million (0.00004%). Although a direct comparison is somewhat tenuous, the data suggest a substantial difference in the susceptibility of rodents and humans to Leydig cell tumorigenesis. This is supported by epidemiology data from compounds that clearly produce Leydig cell tumors in rodent studies but are commonly ingested by humans and are not associated with Leydig cell tumorigenesis in humans.

C8 and other peroxisome proliferators do not produce increases in peroxisomes in Leydig cells and are hypothesized to produce these tumors via a different mechanism than the liver tumors. The mechanism of tumorigenesis is not completely understood, and therefore relevance to humans can not be completely ruled out. However, it is known that non-genotoxic compounds (such as C8) produce Leydig cell tumors by altering the endocrine system. Therefore, a threshold for tumorigenesis is expected. If this is the case, use of a margin of safety approach is appropriate for the quantitative dose-response assessment. It is important to consider the slope of the dose-response at the low end of the observed range in determining an acceptable margin of safety.

VI.3.a.3. Pancreatic Acinar Cell Tumors

C8 and other peroxisome proliferators do not produce increases in peroxisomes in the pancreas and are hypothesized to produce these tumors via a different mechanism than the liver tumors. The mechanism of tumorigenesis is not understood, and therefore relevance to humans can not be completely ruled out. However there is a growing weight of evidence that the pancreatic acinar cell tumors are hormonally mediated, therefore they should be treated similarly to peroxisome-proliferator-induced Leydig cell tumors.

VII. SUMMARY

C8 has moderate acute oral toxicity with LD_{50}'s ranging from 178 mg/kg in male guinea pigs to 680mg/kg in adult male rats. An aqueous paste of C8 produced mild to moderate dermal irritation in rabbits and clinical signs of toxicity were observed at doses as low as 1000 mg/kg. Instillation of solid C8 into the rabbit eye produced moderate corneal opacity, iritis, and conjunctivitis. These ocular effects gradually receded. C8 has high acute inhalation toxicity with a 4-hour ALC of 0.8 mg/L in the rat. Subchronic inhalation exposure to C8 produced reversible liver effects at concentrations as low as 8 mg/m^3 (measured as 7.6 mg/m^3). Oral and skin absorption subchronic studies confirmed the hepatotoxicity of C8 in the rat. In chronic feeding studies in rats, C8 produced an increased incidence of tumors in the liver, pancreas, and testis. C8 was found not to be a developmental toxic or mutagenic in several tests for mutagenicity.

The relevance to human health of tumors induced by peroxisome proliferators in rodents has been the focus of several investigators. Regarding the liver, there is a strong association and probable link between peroxisome-proliferator-induced liver growth and the subsequent development of rodent liver tumors. A combination of *in vivo* and *in vitro* studies as well as epidemiology data, has led several investigators to conclude that humans appear to be insensitive or unresponsive to peroxisome-proliferator-induced hepatic effects, and therefore these nongenotoxic agents pose little or no