

Opinion/Recommendation

Occupational Exposure Limits for ethylidene norbornene, ethyleneimine, benomyl, and 2,3-epoxypropyl methacrylate, and classifications on carcinogenicity

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

Atsuko Araki¹, Kenichi Azuma², Ginji Endo³, Yoko Endo^{*}, Tetsuhito Fukushima⁴, Kunio Hara⁵, Hajime Hori⁵, Seichi Horie⁵, Hyogo Horiguchi⁶, Masayoshi Ichiba⁷, Gaku Ichihara⁸, Masayuki Ikeda⁹, Tatsuya Ishitake¹⁰, Akiyoshi Ito⁵, Yuki Ito¹¹, Satoko Iwasawa¹², Takeyasu Kakumu⁴, Michihiro Kamijima¹¹, Kanae Karita¹³, Takahiko Katoh¹⁴, Toshio Kawai^{*}, Toshihiro Kawamoto⁵, Shinji Kumagai^{*}, Yukinori Kusaka¹⁵, Akiko Matsumoto⁷, Muneyuki Miyagawa¹⁶, Hiroyuki Miyauchi⁵, Yasuo Morimoto⁵, Kasuke Nagano^{*}, Hisao Naito¹⁷, Tamie Nakajima¹⁸, Makiko Nakano¹⁹, Tetsuo Nomiyama²⁰, Hirokazu Okuda²¹, Masayuki Okuda²², Kazuyuki Omae¹⁹, Haruhiko Sakurai¹⁹, Kazuhiro Sato¹⁵, Tomotaka Sobue²³, Yasushi Suwazono²⁴, Toru Takebayashi^{19,‡}, Tatsuya Takeshita²⁵, Akito Takeuchi³, Ayano Takeuchi¹⁹, Masatoshi Tanaka⁴, Shigeru Tanaka²⁶, Teruomi Tsukahara²⁰, Masashi Tsunoda¹², Susumu Ueno⁵, Jun Ueyama²⁷, Yumi Umeda²¹, Kenya Yamamoto²⁸, Yuko Yamano²⁹, Takenori Yamauchi²⁹ and Eiji Yano¹⁶

¹Hokkaido University, ²Kindai University, ³Japan Industrial Safety and Health Association, ⁴Fukushima Medical University, ⁵University of Occupational and Environmental Health, Japan, ⁶Kitasato University, ⁷Saga University, ⁸Tokyo University of Science, ⁹Kyoto University, ¹⁰Kurume University, ¹¹Nagoya City University, ¹²National Defense Medical College, ¹³Kyorin University, ¹⁴Kumamoto University, ¹⁵University of Fukui, ¹⁶Teikyo University, ¹⁷Fujita Health University, ¹⁸Chubu University, ¹⁹Keio University, ²⁰Shinshu University, ²¹Japan Bioassay Research Center, ²²Yamaguchi University, ²³Osaka University, ²⁴Chiba University, ²⁵Wakayama Medical University, ²⁶Jumonji University, ²⁷Nagoya University, ²⁸The University of Tokyo, ²⁹Showa University, [‡]corresponding author and ^{*}independent consultant

(J Occup Health 2018; 60: 333-335)
doi: 10.1539/joh.2018-0137-OP

Journal of Occupational Health is an Open Access article distributed under the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License. To view the details of this license, please visit (<https://creativecommons.org/licenses/by-nc-sa/4.0/>).

Received June 5, 2018; Accepted June 19, 2018

Published online in J-STAGE July 6, 2018

Correspondence to: T. Takebayashi, Department of Preventive Medicine and Public Health, School of Medicine, Keio University (e-mail: ttakebayashi@keio.jp)

Key words: 2,3-epoxypropyl methacrylate, benomyl, carcinogenicity, ethyleneimine, ethylidene norbornene, Occupational Exposure Limit

Occupational Exposure Limits (OELs) for Chemical Substances

Ethylidene norbornene [CAS No. 16219-75-3] is a white to colorless liquid (boiling point 148°C, vapor pressure 560 Pa (20°C)) with a characteristic odor used for the production of automobile synthetic rubber products, ethylene propylene diene methylene linkage. The OEL-Mean of 2 ppm (10 mg/m³) is proposed based on the results of animal experiments¹⁾. In the 14-week inhalation exposure

experiment (5 to 150 ppm) with Fischer 344 rats, swelling and crust formation around the eyes were observed in the female group of 5 ppm or more, and the effects on the thyroid gland (*e.g.*, follicular colloid reduction, hypertrophy, and hyperplasia of follicular epithelial cells, etc.) was observed in the group of 25 ppm or more in males and females. Although the implantation rate and the fertility rate decreased in animals and the incidence of skeletal mutation of the three species of pediatric animals was increased, these effects were observed at concentrations where an increase in the relative weight of the liver to the mother was observed. Thus, we propose the Group 3 for reproductive toxicity²⁾.

Ethyleneimine [CAS No. 151-56-4] is a colorless corrosive liquid with ammonia odor (boiling point 56°C) and vapor pressure of 160 torr (21.33 kPa) (20°C). It is used as production raw materials of pharmaceutical intermediate, polyethyleneimine, amino ethylation acrylic polymers, and the aziridine-based crosslinking agent. This chemical was recommended at 0.5 ppm (0.88 mg/m³) for OEL-M in 1966, added a skin absorption mark in 1990, categorized Group 2B for class of carcinogenicity in 2001, and was classified Group 3 as a reproductive toxicant in 2014. The Japan Society for Occupational Health (JSOH) reevaluated the OEL and other classifications by examining subsequent reports this time. The JSOH proposes 0.05 ppm (0.09 mg/m³) as OEL-M for ethyleneimine based on the results that observed effects such as bronchitis and liver and renal denaturation in a rat inhalation experiment^{3,4)} of 10 mg/m³ (5.7ppm) for 4 hr/day and 1.5 months, and the reproductive toxicity such as decreases in the pregnancy rate exposed to 10 mg/m³ of ethyleneimine among pregnancy rats⁴⁾. The skin absorbency, a carcinogenic classification (Group 2B), and a genotoxicity classification (Group 3) remains the same.

Benomyl [CAS No.17804-35-2] is a carbamate fungicide broadly used for rice, wheat, fruits, vegetables, and flowers, among others, and benomyl wettable powder and benomyl-tiuram wettable powder are registered pesticides in Japan. Benomyl is a white crystalline solid (melting point: 140°C with decomposition, vapor pressure: 5.0 × 10⁻⁶ Pa or lower [25°C]) and is unstable in water. After decomposition, benomyl is converted to carbendazim (metabolite). The OEL-M of 1 mg/m³ for benomyl is newly proposed based on the results of a 90-day nose-only inhalation toxicity study in Sprague-Dawley rats (10, 50 and 200 mg/m³)⁵⁾, in which olfactory-epithelial degeneration was observed in the 50 mg/m³ and higher groups in male and in the 200 mg/m³ group in female. In addition, we propose the classification of benomyl into the second group of both skin sensitization and reproductive toxicity from the results of the animal experiments. Furthermore, since the exposure level below the OEL still requires caution according to an experimental result using pregnant female rats, we notify “#” indication for beno-

myl to call for attention⁶⁾.

2,3-Epoxypropyl methacrylate (Glycidyl methacrylate, GMA) [CAS No. 106-91-2] is a colorless liquid with a characteristic odor (boiling point 189°C, vapor pressure of 0.42 kPa at 25°C) that reacts violently with strong acids, strong bases, and strong oxidants with the generation of fire hazard. It is used mainly as a raw material in the manufacture of acrylic resin, diluent of epoxide-based adhesive, stabilizing agent of polyvinyl chloride, ion-exchange resin, and binder of printing ink. The results of carcinogenicity and genotoxicity studies suggested a possible non-threshold carcinogen for rodents. However, because there is no available scientific knowledge of carcinogenicity in humans, assessing a dose-response relationship in human as a non-threshold carcinogen admits to large uncertainty. Therefore, the JSOH proposes 0.01 ppm (0.06 mg/m³) as the OEL-M for GMA, according to the dose-dependent pathological changes in olfactory and respiratory epithelia in the nasal cavity at concentrations of ≥0.6 ppm in the results of 2-year inhalation studies of B6D2F1/Crlj mice (0.6-10 ppm)⁷⁾. In the assessment, an uncertainty factor for the severity of carcinogenic effect was taken into account. There was sufficient evidence in rats and mice of the carcinogenicity of GMA. The carcinogenicity classification is proposed as Group 2A. In the evaluation, it was taken into account that GMA is mutagenic in a wide range of in-vivo and in-vitro test systems. The OEL-M was set based on the non-carcinogenic effects. Thus, ψ notation is indicated for attention message. Skin absorption notation is indicated and skin occupational sensitizer classification is proposed as Group 2. The reproductive toxicant classification is proposed as Group 3.

Classifications on Carcinogenicity

Regarding the carcinogenicity classification, 2-nitrotoluene is proposed to be a Group 2A carcinogen. The proposed Group 2B carcinogens are vinylidene chloride, quinoline, diazinon, 2,4,6-Trichlorophenol, pyridine, 1-tert-Butoxypropan-2-ol, malathion and β-Myrcene.

The latest OEL recommendations (2018-2019) will appear in the September issue of the Journal of Occupational Health (Volume 60, Number 5). A brief summary of the proposal will be posted on the society's website (<https://www.sanei.or.jp/oel-eng>) in September.

Contributors: All the authors contributed to the 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 the other authors' feedback.

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

References

- 1) Ballantyne B, Norris JC, Dodd DE, et al. Short-term and sub-chronic repeated exposure studies with 5-ethylidene-2-norbornene vapor in the rat. *Journal of Applied Toxicology* 1997; 17(4): 197-210.
- 2) Neepier-Bradley TL, Ballantyne B. Absence of dominant lethal effects in male CD rats exposed to 5-ethylidene-2-norbornene vapor. *Toxic Substance Mechanisms* 1996; 15(4): 389-404.
- 3) ACGIH. Ethyleneimine. In: ACGIH, editor. Documentation of TLVs and BEIs. Ohio: ACGIH; 2009.
- 4) IARC. Aziridine. IARC Monogr Eval Carcinog Risk Humans 1975; 9: 37-46.
- 5) Warheit DB, Kelly DP, Carakostas MC, et al. A 90-day inhalation toxicity study with benomyl in rats. *Toxicological Sciences* 1989; 12(2): 333-345.
- 6) Ellis WG, Semple JL, Hoogenboom ER, et al. Benomyl-induced craniocerebral anomalies in fetuses of adequately nourished and protein-deprived rats. *Teratogenesis, carcinogenesis, and mutagenesis* 1987; 7(4): 357-375.
- 7) Japan Bioassay Research Center (JBRC). Report on carcinogenicity study of 2,3-epoxypropyl methacrylate in mice by two-year inhalation exposure: study no 0795; Hadano. Kanagawa: JBRC; 2015. (in Japanese).