would appear to be of carcinogenic concern.

b. *Mutagenicity.* Propoxur and its metabolites, including catechol, have not been shown to produce detectable gene mutations, with the exception of ''M5'' (equivocal or weakly positive in the Ames assay for *Salmonella typhimurium* strain TA1535). While propoxur appears to give no indications of clastogenic activity in *in vitro* studies submitted by Miles Inc., one published study shows increased incidence of sister chromatid exchange and micronuclei in human lymphocytes following *in vitro* exposure to propoxur. Propoxur also induces S-phase mitosis in bladder epithelial cells suggesting an effect on cell proliferation. The ''M1'' metabolite, catechol, has been shown to be genotoxic in several published studies, including *in vivo* tests, primarily via a clastogenic mechanism. The presence of the ''M9A'' metabolite suggests a possible nitrosation mechanism; the *N*-nitroso derivative of propoxur is a known mutagenic compound. Overall, the indications are that there is, at most, only weak genotoxicity associated with propoxur and/or its metabolites. It is noteworthy that dietary exposure to propoxur has been shown to result in an increased incidence of S-phase in rat urinary bladder epithelial cells (not a genotoxic effect) suggesting that the rat urinary bladder tumors may originate from increased cell proliferation.

c. *Effects of diet and urinary pH on the bladder.* Miles Inc. has submitted a number of studies relating to the effects of diet and urinary pH on the bladder. In a 15–week feeding study, female Wistar rats received 8,000 ppm propoxur in Altromin diet, with or without addition of 2 percent ammonium chloride. Without the ammonium chloride, the urinary pH was more basic by approximately 2 pH units. At termination, hyperplasia of the urinary bladder was present in 8/14 rats not receiving ammonium chloride and in 1/15 rats receiving it. In two other studies with rats given a casein semi-synthetic diet (No. 1/0) and propoxur at 8,000 ppm for 4.8 or 14 weeks, and at 3,000 or 8,000 ppm propoxur for 100 weeks, no histopathologic changes in the urinary bladder were reported. These studies appear to support Miles Inc.'s position that development of the urinary bladder hyperplasia (and subsequent tumor occurrence in rats) is associated not only with administration of propoxur but also with the diet and possibly its effects on urinary pH.

3. *Findings and recommendations of EPA's Scientific Advisory Groups.* In the September 4, 1986 Peer Review of propoxur, the Peer Review Committee reviewed the evidence of carcinogenicity of propoxur from the 1984 rat feeding/carcinogenicity study, and other toxicological data on the chemical. The Peer Review Committee reviewed the carcinogenic potential for classification, and concluded that there was sufficient evidence of carcinogenicity to classify propoxur to Group B2 (Probable Human Carcinogen). The classification was supported by the unusually high incidence of bladder neoplasia, the relative rarity of the bladder tumor in rats, early onset of hyperplasia and papilloma of the bladder, and the somewhat uncommon finding of bladder tumors in the absence of crystalline (usually silica) deposits.

In the second Peer Review of propoxur held on December 6, 1990, the Carcinogenicity Peer Review Committee reviewed the evidence for the Group C Classification of propoxur by the Carcinogen Assessment Group of EPA's Office of Research and Development. The Peer Review Committee agreed to defer discussion of the classification of propoxur until the data from the 1988 rat carcinogenicity study had been reviewed.

In the October 3, 1991 third Peer Review of Propoxur, the Carcinogenicity Peer Review Committee concluded ''that there was insufficient evidence to change the classification of propoxur (Group B2 carcinogen) and method of quantification'' at this time. However, the Committee stated that if a species- and diet-specific effect could be established, and if the genotoxic mode of action were dismissed for propoxur, then ''the use of the conventional low-dose quantitative risk assessment method (Q_1*) might not be appropriate.'' The Committee suggested that ''studies designed to further investigate the mechanism of action and genotoxic potential'' of propoxur be performed. Specifically, the Committee suggested a re-cutting of the bladder sections and that a pathologist (with expertise in bladder neoplasia) read these and re-read the original bladder slides from the 1988 female rat study. The Committee suggested that a pathologist look at sections from all groups for uterine pathology from the same study. The Agency also suggested historical control data from the registrant's testing facility and information on the diet composition (Altromin 1321 compared to other diets). In addition, to better understand possible mechanistic considerations and relate them to the Agency's regulatory position on propoxur, Miles Inc. was advised to clarify propoxur's genotoxic potential and to resolve the discrepancy created by the two dietary regimens.

Miles Inc. has responded, in part, to the suggestions of the third Carcinogenicity Peer Review Committee. The Agency has discussed with the registrant the mechanisms by which the urinary bladder tumors are triggered and the possible relationship of uterine tumors to dietary propoxur. The findings will be evaluated by the Carcinogenicity Peer Review Committee after all the suggested data have been submitted. EPA does not expect that the peer review will conclude that the carcinogenicity of propoxur is a more serious concern than today's document concludes.

4. *Evaluation of carcinogenicity data—Hazard finding.* Following the October, 1991 Peer Review, EPA re-evaluated (Ref. 3) the rat urinary bladder tumor rates from the l984 2–year feeding study. As there was no statistical evidence of increasing mortality with increasing doses of propoxur, the unit risk estimate could be obtained using a linearized Multi-Stage model for each sex group of rats. The resulting unit risk estimates for both males and females were then combined to obtain a geometric mean. The Agency estimated the human equivalent potency (Q_1*) of propoxur to be 3.7×10^{-3} $(mg/kg/day)^{-1}$. The Q_1* represents the 95 percent upper bound confidence limit of tumor induction likely to occur from a given dose of a carcinogen. It is emphasized, that if the mechanism(s) by which the urinary bladder tumors develop in rats involves a threshold level, and/or if these tumors are species-specific, then the risk to humans would be less than indicated by this Q_1*.

5. *Uncertainties in propoxur's role In carcinogenesis.* To date, there is no clear indication as to how propoxur produces hyperplasia and tumors. Bladder tumors are rare in rats, particularly in the absence of crystalline (silica) deposits. It has been suggested that silica deposits may in some way participate in bladder tumor formation, especially in the presence of a diet that may alter the pH of urine in the bladder. It is emphasized that there is no indication of silica deposits in the urinary bladders of rats fed propoxur. However, there may be other factors associated with induction of hyperplasia or the formation of tumors, such as enhancement of the cellular response to growth factors. In addition, the role and relative contributions of the parent compound and its metabolites to the process are unknown.

Miles Inc. has taken the position that propoxur is non-genotoxic, and that an ''epigenetic'' mechanism, such as that