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DATA EVALUATION RECORD

STUDY TYPE: Mammalian cells in culture/forward gene mutation assay in Chinese hamster lung (V79) cells; OPPT 870.5300 [84-2]

DP BARCODE: D243979

SUBMISSION CODE: S538757

P.C. CODE: 129112

TOX. CHEM. NO.: [N/A]

MRID NO.: 44496713

TEST MATERIAL (PURITY): Trifloxystrobin technical (96.4%)

SYNONYMS: CGA 279202 technical

CITATION: Herter, Th. (1995). Gene Mutation Test with Chinese Hamster Cells V9, conducted at the Genetic Toxicology Laboratory of Norvartis Crop Protection, AG, Basle (Switzerland), Test No. 943075 (Novartis Nexus Number 770-95), dated July 5, 1995. MRID NO. 44496713. Unpublished.

SPONSOR: Novartis Crop Protection, Inc. (formerly CIBA-GEIGY), Greensboro, NC

EXECUTIVE SUMMARY: In a mammalian cell forward gene mutation assay (MRID 44496713), duplicate cultures of V79 Chinese hamster lung cells were exposed in three independent trials to Trifloxystrobin technical (96.4%) dissolved in dimethylsulfoxide (DMSO) for five hours at concentrations ranging from 11.11 to 833.5 ug/mL in cultures activated by post-mitochondrial supernatant (S9 fraction) from Aroclor 1254-induced rat liver (supplemented with NADP(H)-generating co-factors), or for 21 hours at test concentrations ranging from 0.14 to 833.5 ug/mL in the absence of such activation. In addition to vehicle (DMSO) controls, additional cultures of V79 cells were exposed to the mutagens dimethylnitrosamine (1.0 uL/mL DMN, active only under metobolic activation) and ethylmethanesulfonate (0.3 uL/mL EMS, active directly without such activation) as positive controls. Following subculturing for 5 to 7 days (expression period) to accumulate any mutations, detection of gene mutation colonies was quantified by comparing 6-thioguanine (6-TG)-resistant colonies in test and vehicle control cultures.

A test article concentration of 833.5 ug/mL was the highest that could be applied to cell cultures, because of severe solubility limitations; precipitation of test substance was also visible at concentrations as low as 150 ug/mL with activation, and 50 ug/mL without. In the first trial, severe (>90%) cytotoxicity was observed at the highest test concentration with/without S9 activation, precluding any analysis of mutation; lesser degrees of cytotoxicity (25-50%) were found at lower concentrations in activated cultures of trial-1 (at 277.8 ug/mL), trial-2(at 300 ug/mL) and trial-3 (at 250 ug/mL). Varying degrees of cytotoxicity were also observed in nonactivated cultures: 50% at 92.6 ug/mL in trial-1; 30% at 100 ug/mL in trial-2, and approximately the same at 150 ug/mL in trial-3. No cytotoxicity was found in activated cultures treated at concentrations less than 150 ug/mL, nor in nonactivated cultures exposed to less than 50 ug/mL. Statistically significant increases in mutant frequency were recorded in activated cultures of trial-1 at 277.8 ug/mL but not at the next lower (nontoxic) concentration (92.6 ug/mL), nor at any nontoxic concentration (11, 33, or 100 ug/mL) below the lethal 300 ug/mL of trial-2. All activated cultures of trial-3, both toxic (200, 250 ug/mL) and nontoxic (100, 150 ug/mL) concentrations provided statistically significant increases in mutant frequencies and the vehicle control frequency was within historical range (0-100 x 10^6). **We conclude that this series of experiments with V79 cells demonstrates a relevant increase in mutant frequencies, though at dose levels of cytotoxicity.** Among nonactivated cultures, consistently significant increased mutation was evident at 92.6 ug/mL in trial-1 and 100 ug/mL in trial-2 (both moderately toxic doses), but nonsignificant in trial-3 at nontoxic (50, 75, or 100 ug/mL) or toxic (150 ug/mL) concentrations. The test article, however, is considered to be equivocal in this part of study since lower absolute number of mutant colonies at 92.6 ug/mL in trial 1 was observed when comprared with negative control (14.4 vs 17.0). Compared to these varied results with the test compound, both positive controls registered strongly positive results in all trials.

This study is classified as acceptable in satisfying the requirements for FIFRA Test Guideline (84-2) mutagenicity (mammalian cell in vitro forward mutation) data.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

NB: This EPA-generated Executive Summary disagrees with the attached CALEPA Toxicology Study Evaluation Worksheet dated 6/4/98 on the conclusion that the increases in mutant frequency were observed at 92.6 ug/mL in trial-1 and 100 ug/mL in trial-2 without activation. The Agency considers that the increases in mutation frequency were acceptable at 100 ug/mL in trail-2 (see above for details).

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DP Barcode:	D243979
HED DOC Number:	013599
Toxicology Branch:	TOX2