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 Endo4, Tetsuhiito Fukushima4, Kunio Harag, Hajime Horie5, Seichi Horie5, Hyogo Horiguchi6, Masayoshi Ichiba7, Gaku Ichihara8, Masayuki Ikeda9, Tetsuya Ishitake10, Akiyoshi Ito11, Yuki Ito11, Satoko Iwasawa12, Takeyasu Kakumur, Michihiro Kamijima11, Kanae Karita13, Takahiko Katoh14, Toshihiko Kawai16, Toshihiro Kawamoto5, Shinji Kumagai8, Yukinori Kusaka15, Akiko Matsumoto1, Muneyuki Miyagawa16, Hiroyuki Miyauchi4, Yasuo Morimoto1, Kasuke Nagano16, Hisao Naito17, Tamie Nakajima18, Makiko Nakano19, Tetsuo Nomiyama20, Hirokazu Okuda21, Masayuki Okuda22, Kazuyuki Omae19, Haruhiko Sakurai19, Kazuhiro Sato15, Tomotaka Sobue23, Yasushi Suwazono24, Toru Takebayashi19, Tatsuya Takeshita24, Akito Takeuchi, Ayano Takeuchi, Masatoshi Tanaka4, Shigeru Tanaka26, Teruomi Tsukahara20, Masashi Tsunoda12, Susumu Ueno1, Jun Ueyama27, Yumi Umeda21, Kenya Yamamoto8, 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, 6Fukusato 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, 1corresponding author and 2independent consultant

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 experiments. 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 toxicity.

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 intermediates, polyethyleneimine, amino ethylamine 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 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 rats.

Benomyl [CAS No.17804-35-2] is a carbamate fungicide broadly used for rice, wheat, fruits, vegetables, and flowers, among others, and benomyl-tiuram wettable powder are registered pesticides in Japan. Benomyl is a white crystalline solid (melting point: 140°C with decomposition, vapor pressure: 5.0×10² 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), 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 benomyl to call for attention.

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).

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.


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


