

inhalation exposure to 1,4-dioxane induces nasal and hepatic tumors, suggestive of the urgent need for a 2-yr bioassay study of rodent carcinogenicity for 1,4-dioxane.

## REFERENCES

- American Conference of Governmental Industrial Hygienists. 2001. 1,4-Dioxane. In *Documentation of the threshold limit values (TLVs) and biological exposure indices (BEIs)* [CD-ROM]. Cincinnati, OH: ACGIH.
- Also, S., Arito, H., Nishizawa, T., Nagano, K., Yamamoto, S., and Matsushima, T. 2005. Thirteen-week inhalation toxicity of *p*-dichlorobenzene in mice and rats. *J. Occup. Health* 47:249–260.
- Agency for Toxic Substances and Disease Registry. 2007. *Toxicological profiles for 1,4-dioxane*. U.S. Department of Health and Human Services. <http://www.atsdr.cdc.gov/toxprofiles/tp187-c6.pdf> (accessed December 20, 2007).
- Bannasch, P., Griesemer, R. A., Anders, F., Becker, R., Cabral, J. R., Della Porta, G., Feron, V. J., Henschler, D., Ito, N., Kroes, R., Magee, P. N., McKnight, B., Mohr, U., Montesano, R., Napalkov, N. P., Nesnow, S., Pegg, A. E., Rao, G. N., Turusov, V. S., Wahrendorf, J., and Wilbourn, J. 1986. Long-term assays for carcinogenicity in animals. In *Long-term and short-term assays for carcinogens: A critical appraisal*, eds. R. Montesano, H. Bartsch, H. Vainio, J. Wilbourn, and H. Yamasaki, pp. 13–83. IARC scientific publication no. 83. Lyon: IARC.
- Barns, D. G., and Dourson, M. 1988. Reference dose (RfD): Description and use in health risk assessments. *Regul. Toxicol. Pharmacol.* 8:471–486.
- Budavari, S. 1989. *The Merck index*, 11th ed. Rahway, NJ: Merck & Co.
- Braun, W. H., and Young, J. D. 1977. Identification of  $\beta$ -hydroxyethoxyacetic acid as the major urinary metabolite of 1,4-dioxane in the rat. *Toxicol. Appl. Pharmacol.* 39:33–38.
- Chemical Daily. 2006. 1,4-Dioxane. In *Chemical products handbook 14906*, pp. 834–835. Tokyo: Chemical Daily Co. Ltd. (in Japanese).
- DeRosa, C. T., Wilbur, S., Holler, J., Richter, P., and Stevens, Y. 1996. Health evaluation of 1,4-dioxane. *Toxicol. Ind. Health* 12:1–43.
- Deutsche Forschungsgemeinschaft. 2003. 1,4-Dioxane. In *Occupational toxicants. Critical data evaluation for MAK values and classification of carcinogens*, Vol. 20, ed. H. Greim, pp. 105–133. Weinheim, Germany: Wiley–VCH.
- European Union Risk Assessment Report. 2002. *1,4-Dioxane*. Vol. 21, PL–2. Ispra: Institute for Health and Consumer Protection, European Chemicals Bureau.
- Fowlie, A. J., Grasso, P., and Benford, D. J. 1990. The short-term effects of carcinogens and sulphur dioxide on the nuclear size of rat nasal epithelial cells. *J. Appl. Toxicol.* 10:29–38.
- Grant, D., and Grasso, P. 1978. Suppression of HeLa cell growth and increase in nuclear size by chemical carcinogen: a possible screening method. *Mutat. Res.* 57:369–380.
- Hecht, S. S., and Young, R. 1981. Metabolic  $\alpha$ -hydroxylation of *N*-nitrosomorpholine and 3,3,5,5-tetradeutero-*N*-nitrosomorpholine in the F344 rat. *Cancer Res.* 41:5039–5043.
- Hirsch, A. R., and Zavala, G. 1999. Long term effects on the olfactory system of exposure to hydrogen sulphide. *Occup. Environ. Med.* 56:284–287.
- International Agency for Research on Cancer. 1999. 1,4-Dioxane. Re-evaluation of some organic chemicals, hydrazine and hydrogen peroxide. *IARC Monogr. Eval. Carcinogen. Risk Hum.* 71:589–602.
- International Programme on Chemical Safety. 1994. *Assessing human health risks of chemicals: Derivation of guidance values for health-based exposure limits*. Environmental health criteria 170. Geneva: WHO. <http://www.inchem.org/documents/ehc/ehc/ehc170.htm> (accessed December 7, 2007).
- Ito, N., Tsuda, H., Tatematsu, M., Inoue, T., Tagawa, Y., Aoki, T., Uwagawa, S., Kagawa, M., Ogiso, T., Masui, T., Imaida, K., Fukushima, S., and Asamoto, M. 1988. Enhancing effect of various hepatocarcinogens on induction of preneoplastic glutathione S-transferase placental form positive foci in rats—An approach for a new medium-term bioassay system. *Carcinogenesis* 9:387–394.
- Japan Ministry of the Environment. 2007. *Pollutant release and transfer register, Fiscal year 2005*. Environmental Health and Safety Division, Environmental Health Department, Japan Ministry of the Environment. <http://www.env.go.jp/chemi/prtr/result/gaiyo.html> (accessed June 19, 2007) (in Japanese).
- Japan Ministry of the Environment. 2002. *Chemicals in the environment, Fiscal year 2001*. Tokyo: Environmental Health and Safety Division, Environmental Health Department, Japan Ministry of the Environment (in Japanese).
- Japan Society for Occupational Health. 1984. 1,4-Dioxane. Documentation for recommendation of occupational exposure limit value for 1,4-dioxane. *Jpn. J. Ind. Health* 26:354–355. (in Japanese).
- Johnstone, R. T. 1959. Death due to dioxane? *AMA Arch. Ind. Health* 20:445–447.
- Kano, H., Umeda, Y., Saito, M., Senoh, H., Ohbayashi, H., Aiso, S., Yamazaki, K., Nagano K., and Fukushima, S. 2008. Thirteen-week oral toxicity of 1,4-dioxane in rats and mice. *J. Toxicol. Sci.* 33:141–153.
- Lewis, R. J. 1993. *Hawley's condensed chemical dictionary*, 12th ed. New York: Van Nostrand Reinhold.
- Mauderly, J. L., Tesarek, J. E., Sifford, L. J., and Sifford, L. J. 1979. Respiratory measurements of unsedated small laboratory mammals using nonrebreathing valves. *Lab. Anim. Sci.* 29:323–329.
- Morita, T., and Hayashi, M. 1998. 1,4-Dioxane is not mutagenic in five *in vitro* assays and mouse peripheral blood micronucleus assay, but is in mouse liver micronucleus assay. *Environ. Mol. Mutagen.* 32:269–280.
- Nagano, K., Katagiri, T., Aiso, S., Senoh, H., Sakura, Y., and Takeuchi, T. 1997. Spontaneous lesions of nasal cavity in aging F344 rats and BDF1 mice. *Exp. Toxicol. Pathol.* 49:97–104.
- Nannelli, A., De Rubertis A., Longo, V., and Gervasi, P. G. 2005. Effects of dioxane on cytochrome P450 enzymes in liver, kidney, lung and nasal mucosa of rat. *Arch. Toxicol.* 79:74–82.
- National Institute for Occupational Safety and Health. 1977. *Criteria for a recommended standard occupational exposure to dioxane*. U.S. Department of Health, Education and Welfare, Centers for Disease Control. Cincinnati, OH: NIOSH.
- National Research Council. 1977. *Guide for the care and use of laboratory animals*. DHEW Publication No. (NIH) 77–23. Bethesda, MD: NIH.
- Organization for Economic Cooperation and Development. 1981. Test guideline 413, Subchronic inhalation toxicity: 90-Day study. In *OECD guidelines for the testing of chemicals*, pp. 1–9. Paris: OECD.
- Parkinson, A. 2001. Biotransformation of xenobiotics. In *Casaretti and Doull's toxicology*, 6th ed., ed. C. D. Klassen, pp. 133–224, New York: McGraw-Hill.
- Rowe, V. K., and Wolf, M. A. 1982. Dioxane. In *Patty's industrial hygiene and toxicology*, 3rd rev. ed., Vol. 2C, eds. G. D. Clayton, and F. E. Clayton, pp. 3947–3956. New York: John Wiley & Sons.

- Sato, K., Kitahara, A., Satoh, K., Ishikawa, T., Tatematsu, M., and Ito, N. 1984. The placental form of glutathione S-transferase as a new marker protein for preneoplasia in rat chemical hepatocarcinogenesis. *Gann* 75:199-202.
- Sontag, J. M., Page, N. P., and Saffiotti, U. 1976. *Guidelines for carcinogen bioassay in small rodents*. NCI-CG-TR-1. Washington, DC: Department of Health, Education, and Welfare.
- Tatematsu, M., Mera, Y., Ito, N., Satoh, K., and Sato, K. 1985. Relative merits of immunohistochemical demonstrations of placental, A, B and C forms of glutathione S-transferase and histochemical demonstration of  $\gamma$ -glutamyl transferase as markers of altered foci during liver carcinogenesis in rats. *Carcinogenesis* 6:1621-1626.
- Torkelson, T. R., Leong, B. K. J., Kociba, R. J., Richter, W. A., and Gehring, P. J. 1974. 1,4-Dioxane. II. Results of a 2-year inhalation study in rats. *Toxicol. Appl. Pharmacol.* 30:287-298.
- Tvedt, B., Skyberg, K., Aaserud, O., Hobbesland, Å., and Mathiesen, T. 1991. Brain damage caused by hydrogen sulfide: A follow-up study of six patients. *Am. J. Ind. Med.* 20:91-101.
- Vyberg, M., and Nielsen, S. 1998. Dextran polymer conjugate two-step visualization system for immunohistochemistry. A comparison of EnVision+ with two three-step avidin-biotin techniques. *Appl. Immunohistochem.* 6:3-10.
- Young, J. D., Braun, W. H., and Gehring, P. J. 1978. The dose-dependent fate of 1,4-dioxane in rats. *J. Environ. Pathol. Toxicol.* 2:263-282.
- Woo, Y. T., Argus, M. F., and Arcos, J. C. 1978. Effect of mixed-function oxidase modifiers on metabolism and toxicity of the oncogen dioxane. *Cancer Res.* 38:1621-1625.

