

WRITTEN COMMENTS ON  
NTP-CERHR EXPERT PANEL REPORT on the  
REPRODUCTIVE and DEVELOPMENTAL  
TOXICITY of ETHYLENE GLYCOL

by

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I have one comment regarding the metabolic scheme and discussion thereof in Section 2.1.3 Metabolism (p. 16, paragraph 1), Figure 2.1 (p.16) and Section 2.6 Summary, General Toxicokinetics (p. 43, paragraph 3). In these sections, the Panel has stated that “glyoxylate is primarily metabolized to formate and then to respiratory CO<sub>2</sub> and to a lesser extent, to urinary oxalate and glycine”. There are two publications which determined the concentration of formate (and other organic acids) after ethylene glycol (EG) ingestion by humans in overdoses and by monkeys. Jacobsen et al (reference 39 in the draft report list) showed that no formate was present in the plasma of EG-intoxicated humans. Clay and Murphy (“On the metabolic acidosis of ethylene glycol intoxication”, *Toxicol Appl Pharmacol* **39**: 39-49, 1977) showed that no formate was present in the plasma nor in the urine of monkeys given doses of EG that produced a severe metabolic acidosis (4 g/kg). Hence, both of these studies showed that formate is, at best, a minor metabolite of glyoxylate, and is not likely the source of CO<sub>2</sub>. The Panel should revise the text of these sections accordingly. There are many pathways by which glyoxylate can be metabolized (see scheme in Jacobsen et al., *Amer J Med* **84**: 145-52, 1988). The primary pathway from glyoxylate cannot be determined from existing studies, but would most likely be either oxalate or glycine. Glycine is the most likely source of CO<sub>2</sub>, since the glycine cleavage reaction directly leads to CO<sub>2</sub>, and glycine also contributes to the folate-dependent one carbon pool, through which it can indirectly lead to CO<sub>2</sub>. Glyoxylate has also been suggested to be metabolized via 2-oxo-4-OH-glutarate to malate, which can also be a source of CO<sub>2</sub>.