United States Environmental Protection Agency | Prevention, Pesticides And Toxic Substances (7501W) | EPA-738-F-95-025 December 1995

R.E.D. FACTS

Cytokinin

Pesticide Reregistration

All pesticides sold or distributed in the United States must be registered by EPA, based on scientific studies showing that they can be used without posing unreasonable risks to people or the environment. Because of advances in scientific knowledge, the law requires that pesticides which were first registered before November 1, 1984, be reregistered to ensure that they meet today's more stringent standards.

In evaluating pesticides for reregistration, EPA obtains and reviews a complete set of studies from pesticide producers, describing the human health and environmental effects of each pesticide. The Agency develops any mitigation measures or regulatory controls needed to effectively reduce each pesticide's risks. EPA then reregisters pesticides that can be used without posing unreasonable risks to human health or the environment.

When a pesticide is eligible for reregistration, EPA explains the basis for its decision in a Reregistration Eligibility Decision (RED) document. This fact sheet summarizes the information in the RED document for reregistration case number 4107, Cytokinin.

Use Profile

Cytokinin is a group of plant regulators that promote cell division, leaf expansion and retard leaf aging. Cytokinin is applied to growing crops (field crops, vegetable crops, small fruits, vines and tree fruit), young trees, ornamentals, and golf courses to increase fruit size, yield, blossoms, branching, healthy appearance, and other desirable growth effects. Cytokinin is comprised of four naturally occurring cytokinins derived from aqueous extract of seaweed meal -- zeatin [6-(4-hydroxy-3-methylbut-trans-2-enylamino)-purine], N^6-methylaminopurine, N^6-dimethylaminopurine, and N^6-isopentenylaminopurine -- and synthetic cytokinin -- kinetin [6-(furfurylamino)purine]. Cytokinins (i.e. naturally occurring) in aqueous extracts of seaweed meal, are derived from the following algae: *Laminaria digitata*, *Laminaria hyperborea*, *Fucus serratus* and *Ascophyllum nodosum*. Several, if not all of these species of algal species are consumed by man and/or livestock. The extracts from these plant species (e.g. the naturally occurring Cytokinins) are exempt from the requirements of tolerances when used as plant regulators in or on many raw agricultural commodities (40 CFR 180.1042).

Formulation Types Registered:

Formulations include a soluble concentrate/liquid (manufacturing use product), and flowable concentrate, soluble concentrate/liquid, ready-to-use liquid (end use products).

Methods and Rates of Application:

Cytokinin may be applied by aircraft, irrigation system, ground spray equipment, seed treatment, or soil incorporation.

Use Practice Limitations:

Preharvest Intervals of 14 or 21 days may be required, depending on the crop.

The Use Practice Limitations listed below do not apply to all uses on all products:

"Do not allow rinse water to contaminate streams, ponds and lakes, as water life may be endangered."

"Do not apply through any type of irrigation system."

"Do not apply to any body of water."

"For terrestrial uses, do not apply directly to water or to areas where surface water is present or to intertidal areas below the mean high water mark."

"Do not connect an irrigation system (including greenhouse systems) used for pesticide application to public water system unless the pesticide label-prescribed safety devices for public water systems are in place."

Regulatory History

The plant growth regulator, Cytokinin, was initially registered in the United States in 1978 as CYTEX® (EPA Reg. No. 35980-1) for applications to certain citrus, fruit and vegetable crops. Cytokinin acts as a plant regulator by promoting cell division; minimizing effects of stress; stimulating roots; increasing yield; increasing vegetative growth; and increasing tuber firmness.

During Phase 4 of the accelerated pesticide reregistration process, the data base for Cytokinin was evaluated and determined to be inadequate in satisfying certain requirements for biochemical pesticides which include plant regulators. A DCI was issued in August 1993 to fill the outstanding data gaps.

Since the DCI, the Agency's initial position regarding these data gaps was re-evaluated. All of these data requirements, except a Non-target insects study, were waived because available information indicates that Cytokinin does not cause unreasonable adverse effects: (1) The principal constituents of Cytokinin, algae and seaweed, are natural components of fish diets, (2) Cytokinin has a very low acute mammalian toxicity, (3) Cytokinin is used as a dietary supplement in animal feeds, and (4) Cytokinin pesticide products are expected to have no adverse effects to fish and wildlife.

Human Health Assessment

Toxicity

In studies using laboratory animals, Cytokinin generally has been shown to be of low acute toxicity. The acute dermal toxicity ($LD_{50} > 2g/kg$), eye irritation (slight irritation), and dermal irritation (slightly irritating) place Cytokinin in Toxicity Category III (the second lowest of four toxicity categories). Cytokinin's oral toxicity ($LD_{50} > 5g/kg$) places it in Toxicity Category IV (the lowest of four toxicity categories).

[NOTE: For acute oral, dietary, mammalian/avian/aquatic toxicity:
Category I = very highly or highly toxic
Category II = moderately toxic
Category III = slightly toxic
Category IV = practically non-toxic]

Dietary Exposure

Only the four naturally occurring Cytokinins, derived from certain algal species, are exempt from the requirement of a tolerance when used as a plant growth regulator (40 CFR 180.1042). At this time, synthetic Cytokinin is not included in this tolerance exemption.

Tolerance exemptions are often based on the results of 90-Day (or longer) feeding and developmental toxicity studies submitted to support reregistration. However, it is the Agency's opinion that these studies can be waived for naturally occurring and synthetic Cytokinin because of low acute mammalian toxicity and very low use rates, which would not significantly increase dietary intake over natural consumption in foods. The Agency, will be proposing an exemption from the requirement of a tolerance for certain Cytokinins (zeatin [6-(4-hydroxy-3-methylbut-trans-2-enylamino)-purine], N^6-methylaminopurine, N^6-dimethylaminopurine, N^6-isopentenylaminopurine), and synthetic cytokinin -- kinetin [6-(furfurylamino)purine] for all raw agricultural commodities (RACs). The exemption will apply only when application rates do not exceed 250 grams of active ingredient/acre/year. The Agency believes this action does not present any unreasonable risk. It is based on Cytokinin's low acute mammalian toxicity, its low use rates, exposure in the diet from numerous

natural plant food sources, and minimal exposure in the diet derived from consumption of treated commodities under the proposed maximum label use rates.

The Agency has concluded that dietary exposure risks from consuming commodities treated with Cytokinin, either naturally occurring or synthetic, are not expected.

Occupational and Residential Exposure

Based on the application methods listed on Cytokinin product labels, the potential for eye, dermal and inhalation exposure to agricultural workers does exist. However, since Cytokinin is in Toxicity Categories III and IV for acute oral, dermal, eye irritation and dermal irritation, to reduce worker exposure. The Agency has concluded that these occupational exposures and subsequent risks will be negligible because of Cytokinin's low acute mammalian toxicity and low use rates. Also, the precautionary product labeling stipulated in the RED document will sufficiently mitigate exposures and any subsequent risks to agricultural workers.

Human Risk Assessment

Since exposures and subsequent risks from Cytokinin applications are not expected, any potential risks from exposure to treated plants will be mitigated by the use of personal protective equipment required by the Worker Protection Standard, supplemented by specific precautionary labeling required by this RED. Post-application reentry workers are required to observe a 12 hour Restricted Entry Interval. Because of Cytokinin's ubiquitous nature and low toxicity, however, it is a candidate for a reduced reentry interval: from 12 hours to 4 fours.

Environmental Assessment

Based on a review of all available ecological data, exposure information, and Cytokinin's non-toxic mode of action, the Agency expects that applications of Cytokinin will pose minimal risk to nontarget wildlife and fish.

Environmental fate studies for biochemicals are not imposed unless adverse effects are observed in ecological effects data. Since no adverse effects are anticipated, the Agency will not, at this time, impose any environmental fate data requirements for the currently registered uses of Cytokinin.

Additional Data Required

EPA is requiring a revised Confidential Statements of Formula (CSFs) and revised product labeling for reregistration.

Product Labeling Changes Required

The Agency has reexamined the toxicological data base for Cytokinin and concluded that the current precautionary labeling (i.e. Signal Word, Statement of Practical Treatment, WPS required labeling, and other label statements associated with mitigating risks) adequately mitigate any risks associated with the use of this plant growth regulator.

Regulatory Conclusion

Based on the reviews of the generic data for Cytokinin, the Agency has sufficient information on health effects and the potential for causing adverse effects in fish and wildlife. The Agency has determined that products containing Cytokinin, when labeled and used as specified in this RED, will not pose unreasonable risks or adverse effects to humans or the environment. Therefore, the Agency concludes that products containing Cytokinin for certain uses that have a tolerance exemption (i.e. food uses/commodities listed in 40 CFR 180.1042) are eligible for reregistration. Other food uses of Cytokinin which do not have an exemption from tolerance requirements (i.e., those food uses/commodities not listed in 40 CFR 180.1042) will become eligible for reregistration only when a tolerance exemption is issued and becomes a final rule. The Agency plans to propose such an exemption and pending public comment, issue a final rule in early 1996.

For More Information

EPA is requesting public comments on the Reregistration Eligibility Decision (RED) document for Cytokinin during a 60-day time period, as announced in a Notice of Availability published in the Federal Register. To obtain a copy of the RED document or to submit written comments, please contact the Pesticide Docket, Public Response and Program Resources Branch, Field Operations Division (7506C), Office of Pesticide Programs (OPP), US EPA, Washington, DC 20460, telephone 703-305-5805.

Electronic copies of the RED and this fact sheet can be downloaded from the Pesticide Special Review and Reregistration Information System at 703-308-7224. They also are available on the Internet on EPA's gopher server, *GOPHER.EPA.GOV*, or using ftp on *FTP.EPA.GOV*, or using WWW (World Wide Web) on *WWW.EPA.GOV*.

Printed copies of the RED and fact sheet can be obtained from EPA's National Center for Environmental Publications and Information (EPA/NCEPI), PO Box 42419, Cincinnati, OH 45242-0419, telephone 513-489-8190, fax 513-489-8695.

Following the comment period, the Cytokinin RED document also will be available from the National Technical Information Service (NTIS), 5285 Port Royal Road, Springfield, VA 22161, telephone 703-487-4650.

For more information about EPA's pesticide reregistration program, the Cytokinin RED, or reregistration of individual products containing Cytokinin, please contact the Biopesticides and Pollution Prevention Division (7501W), OPP, US EPA, Washington, DC 20460, telephone 703-308-8712.

For information about the health effects of pesticides, or for assistance in recognizing and managing pesticide poisoning symptoms, please contact the National Pesticides Telecommunications Network (NPTN). Call toll-free 1-800-858-7378, between 9:30 am and 7:30 pm Eastern Standard Time, Monday through Friday.