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8EHQ-96-13838

December 16, 1996

TSCA Document Processing Center (7407)  
ATTN.: Section 8e Coordinator  
Office of Pollution Prevention and Toxic Substances  
Environmental Protection Agency  
401 M Street, S.W.  
Washington, DC 20460

**8EHQ-1296-13838**

**Contains No CBI**

RE: Toxicology Testing on a New Hydrofluorocarbon

Dear Sir:

As a component of our research program on alternate fluorocarbons, AlliedSignal has been evaluating the performance and toxicity of 1,1,1,3,3-pentafluoropropane (HFC 245fa). This material is a research chemical and is not in commerce nor is it listed on the TSCA inventory.

HFC 245fa has been evaluated in a series of toxicology studies which included Ames, human lymphocyte chromosome aberration and mouse micronucleus genetic assays; a cardiac sensitization assay in dogs; a dermal toxicity study in rabbits; an inhalation developmental toxicity study in rats and acute, subacute and subchronic inhalation toxicity studies in rats. Most of these studies have been completed, the subchronic inhalation toxicity and developmental toxicity studies are still undergoing final analysis. These reports are expected in the first quarter of 1997. In general, the results, which are summarized below, have demonstrated that HFC 245fa is of minimal toxicity and it is a leading candidate for the next generation of hydrofluorocarbons, especially as a replacement for HCFC 141b.

The Ames Test was conducted using five histidine-dependent strains of *Salmonella typhimurium* and one tryptophan-dependent auxotroph of *Escherichia coli* exposed to HFC-245fa material in the gaseous phase. The study was conducted in the presence and absence of S-9 mix and employed five atmospheric concentrations of HFC-245fa at 2.5, 5, 10, 20 and 40% v/v (nominal). Control cultures were also employed. Results indicated that there were no increases in reversion in any of the six bacterial strains following exposure to any of the concentrations, either in the presence or absence of S-9 mix. It was concluded that HFC-245fa in gaseous phase did not exhibit any mutagenic activity under the condition of this test.

HFC-245fa was also assessed for its mutagenic potential with an *in vitro* mammalian cytogenetic test using cultured human lymphocytes. Tests were conducted in the presence of S-9, a rat liver-derived metabolic activation system, at concentrations of 30, 50 and 70% v/v and in the absence of S-9 at concentrations of 10, 20 and 30% v/v. In the presence of S-9, no real evidence of toxicity was apparent at any exposure concentration. Furthermore, there were no biologically or statistically significant increases in aberrant cell frequencies recorded at any of the concentrations tested in the presence of S-9. In the absence of S-9, no toxicity was apparent in cultures exposed to 10 and 20%, however, there was evidence of toxicity in



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cultures exposed to 30%. Also in the absence of S-9, mean aberrant cell frequencies were 7, 7.5 and 12% at concentrations of 10, 20 and 30%, respectively. Overall, HFC-245fa showed weak clastogenic activity in the absence of metabolic activation, but only at these very high concentrations.

An *in vivo* mouse micronucleus test was also used to evaluate the mutagenic potential of HFC-245fa. The *in vivo* mouse micronucleus study assessed the potential ability of this material to effect chromosome structure in bone marrow following an acute four-hour inhalation exposure of 101,300 ppm to mice. There was no evidence of bone marrow toxicity at this exposure level. It was concluded that the compound was inactive in this study since there was no evidence of induced chromosomal or other damage leading to micronucleus formation in polychromatic erythrocytes of treated mice 24 or 48 hours after exposure to HFC-245fa by inhalation.

Even though a response was seen in one of the assays, this response was slight and only seen in the absence of metabolic activation and at very high concentrations. Overall, the weight of evidence indicates that HFC 245fa is not a mutagen. These results are very similar to those obtained with HCFC 141b.

In the cardiac sensitization screening study, beagle dogs were administered adrenaline by intravenous injection before and during inhalation exposure to the test substance. Positive evidence of cardiac sensitization would be observed as the presence of cardiac arrhythmias (rapid, potentially fatal heart beat). HFC-245fa was administered to the dogs at concentrations of 10,000 ppm and 20,000 ppm (1% and 2%, respectively) using a snout-only breathing system. There were no positive responses seen during this screening study. It was concluded that HFC-245fa has no cardiac sensitization potential at concentration of up to 20,000 ppm v/v in air. These results are better than CFC 11 and HCFC 141b, which showed effects at 10,000 ppm.

The potential for this material to cause dermal toxicity was evaluated following a single dermal administration of 2 ml/kg (2000 mg/kg) of HFC-245fa to a group of five male and five female rabbits. There was no death and no sign of reaction to treatment. The rabbits achieved expected body weight gains, organ weights were unremarkable and there was no significant macroscopic lesion. Under the conditions of this study, the acute dermal LD<sub>50</sub> of HFC-245fa was greater than 2 mL/kg (2000 mg/kg), indicating that this material is of low percutaneous toxicity.

The developmental toxicity study is still in progress. In a pilot developmental toxicity study, exposures of pregnant rats to levels of HFC 245fa up to 50,000 ppm, the highest level tested, did not cause adverse effects on the development of the pups. A preliminary review of the data from the main study appears to support this conclusion. The final report is expected in the first quarter of 1997.

HFC-245fa was initially assessed for its acute inhalation toxicity potential by exposing a single group of five male and five female mice to a single, four-hour continuous, snout-only exposure in a recirculating atmospheric chamber containing approximately 100,000 ppm (101,300 ppm was the actual concentration measured in the chamber) of the test material. A similarly constituted control group was exposed to recirculated room air. There were no deaths

during the study, however, underactivity was evident for all treated animals. This effect was immediately reversible upon completion of the 4-hour exposure. There was no effect on body weight gain, no macroscopic pathology findings and no effects upon the lung, liver and kidney weights. The median lethal concentration (LC<sub>50</sub>) for HFC-245fa vapor is greater than 101,300 ppm.

Its acute inhalation toxicity was also assessed in rats. Groups of five male and five female rats received a single, 4-hour whole body exposure in chamber containing 14.3% v/v or 20.3% v/v of HFC-245fa. All rats were observed for 14-days following exposure. Clinical signs during exposure at both exposure levels included exaggerated respiratory movements, the adoption of an abnormal posture, and reduced response to external stimuli. There was evidence of an anesthetic effect during exposure to high concentrations of HFC-245fa. These effects were transient and all rats recovered rapidly when removed from the exposure chamber. No clinical signs were reported during the 14-day observation period. Exposure to HFC-245fa did not have an effect on the rate of bodyweight gain at either exposure level. Lung weight to bodyweight ratios for both groups were similar to control values. There were no deaths or macroscopic abnormalities in rats exposed to measured concentrations of HFC-245fa at either 14.3% v/v or 20.3% v/v. Under the conditions of this test, HFC-245fa has an LC<sub>50</sub> (4-hour) value greater than 20.3% v/v or 203,000 ppm. These results are better than seen with HCFC 141b, where the 4-hour LC<sub>50</sub> in the rat was 62,000 ppm.

To help establish the experimental parameters for the subchronic inhalation toxicity studies, a subacute study was conducted. In this study, groups of five male and five female rats received 6-hour exposures, 5 days/week for two weeks to levels of 0 (control), 2,000, 10,000 and 50,000 ppm of HFC 245fa. There was no mortality, body weights and clinical observations of the exposed animals did not show evidence of treatment related effects. In fact, the only notable findings were increased levels of blood urea nitrogen and of two serum liver enzyme activities (GPT and GOT). These results were observed generally in all treatment groups but without a marked dose response. As there were no histopathological changes in either the kidneys or liver (or any other organ), the significance of these findings is uncertain. It would not appear that they represent an adverse finding.

To address multiple regulatory requirements, a combined 28-day inhalation study with a recovery group and a 13-week inhalation toxicity study was conducted. The exposures were 6 hours per day, 7 days per week for the 28-day study and 6 hours per day, 5 days per week for the 13-week study. The recovery group was held for a two-week post-exposure period, comprised of five males and five females in the control and high exposure level group.

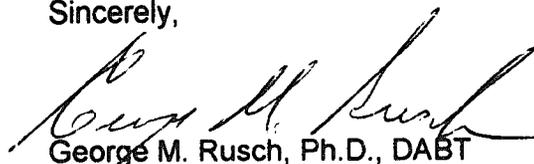
The two primary treatment populations consisted of five groups of twenty male and twenty female rats. Half were sacrificed after 28 days of exposure, the remaining animals were sacrificed after 13 weeks. The exposure levels used in this study included 0 (control), 500, 2,000, 10,000 and 50,000 ppm. The results described below are preliminary and are based on unaudited summaries. The final reports for these studies are not due until the first quarter of 1997. Dose related increases were seen in urinary fluoride levels, water consumption and urine volumes. These findings suggest some metabolism of the HFC 245fa. Additionally, increases were again seen in blood urea nitrogen levels and serum liver enzyme activities (GPT, GOT and, on one occasion, alkaline phosphatase). Generally, the increases did not follow an exposure level-related pattern, but tended to represent a plateau above the control values. As with the two-week study, there were no morphological changes to either the

kidneys or liver. The significance of these clinical chemistry observations is, therefore, unknown. Histopathological examination of the heart showed an increased frequency of myocarditis (inflammation of the heart muscle) in both male and female rats in the 10,000 and 50,000 ppm exposure level groups sacrificed after 13 weeks of exposure. No significant increases were seen at 50,000 ppm after 28 days. (Only the controls and 50,000 ppm group were evaluated at this interval.) Also, no significant increases were seen in the 500 or 2,000 ppm exposure level groups after 13 weeks of exposure. This finding was reported as slight to minimal in degree but was not anticipated. Upon receipt of the final report, we will review this data in depth and consider what additional information we may need to complete our risk assessment on HFC 245fa. For the present, we still feel this is a material of low toxicity, with a high potential to be used in applications such as those currently covered by HCFC 141b. In fact, in most aspects, its toxicity is less than that exhibited by HCFC 141b.

The U.S. EPA is being notified of the observation of myocarditis as a "For Your Information" finding since it is an unexpected observation. However, given the high exposure levels and lengthy exposure period which were required to elicit this minimal response, and the fact that HFC 245fa is not currently in commerce and potential exposures are minimal, this finding is not considered to be a significant new risk.

We will forward a copy of the final report when we receive it. Our present conclusions are based on a review of preliminary, summary data supplied by the laboratory conducting the study on our behalf. As such, the findings and conclusions described in our summary of the 90-day, inhalation toxicity study are subject to possible modification when the full study report becomes available. If you have any questions, please contact me at your convenience. My telephone number is 201/455-3672.

Sincerely,



George M. Rusch, Ph.D., DABT  
Director of Toxicology & Risk Assessment

GMR:rb

cc: Mr. J.B. Charm  
Mr. W.M. Corcoran  
Dr. R. Rubenstein  
Mr. D. Weidman

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