.4 mg/m$^3$) according to non-carcinogenic health effects. Polychlorinated biphenyls (PCB) was upgraded from group 2A to group 1 because of the increased risk of liver and biliary cancers and malignant melanoma in cohort and case-control studies. Adenomas and carcinomas of the liver were observed in rodents. Note that OEL-M for PCB remains defined as 0.01 mg/m$^3$ according to adverse noncarcinogenic health effects, such as chloracne.

Skin occupational sensitizer classification for trichloroethylene is proposed as group 1 according to the positive results of patch tests of trichloroethylene and its metabolites, chloral hydrate, trichloroethanol, and trichloroacetic acid, in patients with systemic hypersensitivity syndrome and in the guinea pig maximization test.

Among OELs of physical agents, IEC 61252 Ed.1.1 2002-03 and ANSI S1.25-1991 are added as reference measurement methods for noise exposure.

The latest recommendation for OELs (2016-2017) will

appear in the September issue of the Journal of Occupational Health (Volume 58, Number 5), and a brief summary of the proposal will be posted at the Society's website (https://www.sanei.or.jp/oel-eng) in September.

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Conflict of Interest: The committee declares that have no conflicts of interest

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