

ii. *References.* a. Clariant GmbH, 2000. Unpublished. Letter of Dr. Kreiling dated 23.08.2000. Dow Chemical Co., 1987. Monochloroacetic acid: an acute vapor inhalation limit study with Fischer 344 rats. Unpublished Report, Dow Chemical Company, Midland, USA.

b. Maksimov, G.G. and O.N. Dubinina, 1974. Materials of experimental substantiation of maximally permissible concentration of monochloroacetic acid in the air of production area. *Gigiena Truda i Professional nye Zabolevaniya*. 9:32–35.

c. Rogers D.R. 1995. Accidental fatal monochloroacetic acid poisoning. *American Journal of Forensic Medicine and Pathology*. 16:115–116.

5. *Fluorine*—i. *Description.* Fluorine is a reactive, highly irritating and corrosive gas used in the nuclear energy industry, as an oxidizer of liquid rocket fuels, and in the manufacture of various fluorides and fluorocarbons. Fluorine is a severe irritant to the eyes, mucous membranes, lungs, and skin; the eyes and the respiratory tract are the target organ/tissues of an acute inhalation exposure. Death is due to pulmonary edema. Data on irritant effects in humans and lethal and sublethal effects in five species of mammals (dog, rat, mouse, guinea pig, and rabbit) were available for development of AEGL values.

Regression analyses of the concentration-exposure durations (for the fixed endpoint of mortality) for all of the animal species reported in the key study (Keplinger and Suissa 1968) determined that the relationship between concentration and time is  $C^n \times t = k$ , where  $n =$  approximately 2 (actual value of  $n$  for the most sensitive species in irritation and lethality studies, the mouse, is 1.77). This concentration exposure duration relationship was applied both the AEGL-2 and AEGL-3 levels because the irritant and corrosive action of fluorine on the respiratory tissues differs by only a matter of degree for these AEGL levels:

a. Respiratory irritation with edema resulting in mild, reversible lung congestion, and

b. Severe respiratory irritation resulting in severe lung congestion. Although the data base for fluorine is small, the data from the key study, augmented with data from several other studies, were considered adequate for derivation of the three AEGL classifications for four time periods.

The AEGL-1 was based on the observation that human volunteers could tolerate exposure to 10 ppm for 15 minutes without irritant effects (Keplinger and Suissa 1968). Although

this value is below the definition of an AEGL-1 (notable discomfort), it provides the longest exposure duration for which no irritation in humans was reported. An intraspecies uncertainty factor of 3 was applied because fluorine is highly corrosive to the tissues of the respiratory tract and effects are not expected to vary greatly among individuals, including susceptible individuals. Although no data on asthmatics were found, the uncertainty factor of 3 was considered adequate to protect this sensitive subpopulation because the value was a NOAEL and because shorter-term, repeated exposures produced no substantially greater effects in healthy individuals. The value is supported by a second study in which volunteers “tolerated” exposure to 10 ppm for an undefined period of time. Furthermore, occupational exposure concentrations for healthy adults have ranged up to 17 ppm, albeit for short, undefined periods of time (Lyon 1962). A modifying factor of 2 was applied based on a limited data base. The resulting value of 1.7 ppm was used across all AEGL-1 exposure durations because at mildly irritating concentrations there is accommodation to irritating gases. As noted, this value is supported by limited workplace monitoring data: Workers exposed to fluorine at average yearly concentrations up to 1.2 ppm (range, 0.0–17 ppm) over a 4-year period reported fewer incidences of respiratory complaints or diseases than a similar group of nonexposed workers (Lyon 1962). The workers are assumed to encompass a small range of sensitivity; the additional intraspecies uncertainty factor of 3 was considered sufficient to protect sensitive individuals.

Mild lung congestion was selected as the threshold for irreversible, long-lasting effects as defined by the AEGL-2. The AEGL-2 was based on an animal study in which mild lung congestion was observed in mice at 67 ppm for 30 minutes and 30 ppm for 60 minutes (Keplinger and Suissa 1968). Effects were slightly less serious in three other species. Although concentrations causing irritant effects or lethality for three other species for the same time periods suggested similar species sensitivity, the mouse data, because of slightly lower values, were chosen as the basis for developing the AEGL-2 and AEGL-3. Because similar sensitivity was observed among five species in the key study, no uncertainty factor for interspecies variability was applied. Fluorine is a highly corrosive gas that reacts directly with the tissues of the respiratory tract, with no pharmacokinetic component involved

in the toxicity; therefore, there is likely to be little difference among individuals in response to fluorine at concentrations that define the AEGL-2. The 30- and 60-minute values for the mouse were divided by an intraspecies uncertainty factor of 3 to protect sensitive individuals, since effects are not likely to differ greatly among individuals, and by a modifying factor of 2, based on a limited data base. The 30-minute value was used for the 10- and 30-minute AEGL-2 and the 60-minute value was used for the 60-minute AEGL-2. The 4-hour AEGL-2 value was scaled from the 60-minute value based on the  $C^{1.77} \times t = k$  relationship. The value of  $n$  was derived from regression analysis of the mouse lethality data in the key study. The 8-hour-AEGL-2 value was set equal to the 4-hour value because at low concentrations the hygroscopic fluorine would react with and/or be scrubbed by the nasal passages and because at low concentrations there is accommodation to irritant gases. The 10- and 3-minute AEGL-2 values are supported by studies in which human volunteers found short-term exposures to 15–25 ppm irritating to the eyes, nose, and throat (Rickey 1959; Keplinger and Suissa 1968).

The AEGL-3 values were derived from the highest exposures that resulted in no deaths in five species over four exposure durations (13 tests) for up to 45 days post exposure, but did produce severe lung congestion in the mouse (Keplinger and Suissa 1968). Severe lung congestion in the sensitive mouse was considered the threshold for lethality as defined by the AEGL-3. For the mouse, the 60-minute value was 75 ppm. Because of the similar species sensitivity in the key study, based on both irritant effects and lethality, no uncertainty factor for interspecies variability was applied. The values were divided by an uncertainty factor of 3 to protect sensitive individuals (fluorine is a highly reactive, corrosive gas whose effect on respiratory tract tissues is not expected to differ greatly among individuals) and by a modifying factor of 2, based on a limited data base. Using the 60-minute value of 75 ppm, AEGL-3 values for the other exposure times were calculated based on the  $C^{1.77} \times t = k$  relationship. The value of  $n$  was derived from regression analysis of the mouse lethality data in the key study. The 8-hour value was set equal to the 4-hour value because fluorine would react with or be scrubbed by the nasal passages at fairly low concentrations. The safety of setting the 8-hour value equal to the 4-hour value is supported by another study in which a 7-hour experimental exposure concentrations