CYCLOHEXIMIDE

Task 3: Environmental Fate Profile

Contract No. 68-01-5830

Final Report

October 26, 1981

SUBMITTED TO:

Environmental Protection Agency
Arlington, Virginia 22202

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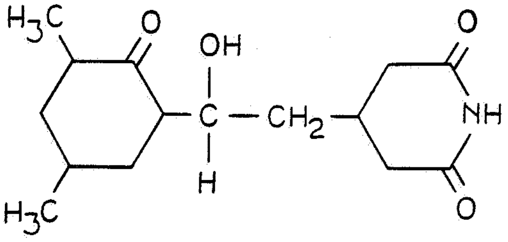
CYCLOHEXIMIDE

Task 3

CYCLOHEXIMIDE, ACTI-AID, ACTI-DIONE,
ACTISPRAY, HIZAROCIN



3-{2-(3,5-Dimethyl-2-oxocyclohexyl)-2-hydroxyethyl-}glutarimide

Environmental Fate Profile

Available data are insufficient to fully assess the environmental fate of cycloheximide.

Cycloheximide is dehydrated in solution to yield trans-anhydrocycloheximide, which is rehydrated to yield α-epicycloheximide and/or α-epi-Naramycin B (Garrett and Notari, 00011594). Dehydration is very rapid in alkaline and highly acidic solutions (Garrett and Notari, 00011595). The slowest rate of dehydration occurs at pH 4.4, and the rate increases with increasing temperature. Precise estimates of reaction rates and product values under typical environmental conditions are not available. Based on the available data, however, maximum yields of these products are expected to be >10% of the applied cycloheximide. A minor transformation product (<10%) may be derived from the isomerization of trans-anhydrocycloheximide to yield the cis isomer and then rehydration to give isocycloheximide, but this has not been definitively shown (Garrett and Notari, 00011594).

The glutarimide ring of cycloheximide, its isomers, and anhydrocycloheximide is readily hydrolyzed to yield the monocarboxylic acid amide (Garrett and Notari, 00011594 and 00011595). The reaction occurs instantly in highly alkaline solutions, and the rate decreases with decreasing pH. Further hydrolysis yields ammonia and the dicarboxylic acid. The latter reaction is favored in acidic solutions but is rate limiting in alkaline solutions.

At 20-30 C, hydrolysis reaches 10% completion in 2-3 hours and 7-11 days at pH 9 and 7, respectively. The experimental conditions of these studies were often outside of the range of interest for the development of useful environmental fate information. Another hydrolysis reaction in alkaline solutions was observed by Kornfeld (05013827). This reaction occurred at the α-carbon atom of cycloheximide (and the equivalent position of anhydrocycloheximide) to yield d-2,4-dimethylcyclohexanone. The glutarimide ring was simultaneously hydrolyzed to yield ammonia and propionaldehyde-3,3-diacetic acid. The latter compound is readily oxidized to methanetriacetic acid. This study was done in 5 N NaOH, which is drastically different from usual environmental conditions.

Cycloheximide dissipates rapidly from soil. Cycloheximide, at 0.13-10 ppm, had a half-life of 1.5-3 days in a loam and an unidentified soil at 24 and 28 C, respectively (Gottlieb et al., No MRID), a sandy soil outdoors (in a container) in Florida during January (Petzold et al., 00012843), and a mixture of three soils at 35 C (Petzold and Chapman, 00011196 and 00012845). When [^{14}C]cycloheximide was used in the soil mixture, extractable ^{14}C had a half-life of about 2 days (Petzold and Chapman, 00012845). More than 80% of the applied ^{14}C volatilized during 9 days of incubation, and <15% was unextractable. Microorganisms contribute to degradation of cycloheximide in soil, as determined by comparison of sterile and non-sterile soil samples (Gottlieb et al., No MRID; Petzold and Chapman, 00012845). No data were available on degradation products formed in soil.

Cycloheximide is toxic to fungi. Based on the available data (Anilkumar and Chakravarti, 05019056; Coursen and Sisler, 05013934; Di Menna, 05014316; Gottlieb et al., No MRID; Hacskaylo, 05013615; Martin and Nicolas, 05012807; Naumova and Naumov, 05016140; Partridge, 05016063; Ryder and Peberdy, 05021327; Tani et al., 05013498; Vaartaja and Agnihotri, 05013346), it is expected that cycloheximide in soil at ≥1 ppm will markedly inhibit fungal growth. Cycloheximide, at 0.7 ppm, also induced the elimination of extrachromosomal genes in Saccharomyces cerevisiae (Naumova and Naumov, 05016140). Cycloheximide also is toxic to other eucaryotic organisms. At ∿30 ppm, cycloheximide inhibited respiration by the protozoan Tetrahymena pyriformis (Mefferd and Loefer, 05017110) and rhizoid formation by the green alga Boergesenia forbesii (Ishizawa et al., 05021055).

The growth of most bacteria in soil should not be affected by cycloheximide at low concentrations (≤1 ppm) (Anilkumar and Chakravarti, 05019056). Cycloheximide, at 4,000 ppm, inhibited soil respiration for 6 hours (Vancura and Kunc, 05016745), but no data are available for lower concentrations and longer time periods. The growth of some blue-green algae is inhibited by cycloheximide at ≥50 ppm (Kapoor and Sharma, 05021783; Yopp et al., 05018934). In vitro nitrogen fixation was markedly inhibited by cycloheximide at ≥50 ppm (Kapoor and Sharma, 05021783). Cycloheximide inhibited nodule formation in the symbiotic association between Rhizobium trifolii and clover (Robinson, 05013679).

[^{14}C]Cycloheximide and its residues were very mobile in sand soil. In a rapid leaching study, over 95% of the applied ^{14}C leached through a 12-inch column eluted with the equivalent of 20 acre-inches of water (Staten et al., 00011189). Cycloheximide comprised 64% of the ^{14}C residues. When residues were aged 30 days (Staten et al., 00011190), 52% of the applied ^{14}C was leached, 15% remained in the soil, and 27% had dissipated. In this study, cycloheximide was not detectable in the leachate. In a soil thin-layer chromatography study (Helling et al., 05001190), cycloheximide was mobile to very mobile (R_f, 0.89) in a silty clay loam soil.

Cycloheximide dissipated rapidly under field conditions (Petzold et al., 00012843), with a half-life of 2 days in sandy soil treated with 4.23% ai WP at ∿0.19 lb ai/A.

Cycloheximide does not accumulate in bluegills. For fish exposed to two doses of [^{14}C]cycloheximide at 0.09 ppm, the maximum bioaccumulation factor for ^{14}C residues was <10 during a 1-month exposure period (Petzold and Chapman, 00012864 and 00012880). Cycloheximide is relatively soluble in water (2.1% at 2 C; the Merck Index, 9th ed., Merck & Co., Rahway, NJ, 1976), and therefore should have a low octanol/water partition coefficient. Cycloheximide had a half-life of about 4-7 days in nonsterile water typical of natural systems (Petzold and Chapman, 00012864 and 00012880; Petzold et al., 00012843).

In summary, cycloheximide has a half-life in soil of about a week or less. The identity of products formed in soil are not known from the available data, but loss of products or parent compound by volatilization is indicated. Cycloheximide will be toxic to fungal and protozoan populations immediately following application, but long-term effects are not expected due to the rapid dissipation rate. Products formed in water are: trans-anhydrocycloheximide; cycloheximide isomer(s) that is probably α-epi-Naramycin B and/or α-epicycloheximide; monocarboxylic acid amides and dicarboxylic acids of cycloheximide, its isomers, and anhydrocycloheximide; and ammonia. Cycloheximide and its residues readily leach in sand soil, and cycloheximide is mobile to very mobile in silty clay loam soil. If cycloheximide enters an aquatic system, it will be rapidly transformed, and residues are not expected to accumulate in aquatic non-target organisms.

Summary of Major Data Gaps

The major data gaps for this chemical are: hydrolysis studies; photodegradation studies in water, on soil, and in air; aerobic soil metabolism studies; two rapid leaching studies in either sandy loam, clay, or clay loam soil; laboratory and field volatility studies; and terrestrial field dissipation studies. Reentry data may be required as determined by further review.

Label Restrictions

At present, there are no label restrictions regarding the environmental chemistry of cycloheximide.

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