DATA REQUIREMENTS IN FULFILLMENT OF §408 OF THE FEDERAL FOOD, DRUG AND COSMETIC ACT

Sufficient toxicology data are available to show that the proposed insect repellent uses of IR3535 do not pose a significant risk to human health, including infants and children. There is no indication from the results of the toxicology studies that any potential increased sensitivity to infants and children occurs with the use of IR3535.

Acute Toxicity

Acute toxicity studies were conducted with the technical grade active ingredient (TGAI). The following table summarizes the findings from these acute exposure studies:

Study	Category
Oral	IV
Dermal	IV
Inhalation	IV
Eye Irritation	II
Dermal Irritation	IV
Dermal Sensitization	not a sensitizer

Based upon a history of safe use as an insect repellent for over 15 years in several European countries, IR3535 has not been found to be a sensitizing agent. Additional information pertinent to consumer experience with products containing this material has been collected by Merck KGaA and is included in the registration package for IR3535.

Genotoxicity

Genotoxicity studies indicate that IR3535 does not possess significant potential for genetic risk to humans. *In vitro* tests conducted with and without the presence of a rat liver homogenate metabolic activation system showed no mutagenic effects in an Ames microbial mutation assay at doses up to 5000 mg/plate nor in tests with V79 Chinese hamster cells at doses up to 5000 mg/ml. An *in vitro* test for chromosomal aberrations showed no effects upon incidence of chromosomal aberrations in the test without S9 activation and positive increases in cells with aberrations at the highest two doses tested in the presence of S9 liver homogenate. The positive effects were noted only with the doses that produced significant cytotoxicity to the target cells indicated by adverse effects on the cell monolayer.

An *in vivo* mouse micronucleus test of IR3535 to determine potential to produce chromosome damage showed no positive effects from doses up to 2000 mg/kg with cells evaluated at 24, 48 or 72 hrs post-dosing. Consideration of the overall genotoxicity evidence indicates that IR3535 lacks significant genotoxic potential and would pose no significant genetic risk to humans.

Developmental and Reproductive Toxicity

IR3535 does not pose a significant risk to humans with respect to developmental or reproductive hazard potential. In a developmental toxicity study by oral administration to Rabbits, there was no evidence of effects on embryonic viability or development and no treatment-related fetal malformations or developmental variations. The NOAEL for developmental toxicity was 600 mg/kg/day, the highest dose tested. A two-generation reproductive toxicity study in rats dosed orally with IR3535 showed a systemic and reproductive NOAEL of 0.3 ml/kg/day and a LOAEL of 1 ml/kg/day (equivalent to approximately 1000 mg/kg/day).

Sub-chronic Toxicity

A 90-day dermal toxicity study of IR3535 in rats showed no treatment-related systemic effects at application rates up to and including 3000 mg/kg/day. Parameters evaluated in this study included body weight, body weight gain, food consumption, organ weights, clinical chemistry/hematology and clinical observations. The NOEL for this study was 3000 mg/kg/day, the highest dose tested.

Endocrine Effects

No specific tests have been conducted with IR3535 to determine whether it may have an endocrine disrupting activity. However, based upon the results of the animal bioassays, there is no evidence to suspect that IR3535 is an endocrine disrupting agent.

Additional Toxicological Considerations

There have been no indications of treatment-related signs of neurotoxicity or immunotoxicity in observations during the acute toxicity tests or in repeated dosing studies, including the subchronic 90-day rat dermal study, the rabbit developmental toxicity study and the 2-generation rat reproduction study. A battery of neurotoxicity tests on IR3535 treated rats was incorporated into the overall protocol for the 2-generation

reproduction study, with emphasis on assessment of these parameters among weanlings. No adverse neurological effects were found. No reported signs of significant adverse effects to humans have been encountered during a 20-year period of substantial use of IR3535 formulations in Europe.

Aggregate Exposure

There are no intended uses of IR3535 other than in insect repellents. There is no potential for aggregate exposures from dietary or water sources.

The NOAEL from the 2-generation reproductive study in rats was 300 mg/kg/day by oral gavage. Based upon conservative assumptions for dermal exposure, an adult would be exposed to 5.8 mg IR3535/kg per application, while a child 1-2 years old would be exposed to 14.4 mg IR3535/kg per application. From this, a Margin of Exposure (MOE) following dermal application in adults is 129 and in children is 52 based upon this endpoint. Given its classification and nature as a Biochemical pesticide, these MOEs will provide adequate protection.

Cumulative Exposure

There is no indication of cumulative toxicological effects of other environmental agents with IR3535.

Safety Determination

General Population. Based upon expected dermal exposure as an insect repellent, there is a reasonable certainty of no harm resulting from exposure of IR3535 to the general population.

Infants and Children. The toxicological data indicate that IR3535 is not a developmental, reproductive, immunological, or neurological toxicant, and that infants and children are not sensitive subpopulations. There is a reasonable certainty that no harm will result from exposure of IR3535 to infants and children.