incident. This effect level was considered to be below that defined for AEGL-2. All experimental studies used patients who had stable exertional angina and did not experience angina while at rest. Thus, it is considered likely that in more susceptible individuals (a part of the patients with unstable angina pectoris might belong to this group) CO exposure alone could increase angina symptoms. In hypersusceptible patients, more severe effects, even including myocardial infarction, cannot be ruled out.

In contrast to the anecdotal case reports on myocardial infarction discussed in the derivation of AEGL-3, the studies investigating electrocardiogram changes and angina symptoms in patients with coronary artery disease, used here for the derivation of AEGL-2 values, are high-quality, well-conducted experimental studies with well-characterized exposure conditions and information on interindividual variability.

An exposure concentration of 4% COHb is unlikely to cause a significant increase in the frequency of exercise-induced arrhythmias. This effect has been observed at a COHb of 5.3% but not of 3.7% (Sheps et al. 1990, 1991). In another study, no effect of CO exposure on ventricular arrhythmia was found at 3% or 5% COHb (Dahms et al., 1993). No experimental studies in heart patients are available that used significantly higher levels of COHb.

Use of a concentration of 4% COHb as a point of departure for the derivation of AEGL-2 values is supported by the studies in animals: a COHb of 9.3% resulted in a reduced threshold for electric-shock-induced ventricular fibrillation in monkeys (DeBias et al. 1976) and a COHb of 6.3-6.5% increased the vulnerability of the heart to electrically induced ventricular fibrillation in healthy dogs (Aronow et al. 1979). These animal studies suggest that a level below 6-9% COHb should be selected for AEGL-2 derivation to protect individuals with compromised cardiac function.

A total uncertainty factor of 1 for intraspecies variability was considered adequate based on supporting evidence in other susceptible subpopulations (children, pregnant women, older people and smokers):

1. The derived AEGL-2 values would result in a COHb of 4.9-5.2% in 5-year-old children (see Table B-2 in Appendix B). This level is considered protective of neurotoxic effects in children: (1) In the study by Klasner et al. (1998), acute neurotoxic effects, such as headache, nausea, dizziness, dyspnea, and vomiting, were found at a mean COHb of 7.0% (measured after a mean time of 1 h [up to 2 h] after removal of the children from the CO atmosphere). That result suggests that at the end of exposure, COHb had been from 10% to 14%. These values were estimated using the mathematical model of Coburn et al. (1965) and Peterson and Stewart (1975). (2) In the study by Crocker and Walker (1985), a threshold of 24.5% COHb for syncopes in children, an effect that was considered to impair the ability to escape, was reported. (3) In the study by Klees et al. (1985) that investigated long-lasting neurotoxic effects (defects in the cognitive development and behavioral alterations) in children, the lowest concentration resulting in cognitive development defects was 13% COHb in the