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January 28, 2005

Via Federal Express

3p.

Document Processing Center (Mail Code 7407M)
Room 6428
Attention: 8(e) Coordinator
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
1201 Constitution Ave., NW
Washington, D.C. 20460

CONTAINS NO CBI

8EHQ-0105-15412

Dear 8(e) Coordinator:

8EHQ-03-15412
1-Decanol, 3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluoro-
[CAS # 678-39-7]

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This letter is to inform you of the results of a recently completed absorption, distribution, metabolism, and elimination (ADME) study in the rat, along with comparative *in vitro* metabolism experiments using rat and human hepatocytes with the above referenced test material. This letter is "For Your Information" as a follow-up to qualitative data supplied to the Agency on November 25, 2002 [AR226-1141].

Male and female rats were administered a single oral dose of the test material formulated in a 0.5% aqueous methylcellulose vehicle at the target dose levels of 5 mg/kg and 125 mg/kg. The formulated doses were fortified with radiolabeled [^{14}C] test material, which was uniformly blended into the dose solution prior to administration. In addition, male and female rats were administered a single dermal application of the test material formulated in the 0.5% methylcellulose vehicle at a target dose of 125 mg/kg. Following oral and dermal dosing, rats were housed individually in glass metabolism units suitable for the separate collection of urine and feces. The dermal dose remained in contact with the dorsal skin for 6 hours. At the end of the 6-hour exposure, the application site was washed to remove excess dose. At 168 hours post-dosing, rats were anesthetized by carbon dioxide exposure and sacrificed by exsanguination. At sacrifice, selected tissues were taken for radioanalysis, and distribution and total recovery of the administered dose was determined.

In order to resolve the origin of radioactivity eliminated in the feces following oral dosing, bile duct-cannulated male and female rats were administered a single oral dose of the test material in the 0.5% methylcellulose vehicle incorporating radiolabeled test material at both the 5 and 125 mg/kg dose levels. Following dosing, rats were housed individually in glass metabolism units. Bile was collected for 120 hours and analyzed for total radioactivity by liquid scintillation counting.

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In separate experiments, the plasma kinetics of the test material, its acid form and ammonium perfluorooctanoate (PFOA) was determined. Groups of male and female rats were administered a single oral dose of test material in the 0.5% methylcellulose vehicle incorporating radiolabeled test material at both 5 and 125 mg/kg. Following dosing, rats were maintained in glass metabolism units and serial blood samples were collected post-dose for 7 days. Whole blood was centrifuged to isolate plasma, which was analyzed for total radioactivity by liquid scintillation counting, for the test material by GC-MS SPME, and for PFOA and the acid form of the test material by LC-MS.

In an attempt to gain insight into species similarities and differences in the clearance and metabolism of test material, rat and human hepatocytes were incubated in a closed container with the test material and serial time-course samples were taken and monitored for the test material (disappearance) by GC-MS SPME. Additional incubations were conducted with radiolabeled test material to aid in metabolite identification.

Representative samples of urine, feces extracts, bile extracts, and plasma extracts, and extracts from rat and human hepatocyte incubations, were profiled by LC-ARC radiochromatography and screened by LC-MS, along with matrix control samples to resolve metabolites as a result of the test material exposure.

In the oral studies designed to assess distribution and total recovery, the results show that following a 5 mg/kg single oral dose of the test material to male and female rats, approximately 37% of the administered dose transited the GI tract as intact parent and was not absorbed. The portion of unabsorbed parent alcohol was 1.3-fold higher at the 125-mg/kg-dose level (~50%). Based on analysis of feces and the biliary elimination studies, the percent of administered dose that was absorbed following a 5 and 125 mg/kg single oral dose of the test material was approximately 52% and 26%, respectively. The test material was metabolized and eliminated mainly in the feces via the bile as glutathione conjugates. Elimination via the urine was a minor elimination pathway (<4%). The urine contained low levels of PFOA (<1%) and numerous other hydrophilic metabolites. Tissue residue levels of total radioactivity were generally greater than levels in the whole blood at 7 days post-dose. The greatest concentration of radioactivity was in the fat, liver, thyroid, and adrenals, and was generally less than 50 ppm.

Following dermal application, the test material volatized from the skin surface or was removed by washing at the end of the 6-hour exposure. Systemic absorption following dermal exposure to the test material was negligible.

Plasma kinetics of the test material at both the 5 and 125 mg/kg dose levels were low and short-lived following oral doses. The maximum concentration (Cmax) of the test material following oral administration at 5 and 125 mg/kg was not proportional to the dose. The time to reach maximum concentration (Tmax) was slightly longer at the high dose level. Following oral dosing at the 125-mg/kg-dose level, there was a proportional increase in area under the curve (AUC) for females only, when compared to the 5-mg/kg-dose level. The plasma terminal elimination phase was principally governed by PFOA, which was typically longer in males than in females.

In the *in vitro* metabolism experiments, clearance of the test material was more rapid for rat hepatocytes than for human hepatocytes, suggesting that *in vivo* hepatic first-pass clearance of the test material absorbed from the GI tract may be more extensive for rats than for humans. However, given that a single subject represented the human hepatocyte sample, broad interspecies conclusions could not be drawn.

A copy of the final report for this study will be submitted to the Agency when available.

Sincerely,

A. Michael Kaplan

A. Michael Kaplan, Ph.D.
Director – Regulatory Affairs and Occupational Health

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