110

020503 17

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

SEP 6 1990

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: PP#0E3862 - Chlorine Dioxide on Mushrooms.
Review of Data to Support Request for Exemption from the Requirement of a Tolerance.
(MRID Nos. 414676-00 thru -02) [DEB No. 6664]
(HED Project No. 0-1251A)

FROM: Francis D. Griffith, Jr., Chemist
Dietary Exposure Branch
Health Effects Division (H7509C)

TO: Hoyt L. Jamerson, PM 43 Minor Use Officer
Registration Support Branch
Registration Division (H7505C)

and

Toxicology Branch - Herbicide, Fungicide and Antimicrobial Support
Health Effects Division (H7509C)

THRU: Richard D. Schmitt, Ph.D., Chief
Dietary Exposure Branch
Health Effects Division (H7509C)

EXECUTIVE SUMMARY OF CHEMISTRY DEFICIENCIES

1. Revise label.
2. Need methods for trihalomethanes (THMs), total organic halides (TOXs), and inorganic chlorides on mushrooms.
3. Storage stability data.
4. Crop field trials on mushrooms from California and Pennsylvania for THMs, TOXs, and inorganic chlorides.

(1)

CONCLUSIONS

1. **DEB Conclusion on Directions for Use**

The petitioner needs to revise the label to have the total numbers of applications, repeat application intervals, amount of ClO_2 applied per square foot of mushroom bed, and total amount of ClO_2 applied per mushroom production "season" specified in the directions for use.

2. **DEB Conclusions on Nature of the Residue - Plants and Livestock**

The nature of the residue in plants and animals is adequately understood. ClO_2 undergoes redox, not enzymatic reaction with living tissue to produce Cl^- and ClO_2^-/ClO_3^-. These reactive species further react with tissue to form additional compounds. These compounds are measured as inorganic chloride, trihalomethanes(THMs), and total organic halides(TOXs).

3. **DEB Conclusion on Residue Analytical Method**

The petitioner needs to submit validated residue analytical methods for TOXs, THMs, and inorganic chlorides on mushrooms.

4. **DEB Conclusion on Storage Stability**

The petitioner needs to generate concurrent storage stability data on mushrooms for the THMs (e.g., CCL_4, $CHCl_3$, CH_2Cl_2) in the 10 ppm range. Storage stability data generated on THMs will suffice for the TOXs. Storage stability data for inorganic chlorides in mushrooms are not required.

5. **DEB Conclusion on Magnitude of the Residue - Crop Field Trials**

The petitioner needs to present crop field trial residue data from use of ClO_2 at the proposed use rate of Oxine or Oxysan and at an exaggerated use rate in California and Pennsylvania. Residue data on mushrooms should be generated using validated methods for TOXs, THMs, and inorganic chlorides. Control mushrooms should be grown at each test site and analyzed for the same residues.

6. **DEB Conclusion on Magnitude of the Residue - Processed Food/Feed**

There are no processed commodities or livestock feed items associated with mushroom production. Thus, no ClO_2 mushroom processing studies or feed/food additive tolerances are required.

2

7. DEB Conclusion on Magnitude of the Residue - Meat/ Milk/Poultry/Eggs

Since mushrooms are not a livestock feed item, neither ruminant and poultry feeding studies nor ClO_2 tolerances in milk, meat, poultry, and eggs are required.

8. Harmonization of Tolerance

There are no problems with compatibility with either tolerance levels or an exemption from the requirements of a tolerance with Canadian, Mexican, or Codex regulations.

RECOMMENDATION

DEB cannot recommend, at this time, for the requested exemption from the requirement for a tolerance for chlorine dioxide on mushrooms for reasons cited above in our Executive Summary and further explained in our Conclusions 1, 3, 4, and 5.

For further considerations of the proposed exemption from the requirements of a tolerance, the petitioner should be advised to resolve the deficiencies noted above.

DETAILED CONSIDERATIONS

Background

Dr. W.L. Biehn, Associate Coordinator, and Dr. R.H. Kupelian, National Director, on behalf of the Interregional Research Project No. 4 (IR-4) and the Agricultural Experimental Station of California request an exemption from the requirements of a tolerance for chlorine dioxide on mushrooms.

Chlorine dioxide (from Oxine) is currently approved by EPA/FDA as an **indirect** food additive for use as a sanitizer on food contact surfaces (see FDA Food Additive Petition No. 5H3889). This regulation is published in 21 CFR 178.1010(b)(34) for an aqueous solution of an equilibrium mixture of oxychloro species, and 21 CFR 178.1010(c)(29) for concentrations of ClO_2 in solution.

No Registration Standard exists for ClO_2. In February 1986, the Guidance Document for calcium and sodium hypochlorite salts lists no chemistry deficiencies. This conclusion cannot be transferred to chlorine dioxide.

There are no established tolerances or exemptions from the requirement of a tolerance for chlorine dioxide. This is the first proposed direct use for chlorine dioxide on a RAC. The concentration of ClO_2 proposed for use on mushrooms is 50 ppm per application using multiple applications.

FDA has raised no objections to use of ClO_2 as a one- time sanitizing rinse at 5.0 ppm on uncut and unpeeled fruits and vegetables, and at 5 ppm on cut and peeled potatoes. However, DEB did not note this use is in the current regulations.

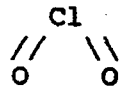
There is a 24(c) [SLN] Registration in California for use of oxine as a general farm sanitizer for bacterial control in mushroom production facilities.

CHEMICAL IDENTITY

GRN 61-1 - Product Identity and Disclosure of Ingredients

The registrant is required to provide the name, nominal concentration, and certified limits of each active ingredient, and the name, nominal concentration, and upper limit of each impurity. For each active ingredient, the information should include the molecular, empirical, or structural formulas, the CA name, CAS Number, and molecular weight.

Oxine or Oxysan (stabilized chlorine dioxide) have not been given an ANSI, ISO, or BSI name. The structure of chlorine dioxide is given below:



The chemical name is chlorine dioxide.
Other identifying characteristics and codes are:

Empirical Formula:	ClO_2
Molecular Weight:	67.45
CAS Registry No.:	10049-04-4
Shaughnessy No.:	020503
Caswell No.:	179A

No additional information is required for this topic.

The company has registered end-use products Oxine (EPA Registration No. 9804-1) and Oxysan (EPA Registration No. 9804-1-61180) that are used to generate ClO_2.

GRN 61-2 - **Description of the Beginning Materials and Manufacturing Process**

GRN 61-3 - **Discussion of Formation of Impurities**

The Guidelines require that the suppliers of beginning materials be identified and that a full description of the beginning materials be provided. The description of the manufacturing process should include a discussion of each individual reaction in the process, the relative amount of the reacting materials, the physical condition of each step, and any purification procedures. A discussion is required to account for the presence of potential or actual impurities based upon knowledge of the composition of beginning materials, desired and side reactions of the manufacturing process, and contamination or degradation of the active material.

The information and data that the petitioner has supplied are discussed in Confidential Appendix A.

The names of suppliers of raw materials has been supplied and the manufacturing process has been adequately described. The mechanism for formation of impurities is adequately described. No further data are required for these topics.

62-1 - **Preliminary Analysis**

62-2 - **Certification of Limits**

62-3 - **Analytical Methods to Verify Certified Limits**

Generally, five or more samples (representative of different manufactured batches) should be analyzed by appropriate methods for active ingredients and each impurity, with results given for each sample.

The information and data that the petitioner has supplied oncertified limits and the formulation analytical method are discussed in Confidential Appendix B.

The petitioner has provided adequate information on limits of the ingredients and has provided an acceptable formulation analytical method to verify concentrations. No further data are required for this topic.

63-2 thru 63-13 - **Physical and Chemical Characteristics**

Please note that DEB no longer addresses the physical/chemical properties of manufacturing-use products. These will be considered later by the Registration Division as manufacturers respond to the "Data Call-In" program. DEB still reviews physical/chemical properties of technical grades of the active ingredient.

63-2 - Color

Clear, colorless

63-3 - Physical State

Liquid

63-4 - Odor

Extremely faint, chlorine-like odor

63-5 - Melting Point

-59 °C

63-6 - Boiling Point

+11 °C

63-7 - Density

Liquid at 0 °C	1.64
Vapor	2.40

63-8 - Solubility

Water 6.0 g/L

63-9 - Vapor Pressure

490 or 512 Torr at 0 °C

63-10 - Dissociation Constant

-N/A-

63-11 - Octanol/Water Partition Coefficient

-N/A-

63-12 - pH

-N/A-

63-13 - Stability

Gas is explosive in concentrations above 20 percent.

Nonexplosive in solution.

Decomposes slowly in solution (pH 2, 2 °C, dark) at a rate of 1 percent per day.

DEB concludes no further information is required for the physical and chemical characteristics of ClO_2.

DIRECTIONS FOR USE

Once the 500 ppm ClO_2 solution is prepared, it is diluted to 50 ppm ClO_2 (add 10 gallons of clean potable water to the 1 gallon of technical stabilized ClO_2 solution). Mushrooms are irrigated/watered as needed to control bacterial blotch. If bacterial blotch is severe, irrigate mushrooms with ClO_2 solution as needed after casing. If the bacterial blotch is low to moderate, water mushrooms as needed after pin formation with the 50 ppm ClO_2 solution.

Do not harvest mushrooms within 24 hours of last application.

The petitioner needs to revise the label to have total number of applications, repeat application intervals, amount of ClO_2 applied per sq ft of mushroom bed, and total amount of ClO_2 applied per mushroom production "Season" specified in the directions for use.

On the Oxine label for use of ClO_2 as a terminal sanitizing rinse in mushroom facilities, the concentration of ClO_2 is 100 ppm. The petitioner needs to make sure that directions for use of the 100 ppm sanitizing rinse for facilities are not confused with directions for a 50 ppm watering/irrigation in the production of mushrooms.

NATURE OF THE RESIDUE - PLANTS AND LIVESTOCK

No plant metabolism data were submitted. The petitioner presented summary discussions of $^{36}ClO_2$ metabolism in rats. ClO_2 is a strong oxidizing agent. As such, it (and ClO_2^-) are not enzymatically metabolized but have simple redox reactions with tissues. The "metabolites" formed should be the same for all living species.

ClO_2 (and ClO_2^-) are rapidly reduced following ingestion. In rats ^{36}Cl levels peaked in plasma at 30 minutes then gradually declined through 72 hours. Approximately 38 percent of the ^{36}Cl was excreted via urine and feces and none was lost via expiration. Urine samples were examined to determine metabolites of $^{36}ClO_2$. "Metabolites" identified were $^{36}Cl^-$, $^{36}ClO_2^-$, and $^{36}ClO_3^-$. Twenty-seven percent of the oral dose of $^{36}ClO_3$, was $^{36}Cl^-$, 3.4 percent was $^{36}ClO_2^-$, and 0.7 percent was $^{36}ClO_3^-$. The maximum levels of $^{36}ClO_2^-$ and $^{36}ClO_3^-$ were excreted in the 12 to 24 hours time after dose and maximum $^{36}Cl^-$ was excreted at 24 to 48 hours after the dosing. Tissue levels were highest in kidney, then in descending order were lung, stomach, intestine, liver, spleen, and thymus.

The nature of the residue in rats was confirmed using $^{36}ClO_2^-$. $^{36}Cl^-$ was the major metabolite in urine with no $^{36}ClO_2$ or $^{36}ClO_3^-$ detected in urine.

The nature of the residue in animals is adequately understood. $^{36}ClO_2$ undergoes redox not enzymatic reactions to produce $^{36}Cl^-$ and $^{36}ClO_2/^{36}ClO_3^-$. The reactive species further react with tissue to form other compounds and can be measured as total inorganic chlorides, THMs, and total organic halides.

DEB is willing to translate the $^{36}ClO_2$ rat metabolism data to plants and conclude the same metabolites will be produced and measured as total inorganic chlorides, THMs, and total organic halides.

No further $^{36}ClO_2$ plant or animal metabolism studies are necessary for this petition.

RESIDUE ANALYTICAL METHODS

The petitioner has not submitted any residue analytical methods.

The petitioner is requested to submit validated residue analytical methods for TOXs, THMs and inorganic chloride in/on mushrooms.

For the TOX method, DEB suggests a limit of detection in the ppb range and use of GC with a halogen specific detector. For THMs, DEB suggests modification of EPA Method 5020/801 (an automatic headspace analysis with GC/HECD system). For total inorganic chloride, DEB suggests use of a specific ion electrode method.

Note to PM

Methods for TOXs, THMs, and inorganic Cl were presented for "ClO_2" residues on grapes by another registrant.

STORAGE STABILITY

No storage stability data for residues of ClO_2 and its metabolite in mushroom were presented.

DEB suggests the petitioner generate concurrent storage stability data for the THMs (e.g., CCl_4, $CHCl_3$, CH_2Cl_2) in or on mushrooms in the 10 ppm range. Storage stability data on the THMs will suffice for TOXs provided it is concurrent. Storage stability data are not necessary for the inorganic chlorides.

MAGNITUDE OF THE RESIDUE - CROP FIELD TRIALS

The petitioner presented no crop field trial residue data of ClO_2 on mushrooms. The petitioner presented efficacy studies on

use of ClO_2 watering/irrigation in mushrooms production. In these studies, ClO_2 was used at a rate of 81 mL of 50 ppm solution/square foot (proposed use?). Application rates per square foot ranged from 1/4X to 2X of the 81 mL/sq ft rate and total applications ranged from 14 to 27 for the five efficacy studies. Based on the amount of ClO_2 used, the number of applications, and the amount of mushroom produced, DEB reasonably expects ppm levels of "ClO_2 equivalents" to be present in mushrooms. Thus, crop field trial residue data are needed to show what is present and how much.

DEB needs ClO_2 on mushroom crop field trial residue data from California and Pennsylvania. After the petitioner has revised the label for use of ClO_2 on mushrooms, mushrooms should be treated at the proposed use rate and at an exaggerated use rate. The level of ClO_2 used in the exaggerated part of the study should be at a level as not to cause physiological damage to the mushroom. Once the residue analytical methods are validated, then residue data should be gathered for inorganic Cl, THMs, and TOXs. Control mushrooms should be grown at each location and analyzed for background levels of inorganic Cl, toxicity, and THMs.

MAGNITUDE OF THE RESIDUE - PROCESSED FOOD/FEED

There are no processed food commodities or livestock feed items associated with mushroom production. No mushroom processing studies or FATs are required.

MAGNITUDE OF THE RESIDUE - MEAT/MILK/POULTRY/EGGS

Since mushrooms are not a livestock feed item, neither ruminant nor poultry feeding studies are required. The petitioner does not need to propose any ClO_2 tolerance for meat, milk, poultry, and eggs.

Other Considerations - HARMONIZATION OF TOLERANCE

An International Residue Limit Status Sheet is attached to this review. There are no problems of compatibility with either tolerance levels or an exemption from the requirements of a tolerance with Canadian, Mexican, and Codex regulations.

Attachment: International Residue Limit Status Sheet

cc with Confidential Appendices A and B: R.F., PP#0E3862, Reviewer (FDG), PIB/FOD (Furlow).

cc without CBI: Circ (7), R.D. Schmitt.

H7509C:DEB:Reviewer (FDG):CM#2:557-0826:JOB: 57305:I:WP5.0:C.Disk:KENCO:08/03/90:DD:VO:EK:DD:ed:fdg:8/13/90.

RDI:SecHd:RSQuick:8/20/90:BrSrSc:RALoranger:8/21/90.

CHLORINE DIOXIDE

PRODUCT CHEMISTRY

CONFIDENTIAL APPENDICIES

Appendix A: 1 Page
Appendix B: 1 Page

Confidential Appendicies to the Scientific Review for the pesticide chlorine dioxide by the Dietary Exposure Branch [Confidential FIFRA Trade Secret/CBI].

RIN-1344-06

HED Letter/Memo. Dated 9/6/90

Page ____ is not included in this copy.

Pages 10 through 12 are not included in this copy.

The material not included contains the following type of information:

__X__ Identity of product inert ingredients.

_____ Identity of product impurities.

__X__ Description of the product manufacturing process.

_____ Description of quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action.

_____ FIFRA registration data.

_____ The document is a duplicate of page(s) _____.

_____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.
