

Opinion/Recommendation

## Occupational exposure limits for ethylene glycol monobutyl ether, isoprene, isopropyl acetate and propyleneimine, and classifications on carcinogenicity, occupational sensitizer and reproductive toxicant

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

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### Occupational Exposure Limits (OELs) for Chemical Substances

Ethylene glycol monobutyl ether [CAS No. 111-76-2], or 2-butoxyethanol, is a colorless liquid at room temperature (boiling temperature 171.2°C; saturated vapor pressure 0.76 mmHg (20°C)) with a gentle odor and is used as a solvent for paints, print inks, dyes, detergents, brake fluids, pesticides, and plasticizers. The Japan Society of Occupational Health (JSOH) proposes 20 ppm (97 mg/m<sup>3</sup>) as OEL-Ceiling (OEL-C) for ethylene glycol monobutyl ether based on human experience that no strong irritative symptom was observed at 20 ppm for 2 hours<sup>1)</sup>, while the symptom appeared when exposed to 98-195 ppm<sup>2)</sup>. Exposure to concentrations below 20 ppm is expected to pre-

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vent hemolytic anemia and to minimize reproductive toxicity. A skin absorption notation and reproductive toxicant classification of group 2 are proposed.

Isoprene [CAS No. 78-79-5] is an odiferous, colorless, volatile liquid (boiling temperature 34°C; saturated vapor pressure 53.2 kPa (20°C) used as a raw material for producing synthetic and natural rubber, polyisobutylene, and butyl rubber. It is inflammable and may form explosive peroxide if polymerized in the presence of heat or various chemicals. The JSOH proposes 3 ppm (8.4 mg/m<sup>3</sup>) as the OEL-Mean (OEL-M) for isoprene based on toxicity testing results. No-observed-adverse-effect-level (NOAEL) in mice was considered 10 ppm based on observed pathological changes: increase in spinal degeneration at or above 70 ppm within a recovery period in male after 26-week inhalation (70-7000 ppm)<sup>3-5</sup>, increased incidence of Harderian gland adenoma at or above 70 ppm, and local metaplasia in airway and olfactory epithelium at or above 140 ppm (male) and 70 ppm (female) in 40- and 80-week inhalation studies<sup>6,7</sup>. Uncertainty factors of 3 were applied considering that epoxide biotransformation was lower in humans than mice. A carcinogenicity classification of group 2B continued to be indicated.

Isopropyl acetate [CAS No.108-21-4] is a colorless liquid (boiling temperature 89°C; saturated vapor pressure 8.05 kPa (20°C)) with sweet fruity odor. It is used as a solvent for paint or print ink, a medical extractant, a food fragrance, a nail enamel and an enamel remover. The JSOH proposes 100 ppm as the OEL-M for isopropyl acetate, based on the results of an animal study and human volunteer experiments, to prevent effects on the eyes and nasal mucosa. In mice, increased incidence of slight atrophy in the nasal cavity was observed at or above 1000 ppm in a 2-year inhalation study (100-4000 ppm)<sup>8</sup>. Eye irritation was observed at concentrations as low as 200 ppm in a human volunteer study<sup>9</sup>.

Propyleneimine [CAS No. 75-55-8], or 2-methylaziridin, a colorless flammable liquid (boiling temperature 66°C; saturated vapor pressure 112 torr (14.93 kPa)) with an ammonia-like odor, is a reactive alkylating agent used for polymers and intermediates for packaging medium, adhesives, textiles, and calendaring production. The JSOH proposes 0.2 ppm (0.5 mg/m<sup>3</sup>) as a revised OEL-M (from 2 ppm in 1967) based on the results of subsequent animal studies. Lowest-observed-adverse-effect-level (LOAEL) in rats was considered 40 mg/m<sup>3</sup> (17.6 ppm) based on observed effects of renal papillary injury and increase in urinary NAG<sup>10</sup>, as well as hind leg paralysis in week 17 with oral administration<sup>11</sup>. Uncertainty factors of 100 were applied to account for LOAEL to NOAEL conversion and interspecies difference. Skin absorption notation and carcinogenicity classification of group 2B continued to be indicated.

### Classifications on Carcinogenicity, Occupational Sensitizers, and Reproductive Toxicant

Regarding carcinogenicity classification, benzo[a]pyrene is proposed to be a group 1 carcinogen with limited epidemiological evidence but sufficient evidence in animal experiments and mechanistic studies. Proposed group 2A carcinogens are formaldehyde (no change), indium and compounds (inorganic, hardly soluble) (no change) and 1,3-propane sultone. Proposed 2B carcinogens are 1-bromopropane, 3-chloro-2-methylpropene (no change), 2,4-D, DDT (no change), *N,N*-dimethyl-*p*-toluidine, molybdenum trioxide, perfluorooctanoic acid, polybrominated biphenyls (no change), and tetrafluoroethylene (no change). The reference values corresponding to an individual excess lifetime risk of cancer for vinyl chloride are proposed to be 1.5 ppm for 10<sup>-3</sup> risk of cancer and 0.15 ppm for 10<sup>-4</sup>, applying the relative risk model in reference to liver cancer mortality in Japan. Skin occupational sensitizer classifications for diethanolamine and ethyl acrylate are proposed as group 2, and that for isophorone diisocyanate as group 3. The reproductive toxicant classification for 2-ethyl-1-hexanol is proposed as group 3.

The latest OEL recommendations (2017-2018) will appear in the September issue of the Journal of Occupational Health (Volume 59, Number 5). A brief summary of the proposal will be posted at the society's website (<https://www.sanei.or.jp/oel-eng>) in September.

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

*Conflicts of interest:* The committee declares that have no conflicts of interest.

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