Xanthine (116900) and Oxypurinol (447509) Technical Document

Issued: 4/99

I. Executive Summary

A. Identity

The manufacturing use product, Xanthine and Oxypurinol Manufacturing Use Concentrate, EPA Registration No. 71144-E contains 50% xanthine (CAS number 69-89-6) and 50% oxypurinol (CAS number 2465-59-0). The end-use product, Ecologix^{TM} Cockroach Bait, EPA Registration No. 71144-R contains 1% xanthine and 1% oxypurinol as its active ingredients. The components of both the manufacturing use and the end use products are adequately identified and the product chemistry data submitted satisfies the requirements for product identity.

B. Use / Usage

The manufacturing use product (MUP) will be used in the formulation of cockroach baits for commercial and/or domestic indoor use. The end-use product will be used to control cockroaches in commercial, industrial and residential areas. The Agency has classified this use as an indoor non-food use because the active ingredients are formulated into a solid pellet that is enclosed in a bait station and there are no volatile components. The bait use directions state that stations should be placed in areas where cockroaches have been seen and where they hide such as in dark, warm, damp locations near food and water. There are no usage data yet since this is the first registration for this product.

Oxypurinol, one of the components of the end-use product and MUP, is a metabolite of the human drug allopurinol (refer to section II (F) for structures) which has been used in the treatment of gout, hematological disorders and in antineoplastic therapy. Xanthine, the other component, is a naturally occurring intermediate in purine metabolism and is found in all living cells and tissues.

C. Risk Assessment

1. **Human Health Risk Assessment**

    a. **Toxicological Endpoints**

Mammalian toxicity data have been submitted and adequately satisfy data requirements to support registration. Submitted data indicate that the MUP should be classified as Toxicity Category III for acute dermal and inhalation toxicity, Toxicity Category IV for acute oral toxicity and was found to cause slight irritation in a dermal irritation study (Toxicity Category IV) and slight to moderate conjunctival irritation in a eye irritation study (Toxicity Category III). The MUP did not cause dermal sensitization in test animals.

Although published data have indicated possible toxicological endpoints for use in this assessment, none of those endpoints were considered appropriate for assessing risk from use of xanthine and oxypurinol in cockroach bait stations because: (1) the endpoints were observed in patients with health that was compromised before their treatment with allopurinol/oxypurinol or (2) after doses of allopurinol/oxypurinol were administered to laboratory animals by injection which is not comparable to routes of exposure considered in this risk assessment.

b. **Human Exposure**

The Agency has determined that the possibility for human exposure to the active ingredients in the bait would be low based on the following estimates: -the bait station contains 47.2 mg of total active ingredient (23.6 mg oxypurinol which is approximately half of a therapeutic dose [23.6 mg/10 kg child = 2.4 mg/kg and 5 mg/kg is lowest recommended therapeutic dose for allopurinol]). This assessment will only address oxypurinol because xanthine, the other half of the total active ingredient is a naturally occurring substance, part of purine metabolism and excretion, and is not considered to be of toxicological concern (especially at the levels incorporated in the bait).

Because in *in vivo* therapeutic uses, allopurinol is mostly converted to oxypurinol, a comparison can be made with the therapeutic doses of allopurinol to qualitatively characterize the risk potential of the oxypurinol portion of the total active ingredient. Therefore the exposure for consuming all the bait in one station would be:

2.4 mg/kg for 10 kg child

0.4 mg/kg for 60 kg person

0.3 mg/kg for a 70 kg person

These exposure estimates range from 2 to 16.7 fold less than the lowest recommended therapeutic dose. For the 10 kg child or infant, the 2.4 mg/kg dose level is about one-fourth that noted in a nursing infant whose mother was undergoing allopurinol treatment. (see section III (B) (1) (d) under Developmental and Reproductive Toxicity). Therefore, the Agency has concluded that potential risk to infants and children from accidental dietary exposure is very limited.

Although it is possible that adults and children may come into contact with the sealed bait stations, the Agency has determined that health risks are expected to be minimal to nonexistent based on the amount of total active ingredient in the bait and the design of the bait station to assure that the bait pellet will not be easily dislodged from the packaging.

c. **Risk Assessment**

Although published data have indicated possible toxicological endpoints for use in this risk assessment, none of these endpoints were considered appropriate for assessing risks from use of xanthine and oxypurinol in cockroach bait stations for the reasons stated above. Enclosing the small amounts of the active ingredients in bait stations and following the label's instructions for use practically eliminates any exposures, and there is reasonable certainty of no harm resulting from inadvertent exposure to the small amounts of active ingredients contained in a single bait station.

2. **Ecological Risk Assessment**

a. **Ecological Toxicity Endpoints**

No toxic endpoints were identified.

b. **Ecological Exposure**

Nontarget organism requirements data were waived based on low acute toxicity in mammalian species and lack of exposure to the environment.

c. **Risk Assessment**

The use of xanthine and oxypurinol according to label use directions should result in no significant adverse effects to wildlife.

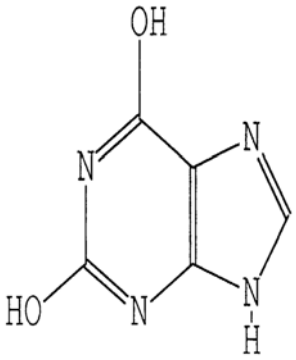
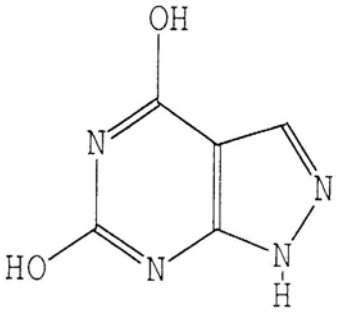
D. Data Gaps / Labeling Restrictions

There are no data gaps.

II.

III. Overview

A. **Active Ingredient Overview**

Compound	**Xanthine**	**Oxypurinol**
Structure		
Common Name:	Xanthine	Oxypurinol
Chemical Name:	3-7-dihydro-1H-purine-2,6-dione	1H-pyrazolo [3,4-d] pyrimidine-4,6-(5H,7H)-dione
Chemical Formula:	$C_5H_4N_4O_2$	$C_5H_4N_4O_2$
Chemical Family:	Purine	Pyrazolopyrimidine
CAS Registry Number:	69-89-6	2465-59-0
OPP Chemical Code:	116900	447509

B. Ecologix TM Cockroach Bait

C. **Nonfood Use Sites**

Residential, warehousing and commercial establishments, including food service, food manufacturing and food processing facilities, hospitals, nursing homes, health care facilities, schools, daycare centers, basements, laboratories, computer and electronic equipment facilities, pet shops, zoos, aircraft, buses, boats and trains.

D. Use Profile

The following is information on the proposed uses with an overview of use sites and application methods.

Type of Pesticide: Insecticide

Use Sites: INDOOR NON-FOOD

The bait use directions specify that stations should be placed in areas where cockroaches have been seen and where they hide such as in dark, warm, damp locations near food and water. Use sites include: residential, warehousing and commercial establishments, including food service, food manufacturing and food processing facilities, hospitals, nursing homes, health care facilities, schools, daycare centers, basements, laboratories, computer and electronic equipment facilities, pet shops, zoos, aircraft, buses, boats and trains.

(The Agency has determined in the past that bait products can be classified as a non-food use when the active ingredients are formulated into a solid that is enclosed in a bait and is not volatile).

Target Pests: Cockroach

Formulation Types: Manufacturing Use Concentrate and end use bait product

Method and Rates of Application: Bait

For light to moderate infestations - use 6 bait stations per 100 square feet of horizontal surface area.

For heavy infestations - label recommends the use of a residual insecticide to reduce populations before placing the bait stations then place 10-12 bait stations per 100 square feet of horizontal surface.

Bait label states this product is a long-term control agent and populations reductions will not be evident for six to ten weeks.

Rate: 0.00166 oz ai per station or 47.2 milligram ai per station (total ai including each active ingredient)

Timing: As needed

Use Practice Limitations:

For effective cockroach control, enough bait stations must be placed in areas of cockroach feeding to insure complete exposure of the cockroach population to the bait.

Do not spray the bait stations with insecticides or household detergents and avoid placing the bait stations on surfaces freshly sprayed with these products.

E. Estimated Usage

None used yet since this will be the first registered product

F. Data Requirements

Most of the supporting information consisted of published references which were summarized, and copies of each reference were attached under MRID 44533101. Most of the publications included in the submission related to allopurinol (see discussion below). The experiments described in the summarized literature consisted primarily of single-dose or limited dose studies designed to investigate specific aspects of the mechanism of action, pharmacology, drug interactions, or other aspects of responses to allopurinol and its metabolite oxypurinol under therapeutic conditions so application of the information from these non-guideline studies to the use of oxypurinol as a pesticide is limited. The references cited in this document are listed in the bibliography.

The mammalian toxicology and ecological effects data requirements for xanthine and oxypurinol have been fulfilled. Product analysis data requirements are adequately satisfied. The data requirements for granting these registrations under Section 3(c)(5) of FIFRA have been reviewed by the Biopesticides and Pollution Prevention Division (BPPD). Based on submitted information and limited potential for exposure, the Agency foresees no unreasonable adverse effects to human health and the

environment from the use of these chemicals and recommends an unconditional registration of these new active ingredients for the proposed uses.

G. Regulatory History

In October 1997 the Agency received applications from Dominion BioSciences Inc. to register both the Xanthine and Oxypurinol Manufacturing Use Concentrate and the end use product, Ecologix™ Cockroach Bait. This action registers the first end use and manufacturing use products for xanthine and oxypurinol as active ingredients.

A notice of receipt of the application for registration for both the Xanthine and Oxypurinol Manufacturing Use Concentrate and the Ecologix™ Cockroach Bait was published in the Federal Register (volume 63, number 155, pages 43177-43178) on August 12, 1998. No comments were received as a result of this publication.

H. Classification

Oxypurinol is the major active metabolite of the human drug allopurinol which has been used since the late 1960's in treating the hyperuricemia associated with gout and some hematological disorders. Allopurinol is also used in antineoplastic therapy. The drug and its metabolite are structurally similar to the natural purine bases hypoxanthine and xanthine, respectively (see Figure 1 below). Both allopurinol and oxypurinol are substrates for and inhibitors of xanthine oxidase which converts hypoxanthine to xanthine and xanthine to uric acid, an end product of purine metabolism in man. Oxypurinol is formed by the action of xanthine oxidase on allopurinol and that metabolite is a noncompetitive inhibitor of the enzyme. The formation of oxypurinol is responsible for the majority of the inhibition of xanthine oxidase which accounts for the major pharmacological effects of allopurinol.

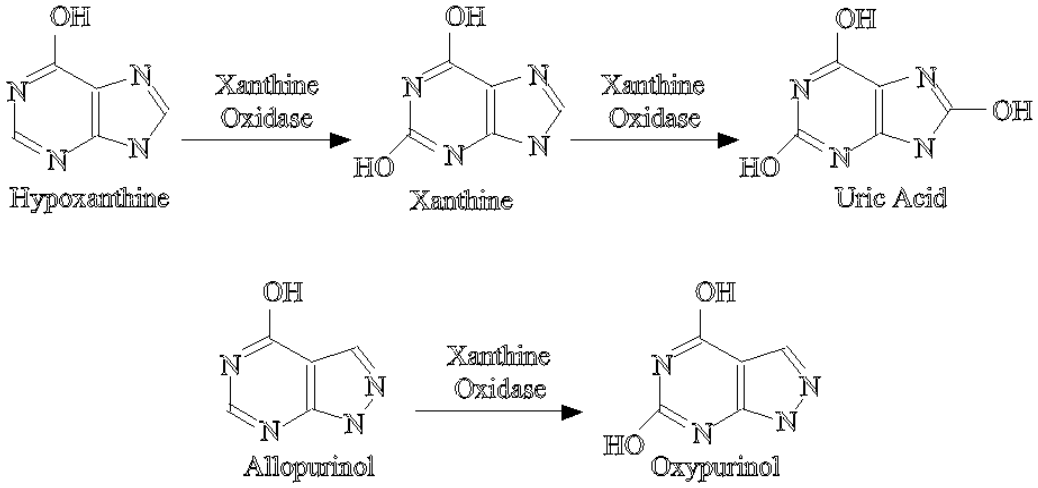


Figure 1: *Metabolic pathway for the conversion of hypoxanthine to xanthine, xanthine to uric acid and allopurinol to oxypurinol*

The Agency has concluded that xanthine/oxypurinol combination products can be considered reduced-risk, biochemical-like chemicals because they may operate through what could be considered a non-toxic mode of action. Although xanthine is a naturally occurring substance (see Figure 2), oxypurinol in the MUP cannot be classified as a biochemical pesticide because it does not fit the current definition which requires that this combination product be functionally identical to naturally occurring substances. That is, the oxypurinol component is a noncompetitive inhibitor of xanthine oxidase and can not functionally substitute for xanthine in purine metabolism.

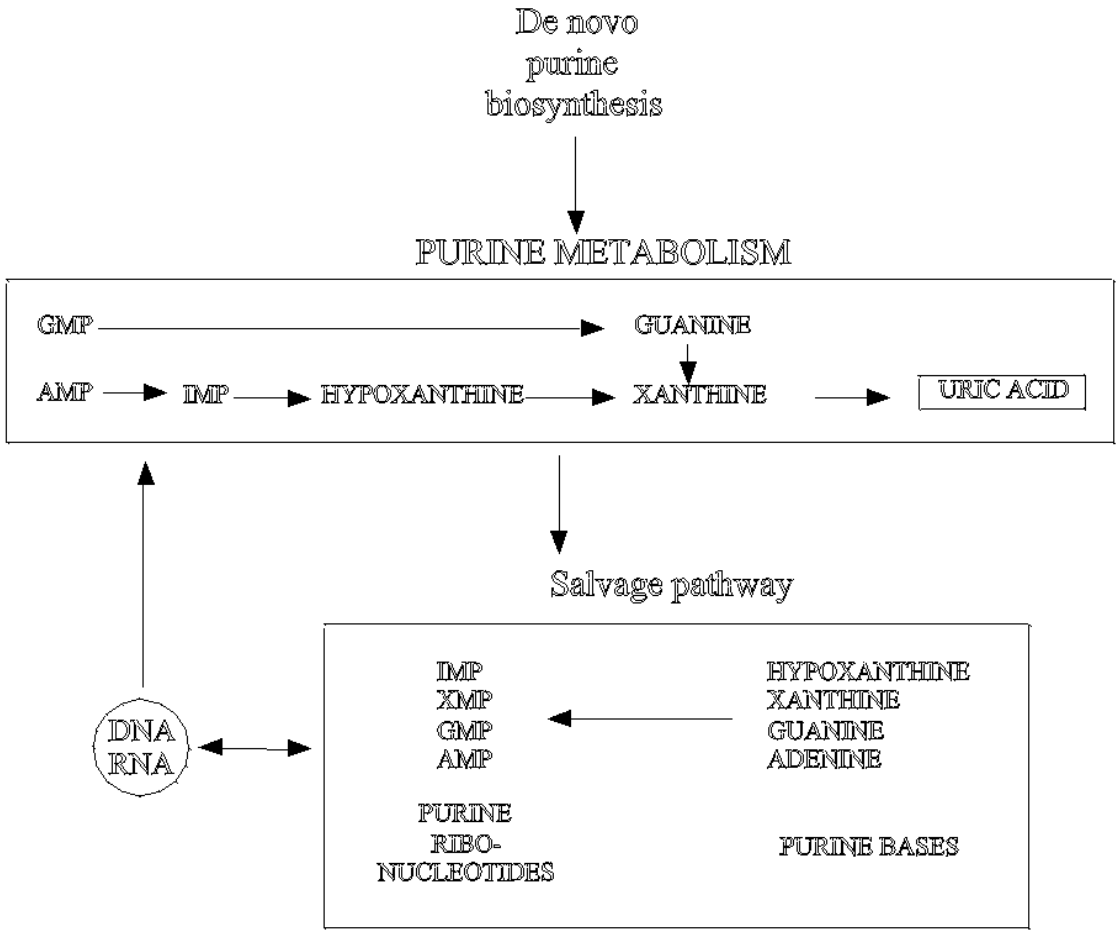


Figure 2: *A diagram (adapted from Murrell and Rapeport, 1986) of purine metabolism illustrating where the xanthine oxidase mediated steps (hypoxanthine xanthine uric acid) are located. De novo purine biosynthesis produces adenosine and guanosine monophosphates (AMP and GMP) which enter the purine metabolic pathway where xanthine oxidase activity produces hypoxanthine, xanthine and uric*

acid. The salvage pathway also uses the purine pool to produce monophosphates of xanthine and inosine (XMP and IMP) as well as AMP and GMP. The AMP and GMP are used as components of nucleic acids (DNA and RNA) or they may be converted to the triphosphate ATP for use in other metabolic processes.

I. Food Clearances / Tolerances

A numeric tolerance or exemption from the requirement of a tolerance is not needed since there are no food uses associated with the registrations.

IV. Science Assessment

A. Physical /Chemical Properties Assessment

All product chemistry data requirements for technical xanthine/oxypurinol are satisfied.

1. **Product Identity and Mode of Action**

   a. **Product Identity:**

   The manufacturing use product, Xanthine and Oxypurinol Manufacturing Use Concentrate, EPA Registration No. 71144-2 contains 50% xanthine (CAS number 69-89-6) and 50% oxypurinol (CAS number 2465-59-0). The end-use product, Ecologix^{TM} Cockroach Bait, EPA Registration No. 71144-1 contains 1% xanthine and 1% oxypurinol as its active ingredients.

   The MUP can be characterized as an off-white solid with a slightly musty odor. It has a melting point of 177 C, a density of 0.65 g/cm^3 at 25 C and a pH of 6.8 - 7.0. The compound was found to be stable at 54C and 25 C for 90 days and one year, respectively.

   b. **Mode of Action:**

   The active ingredients act in combination as nutritional metabolism disrupters to block the production of uric acid needed for cockroach growth and reproduction (egg production) (see Figure 2 above).

2. **Food Clearances/Tolerances**

There are no food uses associated with these registrations, therefore, a tolerance establishment/exemption is not an issue in this case.

3. **Physical And Chemical Properties Assessment**

Table 1. Product chemistry data requirements for the manufacturing use product.

GUIDELINE NO.	STUDY	RESULTS	MRID NO.
151B-10 151B-11 151B-12	Product ID Manufacturing Process Discussion of Impurities	Submitted data satisfies the data requirements for product identity, manufacturing process and discussion of formation of impurities	44416401
151B-13	Analysis of samples	Submitted data satisfy the data requirements for analysis of samples	44416402
151B-15	Certified Limits	Limits listed in the CSF are adequate	CSF
151B-17	PHYSICAL/CHEMICAL PROPERTIES		
151B-17a	Color	Off-white	44416404
151B-17b	Physical State	Solid	44416404
151B-1c	Odor	Slightly musty	44416404
151B-17d	Melting point	177 C,	44416404
151B-17e	Boiling Point		N/A
151B-17f	Density/Specific gravity	0.65 g/cm^3	44416404
151B-17g	Solubility	xanthine - 26 ppm oxypurinol - 106 ppm	44416409
151B-17h	Vapor Pressure	$<1 \times 10^{-7}$ torr	44416410
151B-17i	pH	6.8 (without N_2) 7.0 (under N_2)	44416404
151B-17j	Stability	Stable	44416405

151B-17k	Flammability		N/A
151B-17l	Storage Stability	Stable	44416406 44416412 44416405 44589102
151B-17m	Viscosity		N/A
151B-17n	Miscibility		N/A
151B-17o	Corrosion Characteristics	No change at 54 C, for 45 and 90 days	44416407
151B-17p	Octanol Water Partition Coef.	acceptable	44416408

B. Human Health Assessment

The information submitted in support of the application for registration of Xanthine and Oxypurinol Manufacturing Use Concentrate and the Ecologix™ Cockroach Bait is adequate to satisfy the requirements set forth in 40 CFR 158.690 (c) for indoor non-food uses.

1. Toxicology Assessment

Adequate mammalian toxicology data are available and support registration of the combined active ingredients xanthine and oxypurinol for the uses described in this document. A summary of submitted toxicology studies to support the MUP is presented below.

Table 2. Mammalian toxicity data for MUP

GUIDELINE NO.	STUDY	RESULTS	MRID NO.
	TIER I		
152-10	Acute oral toxicity	LD_{50} > 5000 mg/kg - Toxicity Category IV	44416417
152-11	Acute dermal toxicity	LD_{50} > 2000 mg/kg - Toxicity Category III	44416418

152-12	Acute inhalation toxicity	LC_{50} > 1.9 mg/L - Toxicity Category III	44589103
152-13	Primary eye irritation	Slight to moderate conjunctival irritation - Toxicity Category III	44416419
152-14	Primary dermal irritation	Slight irritation - Toxicity Category IV	44416420
152-15	Dermal sensitization (Buehler method)	Not a sensitizer	44416421
152-16	Hypersensitivity incidents	Any incident must be reported if observed	
	Literature citations	See below	44533101
152-18	Cellular immune response	Waived	

a. **Acute Toxicity**

The registrant submitted acceptable acute toxicity studies for both the manufacturing use (MUP) and the end-use product. The results from testing with the MUP are presented in the table above.

The End-Use Product: (i.) was found to cause slight conjunctival irritation and was placed in Toxicity category III for primary dermal irritation and (ii.) was found to cause very slight erythema and was placed in Toxicity category IV for primary dermal irritation.

Published literature (*Physicians' Desk Reference*, 1994) on allopurinol, indicated that the intraperitoneal LD_{50} in mice is 60 mg/kg with deaths delayed up to five days. The oral LD_{50} in mice was reported to be 700 mg/kg with deaths delayed up to 3 days. The intraperitoneal and oral LD_{50} values in rats were reported to be 750 and 6000 mg/kg in rats, respectively. (It should be noted that because allopurinol is nearly completely converted to oxypurinol in the body, the Agency is using allopurinol data to address toxicity concerns for oxypurinol).

b. **Subchronic Toxicity**

Subchronic studies are not required because of the availability of human clinical data.

c. **Chronic Toxicity and Oncogenicity**

A publication reported (Fukushima and coworkers, 1983) the effects of allopurinol on the incidence of preneoplastic lesions in urinary bladder carcinogenesis initiated by N-nitroso-n-butyl-(4-hydroxybutyl)amine (BBN) in male F344 strain rats. Two control groups of 60 rats were given 0 or 0.01% BBN (w/w) in their drinking water for 4 weeks followed by 34 weeks without BBN to initiate urinary bladder carcinogenesis; two treated groups of 30 rats received the same pretreatments followed by 34 weeks on a diet containing 0.02% allopurinol (w/w, 200 ppm or approximately 10 mg/kg/day). The study report indicated that allopurinol had no effects on food and water consumption, body weight or weight gain, and urinary observations including pH, osmolality, and sediments. Absolute and relative (% body weight) urinary bladder weights were increased significantly ($p<0.01$) in rats given the allopurinol diet following BBN treatment (average weight of 0.16Â±0.04 g compared with 0.12Â±0.03 g in the BBN control group; and 0.04Â±0.01% compared with 0.03Â±0.01% in the allopurinol and non-BBN control groups, respectively). According to the report, there was no significant increase in the incidences of simple hyperplasia and papillary or nodular hyperplasia observed in the two allopurinol treated groups. However, the authors noted an increased density of these lesions in the allopurinol treated groups. The table below summarized the results of this study.

Table 3

Observation	BBN + control diet	BBN + allopurinol	No BBN	No BBN + allopurinol
Number examined	60	28	30	29
Simple hyperplasia (%)	46.7	64.3		
Papillary hyperplasia Incidence (%)Density (lesions per 10 cm of basal memberan)†	45.0 0.6Â±0.8	57.1 1.9Â±2.3**		
Papilloma Incidence (%)	33.3	42.9		
Density (lesions per 10	0.4Â±0.7	0.9Â±1.3		

cm of basal
memberan)†

† Results are presented as mean Â± standard deviation. ** Values differ significantly from controls (Student's t test) P <0.01.

The investigators concluded from these results that allopurinol acted as a promoter in urinary bladder carcinogenesis in the rat based on the increased density of papillary and nodular hyperplasia, and in their discussion of the results they stated:

(Allopurinol) is known to inhibit tryptophan oxygenase and may alter the pattern of urinary tryptophan metabolites...Allopurinol increases the excretion of xanthine in the urine of rats and xanthine crystals are found in the urine of rats treated with allopurinol...Urinary crystals may be a contributory factor in the induction of urinary bladder cancers. In the present work allopurinol...did not cause xanthine crystaluria or any other form of crystaluria. More information is needed to determine the mechanism of the promoting effect of allopurinol on urinary bladder carcinogenesis.

This experiment does not represent a complete assessment of the carcinogenic potential of allopurinol because a dose response relationship was not established (only one dose was tested), only preneoplastic lesions were evaluated, and a specific mechanism for tumor development (initiation/promotion) was investigated for bladder tumors. Also, long term repeated exposures are not expected from the use of oxypurinol in cockroach bait. Therefore, these results do not indicate a toxicological endpoint for use in this risk assessment. No increased incidences of cancer have been reported in patients treated with allopurinol (see section III (B) (1)(g) below).

d. **Developmental and Reproductive Toxicity**

The *Physicians' Desk Reference* (1994) stated that reproductive studies have been performed in rats and rabbits at doses up to twenty times the usual human therapeutic dose with no reports of impaired fertility or harm to the fetus due to allopurinol/oxypurinol administration.

Summary information was provided on a study where pregnant mice were given 50 or 100 mg/ kg of allopurinol/oxypurinol intraperitoneally on gestation days 10 or 13. An increased numbers of dead fetuses were observed in dams given 100 mg/kg allopurinol/oxypurinol. Also, increased numbers of external malformations in fetuses at both the 50 and 100 mg/kg dose levels were reported at gestation day 10 and increased numbers of fetuses with skeletal malformations at both doses on gestation day 13. No further information was provided on these results, but it should be noted that an intraperitoneal LD_{50} of 60 mg/kg was reported for mice (see above discussion of acute toxicity) so the doses tested in the mouse developmental toxicity study should be considered potentially lethal for adult mice as well as their offspring. Since this study used the intraperitoneal route, these results do not indicate an endpoint for use in this risk assessment.

A published report (Kamilli and Gresser, 1993) noted that the average daily dose for a five-week-old infant nursed by a mother who was taking 300 mg/day allopurinol for four weeks was 0.14-0.20 mg allopurinol/kg/day and 7.2-8.0 mg oxypurinol/kg/day. Oxypurinol was found in the infant's plasma 2 hours after breast feeding, but allopurinol was below the limit of detection. The milk/plasma ratio in the mother 2 hours after drug ingestion was 0.9 for allopurinol and 3.9 for oxypurinol.

e. **Mutagenicity**

The registrant submitted acceptable mammalian mutagenicity studies (*Salmonella typhimurium /Escherichia coli* microsome reverse mutation assay) for the manufacturing use product. The assay evaluated the test material and/or its metabolites for their ability to induce reverse mutations at the histidine locus in the genome of *Salmonella typhimurium* tester strains (TA98, TA100, TA1535 and TA1537) and at the tryptophan locus in the *E. coli* tester strain (WP2uvrA) in the presence and the absence of an exogenous metabolic activation system. The test material was not a mutagenic agent.

Information available from a published source (Stevenson, et al., 1976), reported the effects of allopurinol/oxypurinol on chromosomes of lymphocytes from 19 patients receiving allopurinol

and one receiving oxypurinol. Lymphocytes from normal subjects were also evaluated *in vitro*. Metaphase nuclei of these cells were examined for chromosomal damage, and the low frequency of aberrations observed was well within normal limits. It was concluded that allopurinol and oxypurinol had no adverse effects on chromosome structure.

f. **Metabolism**

A published review article (Murrell and Rapaport, 1986) noted that peak concentrations of allopurinol are found within one hour following oral dosing in humans and laboratory animals, and oxypurinol is detected within 15 minutes following oral dosing. In laboratory animals the highest concentrations of allopurinol and oxypurinol are found in the intestines, liver and heart while the lowest concentrations are found in brain and lung, and they indicated that there is extensive uptake of the drug and its metabolite as indicated by a volume of distribution of 1.6 L/kg. In healthy adults the ratio of allopurinol to oxypurinol in urine is about 1:10 which indicates that allopurinol is extensively metabolized to oxypurinol.

In humans, it was reported (Ferner, et. at., 1988) that a 15-year-old girl with normal renal function took 75 tablets of allopurinol (300 mg; 22.5 g total). The patient was treated with gastric lavage and activated charcoal and did not show adverse responses to the allopurinol. Blood samples obtained over 84 hours showed prolonged elimination of allopurinol, with a half-life of 3.6 hours, and oxypurinol, with a half-life of 26 hours.

In another study (Day et. al., 1988), investigators surveyed allopurinol usage in 50 patients of a city teaching hospital. The daily doses in these patients ranged from 50 to 1200 mg with 83% of the patients taking 300 mg daily. A wide range of plasma oxypurinol concentrations was observed (2.8 to 55.8 mg/l with an average of 15.2 mg/l). The population studied included a high proportion of patients with renal impairment and creatinine clearance was a significant determinant of oxypurinol concentrations. There was no significant correlation between plasma urate and plasma oxypurinol concentrations and only a few plasma urate values were above the upper limit of the reference range of the laboratory.

g. **Other Reported Effects in Humans**

According to several published articles (Casas, et al., 1989; Earll, et al., 1983; Elion, et al., 1980; Hande, et al., 1984; Jawad, 1987; Lockard, et al., 1976; Puig, et al., 1989; Simmons, 1989) patients with renal insufficiency have been reported to exhibit hypersensitivity to administration of allopurinol. It was noted that some adverse reactions to allopurinol represent delayed-type hypersensitivity to oxypurinol. (Refer to section III (B) (2) for further details).

According to information from the *Physicians' Desk Reference*, common reactions (approximately 1% of the time) to treatment at therapeutic dose level (5 to 10 mg/kg/day with allopurinol/oxypurinol) include diarrhea, nausea, clinical chemistry changes (alkaline phosphatase increase, SGOT/SGPT increases), acute attacks of gout, and rash. Other less common side effects (incidences less than 1%) at therapeutic doses include ecchymosis, fever, headache, necrotizing, angitis, vasculitis, hepatic necrosis, granulomatous hepatitis, hepatomegaly, hyperbilirubinemia, cholestatic jaundice, vomiting, intermittent abdominal pain, gastritis, dyspepsia, thrombocytopenia, eosinophilia, leukocytosis, leukopenia, myopathy, arthralgia, peripheral neuropathy, neuritis, paraesthesia, somnolence, epistasis, hypersensitivity vasculitis, purpura, vesicular bullous dermatitis, exfoliative dermatitis, eczematoid, dermatitis, pruritis, urticaria, alopecia, onycholysis, lichen planus, and taste.

2. **Dose Response Assessment**

Submitted literature citations of studies, primarily conducted with allopurinol, indicate that the compound may act to promote urinary bladder cancer in rats, has been associated with developmental effects in mice, and has been reported to cause hypersensitivity in patients with renal insufficiency. These sources of information do not indicate endpoints for consideration in a risk assessment of oxypurinol when used as a cockroach bait for the following reasons:

- For the developmental study, the intraperitoneal route of administration was used. This route is inappropriate for this risk assessment. (Refer to section III (B) (1) (d) for further details.
- For the carcinogenicity study, a dose response relationship was not established (only one dose was tested), only preneoplastic lesions were evaluated, a specific mechanism for tumor development (initiation/promotion) was investigated for bladder tumors and long

term repeated exposures are not expected from the use of oxypurinol in cockroach bait. (Refer to section III (B) (1) (c) for further information.

- Hypersensitivity to allopurinol/oxypurinol was observed in patients with renal insufficiency. Hypersensitivity is not expected in healthy members of the general public exposed to the bait.

3. **Dietary Exposure and Risk Characterization**

No in-depth risk characterization will be done because there are no toxic endpoints relevant for the proposed use pattern and comparisons of likely exposure are similar to therapeutic doses.

The Agency has determined that the only dietary exposure would from accidental ingestion of the bait. Estimates indicate that exposure would be low based on the following:

- The bait station contains 47.2 mg of total active ingredient (23.6 mg oxypurinol which is approximately half of a therapeutic dose [23.6 mg/10 kg child = 2.4 mg/kg and 5 mg/kg is lowest recommended therapeutic dose for allopurinol]).

Because allopurinol is mostly converted to oxypurinol a comparison of the contents from ingestion of a single bait station can be made with the therapeutic doses of allopurinol to qualitatively characterize the risk potential from ingestion of the oxypurinol portion of the total active ingredient.

Dosages were estimated for the following groups:

2.4 mg/kg for 10 kg child

0.4 mg/kg for 60 kg person

0.3 mg/kg for a 70 kg person

These exposure estimates range from 2 to 16.7 fold less than the lowest recommended therapeutic dose. For the 10 kg child or infant, the 2.4 mg/kg dose level is about one-fourth that noted in a nursing infant whose mother was undergoing allopurinol treatment. (see section III (B) (1) (d) under Developmental and Reproductive Toxicity).

It should be noted that the oral LD_{50} values in mice and rats are 140 to 1200 times greater than the usual human dose (5 mg/kg/day) for medical purposes.

The Agency concludes that the use of this product, when used according to label directions will not likely result in dietary exposure. Therefore, xanthine and oxypurinol do not require a numeric tolerance or an exemption from the requirement of a tolerance.

4. **Occupational, Residential, School and Day Care Exposure and Risk Characterization**

Human exposure to xanthine/oxypurinol bait is expected to be minimal.

. **Occupational Exposure and Risk Characterization**

This product is not subject to the Worker Protection Standard. Based on the use pattern, the potential for dermal and eye exposure to persons handling the bait exists but is expected to be negligible. Because of lack of mammalian toxicity, as demonstrated in the submitted acute toxicity studies, worker exposure data were not required.

a. **Residential, School and Day Care Exposure and Risk Characterization**

The bait product label allows use in indoor residential, school and day care settings. Although it is possible that adults and children may come into contact with the sealed bait stations, the Agency has determined that health risks are expected to be minimal to nonexistent based on the amount of total active ingredient in the bait, the design of the bait station to assure that the bait pellet will not be dislodged from the packaging, the low toxicity of the active ingredients and appropriate label language of the product.

5. **Drinking Water Exposure and Risk Characterization**

Not required for indoor use in a bait.

6. **Acute and Chronic Dietary Risks for Sensitive Subpopulations Particularly Infants and Children**

There are no food uses associated with the proposed use of the active ingredients. Therefore, acute and chronic dietary risks should be negligible based on lack of exposure.

7. **Aggregate Exposure from Multiple Routes Including Dermal, Oral, and Inhalation**

Based on low application rate, low toxicity and non-food uses, the risks for aggregate exposure from multiple routes are considered negligible.

8. **Cumulative Effects**

Based on low application rate, the unique mode of action for pesticide control of the target pest and the absence of other pesticides known to inhibit xanthine oxidase activity, the risks for cumulative effects are negligible.

9. **Effects on the Endocrine System**

The Agency is not requiring information on the endocrine effects of this compound at this time. Congress has allowed 3 years after August 3, 1996, for the Agency to implement a screening program with respect to endocrine effects. The Agency has considered available information concerning whether this combination product may have an effect in humans similar to an effect product by a naturally occurring estrogen or any other endocrine effects. Although evidence exists that at lethal intraperitoneal doses allopurinol/oxypurinol may have caused developmental effects in mice, there is no known evidence so far that the combination product will act as an endocrine disruptor in humans. This conclusion is supported by the report described in Section III. (B) (1) (d) where no adverse effects were noted in a nursing infant exposed to allopurinol through the mother's milk.

10. **Risk Characterization**

Although published data have indicated possible toxicological endpoints for use in this risk assessment, none of these endpoints were considered appropriate for assessing risks from use of xanthine and oxypurinol in cockroach bait stations because (1) the endpoints were observed in patients with health that was compromised before their treatment with allopurinol/oxypurinol or (2) after doses of allopurinol/oxypurinol were administered to laboratory animals by injection which is not comparable to routes of exposure considered in this risk assessment. In addition, enclosing the small amounts of the active ingredients in bait stations and following the label's instructions for use practically eliminates any exposures, and there is

reasonable certainty of no harm resulting from inadvertent exposure to the small amounts of active ingredients contained in a single bait station.

C. Environmental Assessment

1. Ecological Effects Hazard Assessment

All Tier I ecological effects data requirements are waived based on the proposed use pattern and lack of exposure. The end use product, Ecologix™ Cockroach Bait, containing 0.0472 grams ai / bait station is intended solely for indoor use. Based on the proposed indoor use pattern and quantity of active ingredient in each bait station, the potential for exposure to the environment and/or nontarget organisms is not expected. These products meet the conditions for not requiring ecological effects testing as outlined in 40 CFR 158.690 (d) (2) (i) and these data are waived.

2. Environmental Fate and Ground Water Data

Since Tier II studies were not triggered, there is no requirement for environmental fate data or groundwater data.

3. Ecological Exposure and Risk Characterization

Exposure assessment on this type of product (indoor, reduced risk) are not performed unless significant human health or ecological effects issues arise in the Tier I studies for either of these disciplines (40CFR 158.690(c)).

D. Efficay Data

The Agency has reviewed field trials (MRID 44416426) and laboratory studies (MRID 44416427- 44416429) conducted with the xanthine/oxypurinol bait. The field trial data demonstrate that the end-use product is effective in reducing cockroach populations. The laboratory studies reported that the end use product was effective in controlling cockroach strains resistant to conventional insecticides.

V.

VI. Risk Management Decision

A. Determination of Elegibility for Registration

Section 3(c)(5) of FIFRA provides for the registration of new active ingredients if it is determined that (A) its composition is such as to warrant the proposed claims for it; (B) its labeling and other materials required to be submitted comply with the requirements of FIFRA; (C) it will perform its intended function without unreasonable adverse effects on the environment; and (D) when used in accordance with widespread and commonly recognized practice it will not generally cause unreasonable adverse effects on the environment.

To satisfy criteria "A" above, xanthine/oxypurinol bait is not expected to cause unreasonable adverse effects when used according to label instructions. Criteria "B" is satisfied by the current label and by the data presented in this document. It is believed that this new pesticidal active ingredient will not cause any unreasonable adverse effects, is an effective insecticide when used in cockroach baits, and does provide protection as claimed satisfying Criteria "C". Criteria "D" is satisfied in that the toxicological properties of this product are less toxic than any other conventional pesticide product currently in use.

Therefore, xanthine/oxypurinol is eligible for registration. The only uses are indoor nonfood uses. These uses are listed in Table 4, Appendix A.

B. Regulatory Position

1. Conditional/Unconditional Registration

All data requirements are fulfilled and BPPD recommends unconditional registration of the Xanthine and Oxypurinol Manufacturing Use Concentrate and the end-use product, Ecologix^{TM} Cockroach Bait.

2. CODEX Harmonization

There are no Codex harmonization considerations since there is no food use associated with this registration.

3. Non-food Registrations

There are no non-food issues at this time. The nonfood uses are listed in Appendix A, Table 4.

4. Risk Mitigation

Since there are no risk issues, risk mitigation measures are not required for this indoor cockroach bait.

5. Endangered Species Statement

Not required for indoor cockroach bait.

C. Labeling Rational

It is the Agency's position that the labeling for products containing xanthine/oxypurinol complies with the current pesticide labeling requirements.

1. **Human Health Hazard**

. **Worker Protection Standard**

These products do not come under the provisions of the Worker Protection Standard (WPS), as there are no uses permitted on the label which reasonably permits use in the production of an agricultural plant on any farm, forest, nursery, or greenhouse.

a. **Non-Worker Protection Standard**

There are no non-WPS human health hazard issues.

b. **Precautionary Labeling**

The Agency has examined the toxicological data base for xanthine/oxypurinol and concluded that the proposed precautionary labeling (i.e. Signal Word, Statement of Practical Treatment and other label statements) adequately mitigates the risks associated with the proposed uses.

End-Use product Precautionary Labeling: For the end-use product, EcologixTM Cockroach Bait the following labeling is required:

"CAUTION"

"DO NOT ALLOW CHILDREN OR PETS TO PLAY WITH THE BAIT STATIONS"

On back panel: "Wash thoroughly with soap and water after handling bait stations."

Manufacturing-Use product Precautionary Labeling: For the MUP, Xanthine and Oxypurinol Manufacturing Use Concentrate, the following labeling is required:

"CAUTION"

"HAZARDS TO HUMANS AND DOMESTIC ANIMALS"

"Causes moderate eye irritation. Harmful if absorbed through skin. Harmful if inhaled. Avoid contact with skin, eyes or clothing. Avoid breathing dust. Wash thoroughly with soap and water after handling. Remove contaminated clothing and wash clothing before reuse."

"First Aid"

IF ON SKIN: Wash with plenty of soap and water. Get medical attention.

IF IN EYES: Flush eyes with plenty of water. Call a physician if irritation persists.

IF INHALED: Remove victim to fresh air. If not breathing, give artificial respiration, preferable mouth-to-mouth. Get medical attention."

c. **Spray Drift Advisory**

A spray drift advisory statement is not required for this indoor use.

2. **Environmental Hazards Labeling**

End-Use Product Environmental Hazards Labeling

The environmental hazard statement is not required for the end-use (indoor use).

MUP Environmental Hazards Labeling

The following environmental hazard statement is required on the manufacturing use product:

"Do not discharge effluent containing this product into lakes, streams, ponds, estuaries, oceans, or other waters unless in accordance with the requirements of a National Pollution Discharge Elimination System (NPDES) permit and the permitting authority has been notified in writing prior to discharge. Do not discharge effluent containing this product to sewer systems without previously notifying the local sewage treatment plant authority. For guidance contact your State Water Board or Regional Office of EPA."

3. **Application Rate**

It is the Agency's position, that the labeling for the pesticide products containing xanthine/oxypurinol complies with the current pesticide labeling requirements. The Agency has not required a maximum number of applications for the active ingredients, nor a specified maximum amount of the active ingredient per application.

D. Labeling

1. **End-Use Product name: Ecologix™Cockroach Bait**

Active Ingredient	
Oxypurinol	50 %
Xanthine	1 %
Inert Ingredients 98%	98%
Total	100.00%

2. Signal word is "CAUTION" based on the acute oral toxicity of the end use product.

3. The product shall contain the following information:

4. Product Name

5. Ingredient Statement

6. Registration Number

7. "Do not allow children or pets to play with the bait stations"

8. Signal Word (CAUTION)

9. **Manufacturing Use Product name: Xanthine and Oxypurinol Manufacturing Use Concentrate**

Active Ingredient	
Oxypurinol	50 %
Xanthine	50 %
Total	100.00%

10. Signal word is "CAUTION" based on the acute oral toxicity of the end use product

11. The product shall contain the following information:

12. Product Name

13. Ingredient Statement

14. Registration Number

15. "Keep Out of the Reach of Children"

16. Signal Word (CAUTION)

VII.

VIII. Actions Required by Registrants

Reports of incidences of adverse effects to humans or domestic animals under FIFRA, Section 6(a)2 and incidents of hypersensitivity under 40 CFR Part 158.690(c), guideline reference number 152-16. There are no data requirements, label changes and other responses necessary for the reregistration of the end-use product since the product is being registered after November 1984 and is, therefore, not subject to reregistration. There are also no existing stocks provisions at this time.

IX. Appendix A Use Sites

Table 4 lists the use sites for the product.

Table 4. *Nonfood Use Sites*

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