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Attachments to April 21, 2000 letter to C. Auer from W. Weppner (Dermal Absorption and Intravenous Pharmacokinetics in Rabbits)

3M Technical Reports

1. Single-Dose Intravenous Pharmacokinetic Study of T-6246 in Rabbits. 3M Environmental Laboratory Study # AMDT-042095.1

2. Single-Dose Dermal Absorption/Toxicity Study of T-6049 in Rabbits. 3M Environmental Laboratory Study # AMDT020895.1

3. Single-Dose Intravenous Pharmacokinetic Study of T-6049 in Rabbits. 3M Environmental Laboratory Study #AMDT-112294.1

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Dermal Absorption and Intravenous Pharmacokinetic Studies in Rabbits

Many of the product applications for 3M fluorochemicals involve high-molecular-weight materials which are believed to have limited capacity for dermal absorption. However, low-molecular-weight manufacturing residuals do exist in very small amounts which may have more capacity for dermal absorption and metabolic conversion to perfluorooctanesulfonate. In order to better understand the limits of detectability of absorption and to establish perfluoroctanesulfonate and fluoride ion as adequate markers of dermal absorption of manufacturing residuals, a low-dose dermal absorption study with perfluorooctanesulfonate and two intravenous pharmacokinetic studies were undertaken in New Zealand white rabbits.

To determine detection limits for the dermal absorption study, individual female New Zealand white rabbits were dosed intravenously with deionized water (control), or 0.003, 0.06, and 0.3 mg PFOS / kg and held for 48 hours. Liver samples taken at term were analyzed for total organic fluoride using thermal extraction of fluoride by means of a modified Dohrmann DX2000 Organic Halide followed by analysis for fluoride using an Orion EA940 Expandable Ion Analyzer. The presence of perfluorooctanesulfonate in the 0.3 mg/kg and 0.06 mg/kg dose-group livers was confirmed with electrospray mass spectroscopy. Liver total organic fluorine concentrations at 48 hours post-dose were 1.0 and 0.6 ppm for the 0.3 and 0.06 mg/kg dosed animals, respectively. Specific analysis for perfluorooctanesulfonate anion by electro-spray mass spectroscopy yielded 0.6 and 0.3 ppm for the 0.3 and 0.06 mg/kg dosed animals, respectively. The 0.006 and 0.003 dosed animals' livers did not contain quantifiable levels of fluoride above background. The method was determined to be capable of detecting a dose between 0.01 and 0.06 mg/kg.

In the dermal absorption study, three male and three female albino rabbits per dose group were exposed dermally under occlusion for 24-hours to an aqueous suspension of 0.06 percent perfluorooctanesulfonate at doses equal to 0, 0.003, 0.06, and 0.3 mg / kg and held for 28 days. Liver samples taken at term were analyzed for total organic fluoride using thermal extraction of fluoride by means of a modified Dohrmann DX2000 Organic Halide followed by analysis for fluoride using an Orion EA940 Expandable Ion Analyzer. There was no detectable total organic fluorine above background in the livers. Since it was demonstrated in a rabbit intravenous pharmacokinetic study (T-6246) that an

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intravenous dose of 0.06 mg/kg did result in detectable fluoride as well as perfluorooctanesulfonate in 28-day post-dose livers and a dose of 0.012 mg/kg was not detectable, it can reasonably be concluded that less than 20 percent of the applied perfluorooctanesulfonate was present at 28 days post-dermal-dose. The low dose levels in this study preclude an absolute determination of absorption or non-absorption.

In order to determine the feasibility of using combustion followed by fluoride ion analysis to monitor absorption of fluorochemicals that may convert metabolically to perfluorooctanesulfonate after dermal absortion, perfluorooctanesulfonate (T-6246) was given by intravenous injection to rabbits. Groups of four male and four female new zealand white rabbits (Hra:(NZW)SPF) were dosed with either de-ionized water (vehicle control), or 0.006, 0.012, 0.06 or 0.12 mg/kg perfluorooctanesulfonate. Two animals per sex per dose group were scheduled for sacrifice on day 14 post-dosing and the remaining two animals per sex per dose group were sacrificed on day 28 post-dosing. Blood was collected at 4, 8, 12, 24 and 48 hours, and 8 and 15 days for all rabbits, and 28 days post-dosing for the 28-day sacrifice animals. Liver was collected for analysis at the 15 and 28-day sacrifices. Analysis was performed using thermal extraction of fluoride by means of a modified Dohrmann DX2000 Organic Halide followed by analysis for fluoride using either an Orion EA940 Expandable Ion Analyzer and the Skalar Segmented Flow Analyzer with ion selective electrode. The assumption, based on past work, was made that perfluorooctanesulfonate is not metabolically degraded, and that monitoring total fluoride would provide an adequate means to detect absorbed fluorochemical. The two lower dose groups (0.006 and 0.012 mg/kg) did not have detectable levels of fluoride. The rabbit serum half-life of elimination for the 0.06 and 0.012 mg/kg dose groups were calculated as 28 days and 48 days, respectively. The liver values in the 0.12 mg/kg dose group did not demonstrate much change between the day 15 post-dose sacrifice animals and the day 28 post-dose sacrifice animals. At day 15, liver concentration of fluoride was 1.48 ppm. At day 28, the liver fluoride concentration was 1.23 ppm. Therefore, based on this limited data, the half-life in rabbit liver is significantly greater than 28 days. In addition, it was concluded that 0.06 mg/kg perfluorooctanesulfonate resulted in measurable liver concentrations at twenty-eight days post-dose. This study established a threshold of detection for the combustion method, confirmed the utility of liver total fluoride measurement as a marker for transdermal

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exposure to fluorochemicals which generate perfluorooctanesulfonate as a metabolite, and confirmed the extended half-life of serum and liver elimination in the rabbit.

Methodology and detection limits have improved since these studies were undertaken. The 3M Strategic Toxicology Laboratory has begun a series of studies to develop comparable data on dermal flux of a series of fluorochemicals, starting with perfluoroctanesulfonate. These experiments utilize a reconstituted human epithelial culture (REp) available from SkinEthic, Nice, France. When the perfluorooctanesulfonate study is complete, a copy will be provided.