Absence of Long-Term Human Health Hazards from Exposure to Glutaraldehyde

Based on extensive laboratory studies to date, glutaraldehyde is not classified as a teratogen, an *in vivo*[1] mutagen, or carcinogen. Several laboratory studies[2] have shown that glutaraldehyde does not produce reproductive, teratogenic, embrofetal, or carcinogenic effects. Glutaraldehyde induces genotoxicity in some *in vitro* assays; however, the weight of evidence indicates glutaraldehyde is not an *in vivo* genotoxicant under normal exposure conditions. Epidemiology[3] studies have shown that glutaraldehyde can be safely handled in the workplace when good industrial hygiene practices have been followed.

Developmental Toxicity[4]

Several studies have shown that glutaraldehyde does not produce fetotoxic, embryotoxic, or teratogenic effects.[5]

Reproductive Toxicity

Repeated exposure studies, conducted by various routes and at glutaraldehyde concentrations substantially greater than levels encountered under normal use patterns, indicate a lack of harmful effects to the male and female reproductive tract. There were no harmful effects to male germ cells in a dominant lethal study. No reproductive toxicity occurred in a recent two-generation reproduction study.

Genotoxicity[6]

The genotoxic potential of glutaraldehyde has been extensively studied using *in vitro* and *in vivo* test systems. While *in vitro* assays using cultured bacteria cells yield positive results in some strains, *in vitro* assays have not been predictive of *in vivo* study results using live animals. *In vivo* studies have been uniformly negative, exhibiting no genotoxic effects. No genotoxic potential was demonstrated *in vivo* in a bone marrow cytogenetic study, unscheduled DNA synthesis test, micronucleus study, dominant lethal assay, and sex-linked recessive lethal and reciprocal translocation assays. The difference in results between *in vitro* and *in vivo* assays is not unexpected, based on the ability of the body to rapidly metabolize glutaraldehyde, and to promptly eliminate glutaraldehyde and its metabolites from the bloodstream. Furthermore, the reactivity of glutaraldehyde with tissue proteins limits the ability of the chemcial to reach the genetic material in living animals.

Glutaraldehyde has been examined for mutagenic activity using a wide variety of *in vitro* assays in bacterial and mammalian systems, using tests such as bacterial reverse (Ames) and forward mutation assays, TRp+ reversion, ß-galactosidase induction, other enzyme induction, DNA repair, sister chromatid exchange, unscheduled DNA synthesis, etc. The weight of evidence indicate glutaraldehyde is not an *in vivo* genotoxicant under normal use conditions.

Form No. 253-01444-02/01/02

Chronic Toxicity and Oncogenicity

Based on three chronic studies (2 in rats and 1 in mice), glutaraldehyde is not classified as a carcinogen. In inhalation carcinogenicity studies, where rats and mice were exposed "whole body," no exposure related neoplastic lesions were observed. However, exposure to glutaraldehyde did result in non-neoplastic lesions and inflammation of the nose of both rats and mice.

No evidence of carcinogenic potential were found in these studies.[7]

In a study involving lifetime exposure to glutaraldehyde in drinking water, the only indication of any oncogenic potential was an increased incidence in female, but not male, Fischer 344 rats of large granular cell lymphocytic leukemia. An independent panel of pathology experts reviewed the incidence and stage of involvement of large granular cell lymphocytic (LGL) leukemia to render an opinion on the biological significance of this finding and its relevance for human risk assessment. The expert panel concluded that although the incidence was increased in all treated groups of rats, the dose-response was not proportional despite a 20-fold difference in dosage between the lowest and highest dose levels. Furthermore, the most advanced stages of leukemia occurred in female control rats while the earlier stages of leukemia were greatest in the highest dose group. Although the observed increase in LGL leukemia in female rats had an uncertain relationship to ingestion of glutaraldehyde in the drinking water, the expert panel determined that a finding of increased LGL leukemia in one sex, one species and one strain is not toxicologically relevant to human risk assessment.[8]

Target organ systemic toxicity was not seen in the chronic drinking water study.

Epidemiology Studies

Recent epidemiology studies have shown that glutaraldehyde can be safely handled in conditions of potential industrial exposure where good industrial hygiene practices have been followed. The first study reviewed the mortality patterns of 186 workers employed in a glutaraldehyde production unit between 1959 and 1988. Since 1977, glutaraldehyde vapor concentrations were routinely monitored. Concentrations ranged from 0.01 to 0.17 ppmv, generally averaging 0.05 ppmv. These workers had lower death rates overall and lower cancer death rates than the general population. There were no deaths due to leukemia. Furthermore, there was no increase in cancer with increasing duration of service in the glutaraldehyde production unit.

A second study examined medical records for the occurrence of ocular, skin, and respiratory sensitization in the same group of workers between 1959 and 1992, and additionally in those actively working in glutaraldehyde production or distribution in 1992. While several workers among the group were sensitized to some other industrial chemicals, none showed any sensitization to glutaraldehyde, either by skin or eye contact or by inhalation.

In three extensive human exposure assessments[9, 10, 11] examining the correlation between glutaraldehyde exposure and occupational asthma, none of these studies identified occupational asthma cases among cohorts of workers with the greatest potential glutaraldehyde exposures. Vyas et al., the most extensive study of its kind available to date, demonstrated occular, nasal or lower respiratory symptoms in the majority of nurses examined in the cohort. Of the 340 nurses involved in the study, 232 (approx. 2/3) exhibited some irritant symptoms. Only nasal symptoms, however, showed a statistically significant relationship to peak vapor levels. Significantly, in this large group of nurses, there was no evidence of asthma and no clinical or objective findings that glutaraldehyde is a respiratory sensitizer.

Footnotes

1. *In vivo* means in the living tissues of a plant or animal, as opposed to *in vitro,* which is outside the living body and in an artificial environment. Hence, *in vivo* studies are carried out in living organisms, and *in vitro* studies in culture media.

2. Union Carbide Corporation, A Subsidiary of The Dow Chemical Company. "Toxicology of Glutaraldehyde: Review of Studies and Human Health Effects," revised 1995. An extensive review of published information on toxicological studies and human health effects of glutaraldehyde, covering over 30 years of scientific investigation. Prepared by Bryan Ballantyne, M.D., D.Sc., Ph.D., Director of Applied Toxicology for Union Carbide Corporation.

3. Epidemiology is the study of diseases in human populations.

4. Developmental toxicity is the study of the potential for chemicals to produce adverse effects on the development of the embryo and fetus by maternal exposure.

5. Teratogenicity is the potential for a chemical to induce structural malformations and/or functional disturbances in conceptus which persist into postnatal life.

6. Chun, J.S. and Neeper-Bradley (1994). Glutaraldehyde: two-generation reproduction study in the drinking water of CD® rats. 92U1059 Conducted at Bushy Run Research Center for the Union Carbide Chemical and Plastics Company, Report of The Dow Chemical Company, Midland, MI.

7. National Toxicology Program. Toxicology and carcinogenesis studies of glutaraldehyde (CAS No. 111-30-8) in F344/N rats and B6C3F1 mice (inhalation studies). Technical Report Series No. 490. NIH Publication No. 99-3980, Department of Health and Human Services, Research Triangle Park, NC, September 1999.

8. Hardisty, J.F. (2003). Pathology peer review and pathology working group (PWG) review of large granular lymphocyte leukemia (LGL) in a combined chronic toxicity/oncogenicity study in the drinking water with glutaraldehyde in female Fischer 344 rats. Internal Report of The Dow Chemical Company, Midland, MI.

9. Teta, M.J. *et al.,* (1995). Absence of sensitization and cancer increases among glutaraldehyde workers. Tox. Subs. Mechanisms, 14:293-305.

10. Pisaniello D.L., Gun R. T., Tkaczuk M.N., Nitschke M. and Crea J. (1997). Glutaraldehyde exposures and symptoms among endoscopy nurses in south Australia. Appl. Occup. Environ. Hyg. 12(3): 171-177.

11. Vyas A., Pickering C.A.C., Oldham L.A., Francis H.C., Fletcher A.M. and Merrett T. (2000). Occup Environ Med, 57: 752-759.

For further information visit our website: www.dowbiocides.com or call…

United States and Canada:	1-800-447-4369 (phone) 1-989-832-1560 (phone) 1-989-832-1465 (fax)
Europe:	800-3-694-6367 (phone) 32-3-450-2240 (phone) 32-3-450-2815 (fax)
Pacific:	603-7958-3392 (phone) 603-7958-5598 (fax)
Latin America:	55-11-5188-9555 (phone) 55-11-5188-9937 (fax)
Other Global Areas:	1-989-832-1560 (phone) 1-989-832-1465 (fax)

Printed in U.S.A.

Form No. 253-01444-02/01/02