was considering a Special Review of propoxur (Ref. 1). EPA was concerned with propoxur's potential cancer risk to applicators when applying propoxur indoors and outdoors, to occupants of treated buildings, and from treating pets with propoxur. EPA's concern was based on a 1984 study which reported increases in the incidences of malignant and benign tumors in the urinary bladders of both male and female rats, an increase in incidence of uterine tumors in female rats, and the early onset and increased incidence of hyperplasia of the urinary bladder in these rats. EPA classified propoxur as a Group B2 (probable human) carcinogen. EPA noted that data from the 1987 DCI would be used to refine estimates of risk, and that the registrants' responses to this notification would be considered in its determination whether to initiate a Special Review.

3. *1990 Notice of Intent to Suspend, and 1991 Settlement Agreement.* On October 15, 1990, EPA sent a Notice of Intent to Suspend (NOITS) to Miles Inc. and the five manufacturing-use producers for failure to comply with the terms of the December 14, 1987 DCI regarding certain exposure studies. The requirements of the 1987 DCI were legally binding only for those companies who received the DCI. As a result, only their products were subject to the NOITS. Miles Inc. requested a hearing concerning the NOITS, and subsequently reached a settlement with EPA on June 28, 1991. The agreement noted that Miles Inc. had recently submitted new studies to address the data requirements for indoor pressurized aerosol and granular bait products. EPA agreed to issue a new DCI requiring end-use registrants to submit exposure studies not committed to by Miles Inc., such as a trigger pump spray study. If no other end-use registrant committed to generate data to support these uses, Miles Inc. would amend its labels for its manufacturing-use products to prohibit the unsupported uses. On August 12, 1991, after accepting the aerosol spray and PCO granular bait studies submitted by Miles Inc., EPA withdrew the NOITS on all of the registered products of manufacturing-use producers which these two studies supported. RTU liquid products applied with trigger-pump sprayers subject to the NOITS remained suspended. Subsequently, all registrants with these products amended their propoxur end-use product labels to delete use of RTU liquids with trigger-pump sprayers.

II. Estimation of Propoxur Cancer Risks to RAs, PCOs, and Residents of Treated Buildings

Since the 1988 notification to registrants that EPA was considering a Special Review of propoxur, the Agency has refined its risk assessments. The current risk assessment is discussed in this unit.

A. Hazard Identification — Carcinogenicity

1. *Animal carcinogenicity studies*— a. *Rat studies.* In a 1984 2–year rat chronic feeding/carcinogenicity study, propoxur was administered in a standard European diet (Altromin 1321) to SPF Wistar rats, at concentrations of 0, 200, 1,000, or 5,000 ppm propoxur. At the 1–year interim sacrifice, there was an increased incidence of urinary bladder epithelial hyperplasia in the two highest dose groups of male and female rats. There was also a urinary bladder papilloma in 1 of the 10 highest dose males. Animals that died, were moribund, or were sacrificed at term also had dose-related increases in the degree and extent of urothelial hyperplasia. Highly significant increases in urinary bladder papillomas, carcinomas and combined papillomas/carcinomas (67 to 75 percent verses 0 percent in the controls) were observed in male and female rats at the highest dietary exposure level (5,000 ppm) in this study. Bladder tumors are considered to be relatively rare in rodents, especially in the absence of silica crystalline deposits. Additionally, there was an increased incidence of uterine carcinoma (not statistically significant at $p > 0.05$) in females at the highest dose level. However, it appeared that this tumor had a tendency to develop earlier and/or grow more rapidly than the control group. The urinary bladder findings of the 1984 carcinogenicity study were confirmed in a subsequent 2–year study completed in 1988 with female Wistar rats on an Altromin diet. There were significant increases in urinary bladder papillomas and combined papillomas/carcinomas at the three highest dose levels tested (3,000, 5,000 and 8,000 ppm) and in carcinomas at the highest dose level. The dose-related trends for papillomas, carcinomas and combined papillomas/carcinomas were also significant. Also, the observed hyperplasia of the urinary bladder was dose-and time-dependent. However, a significant comparative pair-wise increase in uterine tumors was not observed in this study.

b. *Mouse studies.* In a 1982 2–year mouse carcinogenicity feeding study, male and female CF1/W74 mice were fed propoxur at dose levels up to 6,000 ppm. No adverse effects on the bladder were noted. Similarly, in a 1988 1–year mouse feeding study, where up to 8,000 ppm propoxur in an Altromin diet was administered to female NMRI mice, no histopathological changes were observed. In a 1992 B6C3F1 mouse carcinogenicity/feeding study using up to 8,000 ppm propoxur in an Altromin diet, there was a dose-related increase in bladder epithelial hyperplasia (classified as minimal and diffuse in all instances) at 2,000 and 8,000 ppm (not at 500 ppm), but no indication of any carcinogenic effect involving the urinary bladder. However, the study did show a dose-related trend of increased incidence of hepatocellular adenomas in males.

c. *Other animal studies.* In a 1988 study, female Syrian hamsters were fed up to 8,000 ppm propoxur in an Altromin diet for 1 year without histopathological effects involving the urinary bladder. In a 1984 1–year dog feeding study, no adverse urinary bladder effects were reported using dose levels up to 1,800 ppm. Also, in a 1985 13–week oral gavage study with Rhesus monkeys, no adverse urinary bladder effects were noted after feeding 40 mg/kg/day of propoxur.

2. *Other studies— a. Metabolism and biotransformation.* Miles Inc. has submitted results of a number of biotransformation studies conducted on different mammalian species (rat, mouse, hamster, monkey, and human). Propoxur is extensively metabolized (more than 10 metabolites have been identified) and many of the metabolites are excreted in the urine. Because propoxur is so completely metabolized, there is very little or no parent compound in urine. One of the metabolites is 1,2-dihydroxybenzene (''M1'' or catechol). In the rat, approximately 7 percent to 20 percent of propoxur is degraded to catechol. Catechol, at high dose levels administered by gavage, has been shown to induce cancer in the glandular stomach of rats. Three other metabolites of propoxur of structural interest are: 2-isopropoxyphenol (''M2''), 2-isopropoxylphenyl-hydroxy-methylcarbamate (''M5''), and 1-hydroxy-2-isopropoxy-4-nitrobenzene (''M9A''). ''M9A'' has a nitro-group added to the phenyl ring of metabolite ''M2,'' and Miles Inc. has proposed that it is formed in the stomach. In human data (Ref. 2), the glucuronide conjugate of ''M2'' was the predominant metabolite found, with trace levels of ''M9A.'' Based on the Agency's current knowledge, none of the metabolites