ppm, the animals went into a state of severe intoxication within 1-2 min and were virtually unable to perform coordinated movements (Purser and Berrill 1983).

In developmental toxicity tests, CO caused an increase in the rate of stillbirths or fetal mortality in pigs after 2-3 days of exposure to COHb at over 23% (Dominick and Carson 1983); in rabbits after continuous exposure to 16-18% COHb throughout gestation (Astrup et al. 1972) as well as after daily exposure to high CO concentrations in cigarette smoke (exposure for 12 min/d on gestational days 6-18, resulting in a COHb of 16%) (Rosenkrantz et al. 1986); in rats after three exposures at 750 ppm for 3 h/d (Choi and Oh 1975); and in mice after exposure at 125 ppm for 11 days (Singh and Scott 1984). Significant memory impairment in behavioral tests were found in young rats after continuous CO exposure throughout gestation (mean maternal COHb was 15.6%) (Mactutus and Fechter 1985).

In monkeys, a COHb of 9.3% resulted in reduced threshold for electric-shock-induced ventricular fibrillation (DeBias et al. 1976). A similar effect was found in dogs at 6.3-6.5% COHb (Aronow et al. 1979). A COHb of 13-15% increased the severity and extent of ischemic injury and the magnitude of ST-segment elevation in a myocardial infarction model in dogs (Sekiya et al. 1983).

SPECIAL CONSIDERATIONS

4.1. Stability, Metabolism, and Disposition

CO is produced endogenously in normal metabolism. When an α-methylene bridge in the heme group of hemoglobin is broken during the catabolic process, one molecule of CO is released. It has been estimated that this production amounts to approximately 0.3 to 1.0 mL/h with an additional 0.1 mL/h resulting from a similar catabolic process involving other heme-containing compounds (e.g., myoglobin as well as cytochrome and catalase enzymes). This endogenous production of CO gives rise to a baseline or back ground level of approximately 0.5-0.8% COHb (NIOSH 1972).

Almost all the CO that has been inhaled is eliminated through the lungs when the previously exposed person enters an atmosphere free of CO. CO not only binds to hemoglobin forming COHb, but 10-50% of the total body store of CO is also distributed to extravascular sites, such as skeletal muscle, where it can bind to myoglobin. Extravascular CO can be slowly metabolized to CO_2 (Fenn 1970). Inside the cells, CO can bind to all heme proteins capable of binding oxygen, such as myoglobin, cytochrome c oxidase, cytochrome P-450 enzymes, and tryptophan oxygenase (WHO 1999a). However, the exact extent of this binding in vivo as well as the physiologic consequences in terms of inhibition of protein and enzyme function and the existence and relevance of possible toxic effects has not been clearly shown until now (cf. extensive discussion in WHO 1999a).