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October 15, 1992

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Office of Pollution Prevention and Toxics
Environmental Protection Agency
401 M Street., S.W.
Washington, D.C. 20460
Attn: Section 8(e) Coordinator (CAP Agreement)

Dear Coordinator:

8ECAP-0025

On behalf of the Regulatee and pursuant to Unit II B.1.b. and Unit II C of the 6/28/91 CAP Agreement, E.I. Du Pont de Nemours and Co. hereby submits (*in triplicate*) the attached studies. Submission of this information is voluntary and is occasioned by unilateral changes in EPA's standard as to what EPA now considers as reportable information. Regulatee's submission of information is made solely in response to the new EPA §8(e) reporting standards and is not an admission: (1) of TSCA violation or liability; (2) that Regulatee's activities with the study compounds reasonably support a conclusion of substantial health or environmental risk or (3) that the studies themselves reasonably support a conclusion of substantial health or environmental risk.

The "Reporting Guide" creates new TSCA 8(e) reporting criteria which were not previously announced by EPA in its 1978 Statement of Interpretation and Enforcement Policy, 43 Fed Reg 11110 (March 16, 1978). The "Reporting Guide states criteria which expands upon and conflicts with the 1978 Statement of Interpretation. Absent amendment of the Statement of Interpretation, the informal issuance of the "Reporting Guide" raises significant due processes issues and clouds the appropriate reporting standard by which regulated persons can assure TSCA Section 8(e) compliance.

For Regulatee,

Mark H. Christman
Counsel
Legal D-7158
1007 Market Street
Wilmington, DE 19898
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3/3/95

ATTACHMENT 1

Submission of information is made under the 6/28/91 CAP Agreement, Unit II. This submission is made voluntarily and is occasioned by recent changes in EPA's TSCA §8(e) reporting standard; such changes made, for the first time in 1991 and 1992 without prior notice and in violation of Regulatee's constitutional due process rights. Regulatee's submission of information under this changed standard is not a waiver of its due process rights; an admission of TSCA violation or liability, or an admission that Regulatee's activities with the study compounds reasonably support a conclusion of substantial risk to health or to the environment. Regulatee has historically relied in good faith upon the 1978 Statement of Interpretation and Enforcement Policy criteria for determining whether study information is reportable under TSCA §8(e), 43 Fed Reg 11110 (March 16, 1978). EPA has not, to date, amended this Statement of Interpretation.

After CAP registration, EPA provided the Regulatee the June 1, 1991 "TSCA Section 8(e) Reporting Guide". This "Guide" has been further amended by EPA, EPA letter, April 10, 1992. EPA has not indicated that the "Reporting Guide" or the April 1992 amendment supersedes the 1978 Statement of Interpretation. The "Reporting Guide" and April 1992 amendment substantively lowers the Statement of Interpretation's TSCA §8(e) reporting standard². This is particularly troublesome as the "Reporting Guide" states criteria, applied retroactively, which expands upon and conflicts with the Statement of Interpretation.³ Absent amendment of the Statement of Interpretation, the informal issuance of the "Reporting Guide" and the April 1992 amendment clouds the appropriate standard by which regulated persons must assess information for purposes of TSCA §8(e).

²In sharp contrast to the Agency's 1977 and 1978 actions to soliciting public comment on the proposed and final §8(e) Policy, EPA has unilaterally pronounced §8(e) substantive reporting criteria in the 1991 Section 8(e) Guide without public notice and comment. See 42 Fed Reg 45362 (9/9/77), "Notification of Substantial Risk under Section 8(e): Proposed Guidance".

³A comparison of the 1978 Statement of Interpretation and the 1992 "Reporting Guide" is appended.

Throughout the CAP, EPA has mischaracterized the 1991 guidance as reflecting "longstanding" EPA policy concerning the standards by which toxicity information should be reviewed for purposes of §8(e) compliance. Regulatee recognizes that experience with the 1978 Statement of Interpretation may cause a review of its criteri. Regulatee supports and has no objection to the Agency's amending reporting criteria *provided that* such amendment is not applied to the regulated community in an unfair way. However, with the unilateral announcement of the CAP under the auspices of an OCM enforcement proceeding, EPA has wrought a terrific unfairness since much of the criteria EPA has espoused in the June 1991 Reporting Guide and in the Agency's April 2, 1992 amendment is new criteria which does not exist in the 1978 Statement of Interpretation and Enforcement Policy.

The following examples of new criteria contained in the "Reporting Guide" that is not contained in the Statement of Interpretation follow:

- o even though EPA expressly disclaims each "status report" as being preliminary evaluations that should not be regarded as final EPA policy or intent⁴, the "Reporting Guide" gives the "status reports" great weight as "sound and adequate basis" from which to determine mandatory reporting obligations. ("Guide" at page 20).
- o the "Reporting Guide" contains a matrix that establishes new numerical reporting "cutoff" concentrations for acute lethality information ("Guide" at p. 31). Neither this matrix nor the cutoff values therein are contained in the Statement of Interpretation. The regulated community was not made aware of these cutoff values prior to issuance of the "Reporting Guide" in June, 1991.
- o the "Reporting Guide" states new specific definitional criteria with which the Agency, for the first time, defines as 'distinguishable neurotoxicological effects'; such criteria/guidance not expressed in the 1978 Statement of Interpretation.⁵
- o the "Reporting Guide" provides new review/ reporting criteria for irritation and sensitization studies; such criteria not previously found in the 1978 Statement of Interpretation/Enforcement Policy.
- o the "Reporting Guide" publicizes certain EPA Q/A criteria issued to the Monsanto Co. in 1989 which are not in the Statement of Interpretation; have never been published in the Federal Register or distributed by the EPA to the Regulatee. Such Q/A establishes new reporting criteria not previously found in the 1978 Statement of Interpretation/Enforcement Policy.

⁴The 'status reports' address the significance, if any, of particular information reported to the Agency, rather than stating EPA's interpretation of §8(e) reporting criteria. In the infrequent instances in which the status reports contain discussion of reportability, the analysis is invariably quite limited, without substantial supporting scientific or legal rationale.

⁵ See, e.g., 10/2/91 letter from Du Pont to EPA regarding the definition of 'serious and prolonged effects' as this term may relate to transient anesthetic effects observed at lethal levels; 10/1/91 letter from the American Petroleum Institute to EPA regarding clarification of the Reporting Guide criteria.

In discharging its responsibilities, an administrative agency must give the regulated community fair and adequate warning to as what constitutes noncompliance for which penalties may be assessed.

Among the myriad applications of the due process clause is the fundamental principle that statutes and regulations which purport to govern conduct must give an adequate warning of what they command or forbid.... Even a regulation which governs purely economic or commercial activities, if its violation can engender penalties, must be so framed as to provide a constitutionally adequate warning to those whose activities are governed.

Diebold, Inc. v. Marshall, 585 F.2d 1327, 1335-36 (D.C. Cir. 1978). See also, Rollins Environmental Services (NJ) Inc. v. U.S. Environmental Protection Agency, 937 F. 2d 649 (D.C. Cir. 1991).

While neither the are rules, This principle has been applied to hold that agency 'clarification', such as the Statement of Interpretation, the "Reporting Guide" nor the April 1992 amendments will not applied retroactively.

...a federal court will not retroactively apply an unforeseeable interpretation of an administrative regulation to the detriment of a regulated party on the theory that the post hoc interpretation asserted by the Agency is generally consistent with the policies underlying the Agency's regulatory program, when the semantic meaning of the regulations, as previously drafted and construed by the appropriate agency, does not support the interpretation which that agency urges upon the court.

Standard Oil Co. v. Federal Energy Administration, 453 F. Supp. 203, 240 (N.D. Ohio 1978), aff'd sub nom. Standard Oil Co. v. Department of Energy, 596 F.2d 1029 (Em. App. 1978):

The 1978 Statement of Interpretation does not provide adequate notice of, and indeed conflicts with, the Agency's current position at §8(e) requires reporting of all 'positive' toxicological findings without regard to an assessment of their relevance to human health. In accordance with the statute, EPA's 1978 Statement of Interpretation requires the regulated community to use scientific judgment to evaluate the significance of toxicological findings and to determining whether they reasonably support a conclusion of a substantial risk. Part V of the Statement of Interpretation urges persons to consider "the fact or probability" of an effect's occurrence. Similarly, the 1978 Statement of Interpretation stresses that an animal study is reportable only when "it contains reliable evidence ascribing the effect to the chemical." 43 Fed Reg. at 11112. Moreover, EPA's Statement of Interpretation defines the substantiality of risk as a function of both the seriousness of the effect and the probability of its occurrence. 43 Fed Reg 11110 (1978). Earlier Agency interpretation also emphasized the "substantial" nature of a §8(e) determination. See 42 Fed Reg 45362, 45363

(1977). [Section 8(e) findings require "extraordinary exposure to a chemical substance...which critically imperil human health or the environment"].

The recently issued "Reporting Guide" and April 1992 Amendment guidance requires reporting beyond and inconsistent with that required by the Statement of Interpretation. Given the statute and the Statement of Interpretation's explicit focus on substantial human or environmental risk, whether a substance poses a "substantial risk" of injury requires the application of scientific judgment to the available data on a case-by-case basis.

If an overall weight-of-evidence analysis indicates that this classification is unwarranted, reporting should be unnecessary under §8(e) because the available data will not "reasonably support the conclusion" that the chemical presents a substantial risk of serious adverse consequences to human health.

Neither the legislative history of §8(e) nor the plain meaning of the statute support EPA's recent lowering of the reporting threshold that TSCA §8(e) was intended to be a sweeping information gathering mechanism. In introducing the new version of the toxic substances legislation, Representative Eckhart included for the record discussion of the specific changes from the version of H. R. 10318 reported by the Consumer Protection and Finance Subcommittee in December 1975. One of these changes was to modify the standard for reporting under §8(e). The standard in the House version was changed from "causes or contributes to an unreasonable risk" to "causes or significantly contributes to a substantial risk". This particular change was one of several made in TSCA §8 to avoid placing an undue burden on the regulated community. The final changes to focus the scope of Section 8(e) were made in the version reported by the Conference Committee.

The word "substantial" means "considerable in importance, value, degree, amount or extent". Therefore, as generally understood, a "substantial risk" is one which will affect a considerable number of people or portion of the environment, will cause serious injury and is based on reasonably sound scientific analysis or data. Support for the interpretation can be found in a similar provision in the Consumer Product Safety Act. Section 15 of the CPSA defines a "substantial product hazard" to be:

"a product defect which because of the pattern of defect, the number of defective products distributed in commerce, the severity of the risk, or otherwise, creates a substantial risk of injury to the public."

Similarly, EPA has interpreted the word 'substantial' as a quantitative measurement. Thus, a 'substantial risk' is a risk that can be quantified, See, 56 Fed Reg 32292, 32297 (7/15/91). Finally, since information pertinent to the exposure of humans or the environment to chemical substances or mixtures may be obtained by EPA through Sections 8(a) and 8(d) regardless of the degree of potential risk, §8(e) has specialized function. Consequently, information subject to §8(e) reporting should be of a type which would lead a reasonable man to conclude that some type action was required immediately to prevent injury to health or the environment.

Attachment

Comparison:

Reporting triggers found in the 1978 "Statement of Interpretation/ Enforcement Policy", 43 Fed Reg 11110 (3/16/78) and the June 1991 *Section 8(e) Guide*.

<u>TEST TYPE</u>	<u>1978 POLICY CRITERIA EXIST?</u>	<u>New 1991 GUIDE CRITERIA EXIST?</u>
ACUTE LETHALITY		
Oral	N}	Y}
Dermal	N}	Y}
Inhalation (Vapors)	} ⁶	} ⁷
aerosol	N}	Y}
dusts/ particles	N}	Y}
SKIN IRRITATION	N	Y ⁸
SKIN SENSITIZATION (ANIMALS)	N	Y ⁹
EYE IRRITATION	N	Y ¹⁰
SUBCHRONIC (ORAL/DERMAL/INHALATION)	N	Y ¹¹
REPRODUCTION STUDY	N	Y ¹²
DEVELOPMENTAL TOX	Y ¹³	Y ¹⁴

⁶43 Fed Reg at 11114, comment 14:

"This policy statements directs the reporting of specific effects when unknown to the Administrator. Many routine tests are based on a knowledge of toxicity associated with a chemical. unknown effects occurring during such a range test may have to be reported if they are those of concern to the Agency and if the information meets the criteria set forth in Parts V and VII."

⁷Guide at pp.22, 29-31.

⁸Guide at pp-34-36.

⁹Guide at pp-34-36.

¹⁰Guide at pp-34-36.

¹¹Guide at pp-22; 36-37.

¹²Guide at pp-22

¹³43 Fed Reg at 11112

"Birth Defects" listed.

¹⁴Guide at pp-22

NEUROTOXICITY	N	Y ¹⁵
CARCINOGENICITY	Y ¹⁶	Y ¹⁷
MUTAGENICITY		
<i>In Vitro</i>	Y ¹⁸	Y ¹⁹
<i>In Vivo</i>	Y}	Y}
ENVIRONMENTAL		
Bioaccumulation	Y}	N
Bioconcentration	Y} ²⁰	N
Oct/water Part. Coeff.	Y}	N
Acute Fish	N	N
Acute Daphnia	N	N
Subchronic Fish	N	N
Subchronic Daphnia	N	N
Chronic Fish	N	N
AVIAN		
Acute	N	N
Reproductive	N	N
Reproductive	N	N

¹⁵Guide at pp-23; 33-34.

¹⁶43 Fed Reg at 11112
"Cancer" listed

¹⁷Guide at pp-21.

¹⁸43 Fed Reg at 11112; 11115 at Comment 15

"Mutagenicity" listed/ *in vivo* vs *in vitro* discussed; discussion of "Ames test".

¹⁹Guide at pp-23.

²⁰43 Fed Reg at 11112; 11115 at Comment 16.

CAS # 1100-88-5; 4736-60-1

Chem: Benzyltriphenylphosphonium chloride; ethyltriphenylphosphonium iodide

Title: The acute oral toxicity and irritation studies of benzyltriphenylphosphonide chloride, Batch No. 94F-015 and ethyltriphenylphosphonium iodide, Batch No. 96K-012

Date: 4/20/77

Summary of Effects: ALD50 = 43 mg/kg;
neurotoxic effects BTPPC;

International Bio-Research, Inc.

Hannover, Germany

Cincinnati, Ohio USA

Miami, Ohio 45147 (513) 831-3114



77-080-21

April 20, 1977

THE ACUTE OF TOXICITY AND IRRITATION STUDIES OF
 BENZYLTRIPHENYLPHOSPHONIUM CHLORIDE, BATCH NO. 94F-015
 AND ETHYLTRIPHENYLPHOSPHONIUM IODIDE, BATCH NO. 96K-012

For Cincinnati Milacron

PURPOSE

This study was conducted to evaluate the acute oral toxicity and primary skin and acute eye irritative potentials of the test materials in accordance with the techniques specified in the Regulations for the Enforcement of the Federal Hazardous Substances Act (Code of Federal Regulations, Title 16, Chapter II, 1976).

TEST MATERIALS

The samples were received from Cincinnati Milacron on January 6, 1977 for use in these studies.

<u>Batch No.</u>	<u>Sample</u>	<u>Description</u>
94F-015	Benzyltriphenylphosphonium Chloride	white crystalline granules
96K-012	Ethyltriphenylphosphonium Iodide	white powder

PROCEDURE

Each test sample was administered orally by stomach tube to five groups, each composed of five male albino rats (Harlan Industries, Inc., weight range 208 to 267 grams). Each sample was administered as a 1% weight per volume suspension in corn oil (Nuzola) at dosage levels of 0.0100, 0.0215, 0.0464, 0.100, and 0.215 and as a 50% w/v suspension in corn oil (Nuzola) at dosage levels of 0.464 grams per kilogram of body weight. These dilutions necessitated use of dosage factors of 1.00, 2.15, 4.64, 10.0 and 21.5 ml/kg for the 1% suspension and 0.93 ml for the 50% suspension which were calculated by the following formula to enable administration of the desired dose of the compounds:

$$\text{Dosage Factor} = \frac{\text{Dose to be given (mg/kg)}}{\text{Concentration of sample (mg/ml)}}$$

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Subsidiary of Hill Top Testing Services, Inc.

Hill Top Research / Woodson-Tenent Laboratories

Food was withheld from the rats for approximately 24 hours prior to dosage. Following dosage, food consisting of commercial pellets and water were available ad libitum. The rats were housed in groups in wire mesh cages suspended above the droppings. All animals were observed closely for gross signs of systemic toxicity and mortality at frequent intervals during the day of dosage, and at least once daily thereafter for a total of 14 days. Gross necropsies were performed on the animals that died. At the end of the 14-day observation period the surviving rats were weighed, sacrificed by cerebral concussion, and gross necropsies were performed. Statistical analysis of the mortality data was by the moving average method.¹

2. Patch Test for Primary Skin Irritation and Corrosivity - Rabbits

Five-tenths gram of each undiluted sample which was moistened with physiological saline to form a paste was applied under a one inch-square surgical gauze patch, two layers thick, to an intact skin area and an abraded skin area on each of six albino rabbits. The application sites were prepared by clipping the hair from the saddle area of the rabbits. The abraded areas were prepared by making minor epidermal incisions with a hypodermic needle. The abrasions were sufficiently deep to penetrate the epidermis but not to induce bleeding. Each patch was held in place with two strips of one-inch adhesive tape. After application of the patches, the trunk of each rabbit was wrapped with rubber tubing which was secured with staples. An outer layer of gauze and tape was placed around the trunk of the animals. The animals were restrained in Newmann harnesses for 24 hours.

At the end of the 24-hour exposure period, the patches were removed and any residual sample was gently sponged from the skin with a moistened towel. The reactions were scored immediately after removal of the patches (24-hour reading), and again two days later (72-hour reading), according to the scale reproduced in Tables 1 and 2 accompanying this report.

3. Acute Eye Application - Rabbits

One-tenth gram of each undiluted sample was applied to the left eye of each of six albino rabbits. The right eyes were untreated and served as controls. Examinations for gross signs of eye irritation were made at 24, 48, and 72 hours following application. Scoring of irritative effects was according to the method of Draize, in which corneal, iris, and conjunctival effects are scored separately.² This method is reproduced in the addendum following Table 4. In this scoring system, injuries to the cornea and iris may represent as much as 80 percent of the total score. Cornea and iris scores are heavily weighted because of the essential role in vision.

¹ Horn, H. J., 1956, *Biometrics* 12 (3): 311-322

² J. H. Draize, "Dermal Toxicity," in Appraisal of the Safety of Chemicals in Foods, Drugs, and Cosmetics. The Staff of the Division of Pharmacology of the Federal Food and Drug Administration (Austin, Texas: The Editorial Committee of the Association of Food and Drug Officials of the United States, 1959), p. 51.

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RESULTS

1. Acute Oral Administration - Rats

Benzyltriphenylphosphonium Chloride, Batch No. 94F-015

The mortality results during the 14-day observation period are presented below. Values are number of animals dead/number of animals tested, cumulative.

Dose gm/kg	Conc. of %	Time of Death									
		Hours				Days					
		1	2	4	24	2	3	4	5	6	7-14
0.0100	1	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5
0.0215	1	0/5	1/5	1/5	1/5	1/5	1/5	1/5	1/5	1/5	1/5
0.0464	1	0/5	0/5	0/5	2/5	2/5	2/5	2/5	2/5	2/5	2/5
0.100	1	1/5	3/5	3/5	5/5						
0.464	50	5/5									

LD₅₀, gm/kg .043
 95% confidence limits, gm/kg .0265 - .0698

At the .0100 gm/kg level all rats exhibited diarrhea during the day of dosage but exhibited normal appearance and behavior throughout the 14 post-dosage day observation period.

At the .0215 gm/kg level, one rat died within two hours following dosage. Other toxic effects included depression, piloerection, depressed righting and placement reflexes, and labored respiration in all rats; squinting was observed in three rats, and excessive salivation and diarrhea were observed in two rats. All of the above signs increased in intensity throughout the day of dosage. By the first post-dosage day toxic signs subsided except for depression, unkempt fur, and urine stains noted in three survivors. By the second post-dosage day and throughout the remainder of the observation period, the survivors exhibited normal appearance and behavior.

The rats at the .0464 gm/kg level appeared normal until the third hour following dosage when three rats exhibited depression. Within four hours, two rats died and all the survivors exhibited depression with depressed righting and placement reflexes, and piloerection; two survivors exhibited diarrhea, squinting, and labored respiration. The survivors exhibited diarrhea for four days following dosage and exhibited normal appearance and behavior by day five and throughout the remainder of the observation period.

Signs of toxicity noted prior to death of the five rats at the 0.100 gm/kg level included comatose appearance, depression, depressed righting, placement, and pain reflexes, labored respiration, pale extremities, hypothermia, piloerection, squinting, and diarrhea stains. The toxic signs began within one hour after dosage and increased in intensity until death occurred in all rats.

All rats at the 0.464 gm/kg level died within 70 minutes following dosage.

Average body weight changes for the surviving rats are shown below.

<u>Dose</u> gm/kg	<u>Average Body Weight</u>		<u>Gain</u> gm
	<u>Start</u> gm	<u>Finish</u> gm	
0.0100	233	345	112
0.0215	237	350	113 (4 rats)
0.0464	238	366	128 (3 rats)

The average body weight gain for each group was normal for the rats of the age, sex, and strain used in this study.

Gross necropsies of the rats which died before termination of the study revealed the following: Externally: At the 0.0215 and 0.0464 gm/kg levels, rats exhibited excessive salivation and diarrhea stains. At the 0.100 gm/kg level; two rats exhibited diarrhea stains, and one exhibited salivation stains. Internally: At the 0.0215 gm/kg level, gross pathological alterations included congested adrenals and kidneys, irritated gastrointestinal tract and peritoneal walls, and diffusely pale liver. At the 0.0464 gm/kg level; internal gross pathological alterations were the same as the above with the addition of stomachs filled with a fluid resembling the sample. At the 0.100 gm/kg level, gross pathological alterations were the same as the above with the addition of congested lungs and three rats exhibiting darkened livers. At the 0.464 gm/kg level, gross pathological alterations included congested lungs and kidneys, stomachs diffusely whitened and thickened and filled with a white, gritty substance resembling the sample. Intestinal tracts were slightly irritated and livers were diffusely pale. No other gross pathological alterations were noted.

Gross necropsies performed at termination revealed one diffusely necrotic liver in one rat at the 0.01 gm/kg level. No other significant gross pathological alterations were seen at any other level tested.

Ethyltriphenylphosphonium Iodide, Batch No. 96K-012

The mortality results during the 14-day observation period are presented below. Values are number of animals dead/number of animals tested, cumulative.

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Dose gm/kg	Conc. of %	Time of Death										
		Hours					Days					
		1	2	4	24	2	3	4	5	6	7-14	
0.0215	1	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5
0.0464	1	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5
0.100	1	0/5	0/5	0/5	4/5	4/5	4/5	4/5	4/5	4/5	4/5	4/5
0.215	1	0/5	1/5	3/5	5/5							
0.464	50	0/5	0/5	0/5	5/5							

LD₅₀, gm/kg 0.0794
 95% confidence limits, gm/kg 0.0584 - 0.0108

All rats at the 0.0215 gm/kg level exhibited depression within two hours following dosage. Within five hours following dosage, toxic signs included depressed righting and placement reflexes, and piloerection and squinting in all rats. Three exhibited diarrhea and stains. These toxic signs remained generally unchanged or decreased slightly throughout the remainder of the day of dosage. By the first post-dosage day and throughout the remainder of the observation period all rats exhibited normal appearance and behavior.

All the rats at the 0.0464 gm/kg level appeared normal until three hours following dosage when one rat appeared depressed. Within five hours, all rats exhibited depression, piloerection, mucoid diarrhea; three rats exhibited depressed righting and placement reflexes, and labored respiration; and two rats exhibited excessive salivation and stains. Toxic signs subsided completely by the first post-dosage day and all rats exhibited normal appearance and behavior throughout the remainder of the observation period.

All rats at the 0.100 gm/kg level exhibited depression and three exhibited depressed righting and placement reflexes and mucoid diarrhea stains one hour following dosage. Within four hours, all rats exhibited more intense depression, depressed righting and placement reflexes, labored respiration, squinting, piloerection, hunched posture, hypothermia, and diarrhea. Three rats exhibited bloody stains around their muzzles and eyes. All toxic signs remained unchanged throughout the day of dosage and all but one rat died before the first post-dosage day. The surviving rat exhibited diarrhea during the first post-dosage day but exhibited normal appearance and behavior throughout the remainder of the observation period.

Signs of toxicity noted prior to death of the rats at the 0.215 gm/kg level included depression, depressed righting and placement reflexes, piloerection, labored respiration, and mucoid diarrhea in all rats, and squinting and hypothermia, pale extremities, and depressed to comatose appearance in the rats surviving beyond three hours after dosing. Onset of the toxic signs was approximately one hour following dosage and increased in intensity prior to death which occurred within two to six hours following dosage.

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Toxic signs observed prior to death of all rats included depressed righting level, depressed to comatose appearance, depressed righting and placement reflexes, piloerection, hypothermia, and labored respiration. Two rats exhibited mucoid diarrhea and squinting. One exhibited depressed pain reflexes. Onset of toxic signs was approximately one hour after dosage.

Average body weight changes for the surviving rats are shown below.

Dose gm/kg	Average Body Weight		Gain gm
	Start gm	Finish gm	
0.0215	241	347	106
0.0464	238	345	107
0.100	245	329	84 (1 rat)

The average body weight gain for each group was within the normal limits or slightly low for the rats of the age, strain, and sex used in this study.

Gross necropsy findings in the rats which died before termination of the study included the following: Externally: All rats at the 0.100, 0.215, and three rats at the 0.464 gm/kg level exhibited diarrhea stains. Excessive salivation stains were exhibited by three rats at the 0.100 gm/kg level, one at the 0.215 gm/kg level, and three at the 0.464 gm/kg level. Internally: At the 0.100 gm/kg level, two exhibited congested lungs; all exhibited congested adrenals and kidneys, irritated gastrointestinal tracts filled with a yellow fluid resembling the sample, diffusely pale livers, moderately irritated and wrinkled peritoneal walls, and slight autolysis. At the 0.215 gm/kg level, internal gross pathological alterations were as above except that no pale livers were observed, four exhibited congested lungs, and three exhibited darkened livers and spleens. At the 0.464 gm/kg level, internal gross pathological alterations were as above, except that four exhibited diffusely pale livers, all exhibited irritation and/or whitening of diffuse areas of the stomach, one exhibited a gastrointestinal tract filled with a clear fluid and slight autolysis. No other gross pathological alterations were noted.

Gross necropsies performed at termination revealed no gross pathological alterations.

2. Patch Test for Primary Skin Irritation and Corrosivity - Rabbits

The results following patch application of samples Benzyltriphenylphosphonium Chloride, Batch No. 94F-015 and Ethyltriphenylphosphonium Iodide, Batch No. 96K-012 to the skin of albino rabbits are shown in Tables 1 and 2 respectively.

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Benzyltriphenylphosphonium Chloride, Batch No. 94F-015

No irritative or corrosive effects were noted at either observation period. However, all rabbits appeared irritable at the 24-hour reading. The Primary Irritation Index was found to be 0.

Ethyltriphenylphosphonium Iodide, Batch No. 96K-012

No irritative or corrosive effects were noted at either the 24 or 72 hour reading. Therefore, the Primary Irritation Index was found to be 0.

3. Acute Eye Application - Rabbits

The results following application of samples Benzyltriphenylphosphonium Chloride, Batch No. 94F-015 and Ethyltriphenylphosphonium Iodide, Batch No. 96K-012 to the eyes of albino rabbits are presented in Tables 3 and 4, respectively.

Benzyltriphenylphosphonium Chloride, Batch No. 94F-015

Within 24 hours following application, the sample produced mortality in five rabbits. Irritative effects in the surviving rabbit at the 24-hour reading included moderate corneal opacity, severe conjunctivitis, and diffuse areas of blanching in the conjunctivae and entire nictitating membrane. Irritative effects increased slightly by the 72-hour reading. Iritis could not be scored at the 72-hour reading due to severe corneal opacity.

Ethyltriphenylphosphonium Iodide, Batch No. 96K-012

Within 24 hours following application, signs of irritation included moderate to severe corneal opacity, mild iritis, and severe conjunctivitis in all rabbits. Blanching of the conjunctivae and nictitating membrane was noted in two rabbits during the observation period. Irritative effects were relatively unchanged during the 72-hour observation period.

SUMMARY

The acute oral toxicity and the primary skin and acute eye irritative potentials of Benzyltriphenylphosphonium Chloride, Batch No. 94F-015 and Ethyltriphenylphosphonium Iodide, Batch No. 96K-012 were evaluated in accordance with the techniques specified in the Federal Hazardous Substances Act (Code of Federal Regulations, Title 16, Chapter II, 1976).

The acute oral LD₅₀ of each sample for male albino rats are listed on the following page.

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<u>Sample</u>	<u>Oral LD₅₀</u>	<u>95% Confidence Limits</u>
Benzyltriphenylphosphonium Chloride, Batch No. 94F-015	0.0430 gm/kg	0.0265 - 0.0698 gm/kg
Ethyltriphenylphosphonium, Iodide, 0.0794 gm/kg Batch No. 96K-012	0.0794 gm/kg	0.0584 - 0.108 gm/kg

Patch application of Benzyltriphenylphosphonium Chloride, Batch No. 94F-015 and Ethyltriphenylphosphonium Iodide, Batch No. 96K-012 to the skin of albino rabbits produced no irritative effects; therefore, the Primary Irritation Index for each sample was found to be 0.

Application of Benzyltriphenylphosphonium Chloride, Batch No. 94F-015 to the eyes of albino rabbits produced death in five rabbits and corneal opacity, conjunctivitis, and blanching of the conjunctivae and nictitating membrane in the surviving rabbit.

Application of Ethyltriphenylphosphonium Iodide, Batch No. 96K-012 to the eyes of albino rabbits produced corneal opacity, iritis, and conjunctivitis in each of six rabbits and blanching of the conjunctivae and nictitating membrane in two rabbits.

Based on these results, Benzyltriphenylphosphonium Chloride, Batch No. 94F-015 is highly toxic by oral ingestion; is not a primary skin irritant or corrosive material; and is an eye irritant as these terms are defined in the above-cited Regulations. Ethyltriphenylphosphonium Iodide, Batch No. 96K-012 is toxic by oral ingestion; is not a primary skin irritant or a corrosive material; and is an eye irritant as these terms are defined in the above-cited Regulations.

Bill Top Toxicology

Submitted by

Terry Turner
Terry Turner
Junior Technician, Toxicology

Approved by

Marian B. Vinegar
Marian B. Vinegar, Ph.D.
Director, Toxicology

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Table 1. Primary irritation scores in rabbits following a 24-hour patch exposure to Benzyltriphenylphosphonium Chloride, Batch No. 94F-015.

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Skin	Time Hours	Score for Rabbit Number						Total Score	Average
		1	2	3	4	5	6		
<u>Erythema and Eschar Formation</u>									
Intact	24	0	0	0	0	0	0	0	0
	72	0	0	0	0	0	0	0	0
Abraded	24	0	0	0	0	0	0	0	0
	72	0	0	0	0	0	0	0	0
<u>Edema Formation</u>									
Intact	24	0	0	0	0	0	0	0	0
	72	0	0	0	0	0	0	0	0
Abraded	24	0	0	0	0	0	0	0	0
	72	0	0	0	0	0	0	0	0

Primary Irritation Index 0

SCORING KEY

- Evaluation of Skin reactions Value
- Erythema and eschar formation:
- No erythema..... 0
 - Very slight erythema (barely perceptible)..... 1
 - Well-defined erythema..... 2
 - Moderate to severe erythema..... 3
 - Severe erythema (bright redness) to slight eschar formation (injuries in depth)..... 4
- Edema formation:
- No edema..... 0
 - Very slight edema (barely perceptible)..... 1
 - Slight edema (edges of area well defined by definite raising)..... 2
 - Moderate edema (raised approximately 1 millimeter)..... 3
 - Severe edema (raised more than 1 millimeter and extending beyond the area of exposure)..... 4

• 101.11 of the Regulations under the Federal Hazardous Substances Act.

Table 2. Primary irritation scores in rabbits following a 24-hour patch exposure to Ethyltriphenylphosphonium Iodide, Batch No. 96K-012.

BEST COPY AVAILABLE

Skin	Time Hours	Score for Rabbit Number						Total Score	Average
		7	8	9	10	11	12		
<u>Erythema and Eschar Formation</u>									
Intact	24	0	0	0	0	0	0	0	0
	72	0	0	0	0	0	0	0	0
Abraded	24	0	0	0	0	0	0	0	0
	72	0	0	0	0	0	0	0	0
<u>Edema Formation</u>									
Intact	24	0	0	0	0	0	0	0	0
	72	0	0	0	0	0	0	0	0
Abraded	24	0	0	0	0	0	0	0	0
	72	0	0	0	0	0	0	0	0

Primary Irritation Index 0

SCORING KEY

Evaluation of skin reactions	Value
<u>Erythema and eschar formation:</u>	
No erythema.....	0
Very slight erythema (barely perceptible).....	1
Well-defined erythema.....	2
Moderate to severe erythema.....	3
Severe erythema (burn reaction) to slight eschar formation (injuries in depth).....	4
<u>Edema formation:</u>	
No edema.....	0
Very slight edema (barely perceptible).....	1
Slight edema (edges of area well defined by definite margins).....	2
Moderate edema (raised approximately 1 millimeter).....	3
Severe edema (raised more than 1 millimeter and extending beyond the area of exposure).....	4

• 191.11 of the Regulations under the Federal Hazardous Substances Act.

Table 3. Eye irritation scores in albino rabbits following application of 0.1 gram of Benzyltriphenylphosphonium Chloride, Batch No. 94F-015.

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Rabbit Number	Time Hours	Cornea		Iris	Conjunctivae			Total Score*	Other
		Opacity	Area		Erythema	Swelling	Discharge		
13	24	Died							
	48								
	72								
14	24	Died							
	48								
	72								
15	24	Died							
	48								
	72								
16	24	Died							
	48								
	72								
17	24	Died							
	48								
	72								
18	24	2	4	0	3	3	3	58	A
	48	2	4	0	3	4	3	60	A
	72	3	4	B	3	4	3	80	MIN,A

*Total score is the sum of the following three sub-totals:
 (a) degree of opacity x area involved x 5
 (b) iris score x 5
 (c) sum of scores for erythema, swelling and discharge x 2
 Total possible score = 110.

A=Diffuse areas of conjunctivae and entire nictitating membrane blanched (whitened).

B=Unable to score due to opacity and swelling.

MIN=Minimum score

Table 4. Eye irritation scores in albino rabbits following application of 0.1 gram of Ethyltriphenylphosphonium Iodide, Batch No. 96K-012.

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Rabbit Number	Time Hours	Cornea		Iris	Conjunctivae			Total Score*	Other
		Opacity	Area		Erythema	Swelling	Discharge		
19	24	2	4	1	3	3	3	63	A
	48	2	4	1	3	3	3	63	A
	72	2	4	1	3	3	3	63	A
20	24	3	4	1	3	3	3	83	
	48	3	4	1	3	4	3	85	A
	72	4	4	B	3	4	3	100	A, I
21	24	2	4	1	3	3	3	63	
	48	2	4	1	3	3	3	63	
	72	2	4	1	3	3	3	63	
22	24	2	4	1	3	3	3	63	
	48	2	4	1	3	4	3	65	
	72	2	4	1	3	4	3	65	
23	24	2	4	1	3	3	3	63	
	48	2	4	1	3	3	3	63	
	72	2	4	1	3	4	3	65	
24	24	2	4	1	3	2	3	51	
	48	2	4	1	3	2	3	61	
	72	2	4	1	2	2	2	57	

*Total score is the sum of the following three sub-totals:

(a) degree of opacity x area involved x 5

(b) iris score x 5

(c) sum of scores for erythema, swelling and discharge x 2

Total possible score = 110.

A=Entire nictitating membrane and diffuse areas of conjunctivae blanched (whitened).

B=Unable to score due to swelling.

MIN=Minimum score

FROM: J. H. Draize, "Dermal Toxicity," in Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics, The Staff of the Division of Pharmacology of the Federal Food and Drug Administration (Austin, Texas: The Editorial Committee of the Association of Food and Drug Officials of the United States, 1959).

DERMAL TOXICITY

TABLE 2
Scale for Scoring Ocular Lesions

(1) Cornea	
(A) Opacity-degree of density (area most dense taken for reading)	
No Opacity.....	0
Scattered or diffuse areas, details of iris clearly visible.....	1
Easily discernible translucent areas, details of iris slightly obscured.....	2
Opalescent areas, no details of iris visible, size of pupil barely discernible.....	3
Opaque, iris invisible.....	4
(B) Area of cornea involved	
One quarter (or less) but not zero.....	1
Greater than one quarter, but less than half.....	2
Greater than half, but less than three quarters.....	3
Greater than three quarters, up to whole area.....	4
Total Maximum = 80	
A X B X 5	
(2) Iris	
(A) Values	
Normal.....	0
— Folds above normal, congestion, swelling, circumcorneal injection (any or all of these or combination of any thereof) iris still reacting to light (sluggish reaction is positive)...	1
No reaction to light, hemorrhage, gross destruction (any or all of these).....	2
Total Maximum = 10	
A X 5	
(3) Conjunctivae	
(A) Redness (refers to palpebral and bulbar conjunctivae excluding cornea and iris)	
Vessels normal.....	0
Vessels definitely injected above normal.....	1
More diffuse, deeper crimson red, individual vessels not easily discernible.....	2
Diffuse beery red.....	3
(B) Chemosis	
No swelling.....	0
Any swelling above normal (includes nictitating membrane).....	1
Obvious swelling with partial eversion of lids.....	2
Swelling with lids about half closed.....	3
Swelling with lids about half closed to completely closed.....	4
(C) Discharge	
No discharge.....	0
Any amount different from normal (does not include small amounts observed in inner canthus of normal animals).....	1
Discharge with moistening of the lids and hairs just adjacent to lids.....	2
Discharge with moistening of the lids and hairs, and considerable area around the eye.....	3
Total Maximum = 20	
Score (A + B + C) X 2	

International Bio-Research, Inc.
Cincinnati, Ohio USA
Hannover, Germany

Miamiville, Ohio 45147 (513) 831-3114

IMPORTANT NOTICE

International Bio-Research, Inc. submits this report with the understanding that no portion of it will be used for advertising or promotion without obtaining our prior written consent to the specific proposed use. When such use is desired we will be glad to assist in the preparation of mutually acceptable excerpts or summaries.

SAMPLE DISPOSAL PROCEDURE

At the conclusion of a test program, two units of each sample used will be stored and remaining samples will be destroyed. No materials will be maintained longer than six months after the completion of the study unless the client notifies International Bio-Research, Inc.

New drugs are exempt from the above procedure. They will be retained or returned to the client.



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

Mark H. Christman
Counsel
E. I. Du Pont De Nemours and Company
Legal D-7010-1
1007 Market Street
Wilmington, Delaware 19898

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MAY 08 1995

EPA acknowledges the receipt of information submitted by your organization under Section 8(e) of the Toxic Substances Control Act (TSCA). For your reference, copies of the first page(s) of your submission(s) are enclosed and display the TSCA §8(e) Document Control Number (e.g., 8EHQ-00-0000) assigned by EPA to your submission(s). Please cite the assigned 8(e) number when submitting follow-up or supplemental information and refer to the reverse side of this page for "EPA Information Requests".

All TSCA 8(e) submissions are placed in the public files unless confidentiality is claimed according to the procedures outlined in Part X of EPA's TSCA §8(e) policy statement (43 FR 11110, March 16, 1978). Confidential submissions received pursuant to the TSCA §8(e) Compliance Audit Program (CAP) should already contain information supporting confidentiality claims. This information is required and should be submitted if not done so previously. To substantiate claims, submit responses to the questions in the enclosure "Support Information for Confidentiality Claims". This same enclosure is used to support confidentiality claims for non-CAP submissions.

Please address any further correspondence with the Agency related to this TSCA 8(e) submission to:

Document Processing Center (7407)
Attn: TSCA Section 8(e) Coordinator
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
Washington, D.C. 20460-0001

EPA looks forward to continued cooperation with your organization in its ongoing efforts to evaluate and manage potential risks posed by chemicals to health and the environment.

Sincerely,

Terry R. O'Bryan

Terry R. O'Bryan
Risk Analysis Branch

Enclosure

12339A



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contains at least 50% recycled fiber

Triage of 8(e) Submissions

Date sent to triage: 12/14/95

NON-CAP

CAP

Submission number: 12339A

TSCA Inventory:

Y N D

Study type (circle appropriate):

Group 1 - Dick Clements (1 copy total)

ECO AQUATO

Group 2 - Ernie Falke (1 copy total)

~~ATOX~~

SBTOX SEN

~~w/NEUR~~

Group 3 - Elizabeth Margosches (1 copy each)

STOX CTOX EPI RTOX GTOX
STOX/ONCO CTOX/ONCO IMMUNO CYTO NEUR

Other (FATE, EXPO, MET, etc.): _____

Notes:

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entire document: <u>0</u> 1 2 pages <u>1, 1st tab</u>	pages <u>1, all tabs</u>
Notes:	
Contractor reviewer: <u>LPS</u>	Date: <u>4/11/95</u>

CECATS/TRIAGE TRACKING DBASE ENTRY FORM

CECATS DATA:
Submission # BEHQ: 1092-12339 SEQ. A

TYPE: INT SUPP FLWP

SUBMITTER NAME: E. I. Dupont de Nemours and Company

INFORMATION REQUESTED: FLWP DATE: _____
0501 NO INFO REQUESTED
0502 INFO REQUESTED (TECH)
0503 INFO REQUESTED (VOL ACTIONS)
0504 INFO REQUESTED (REPORTING RATIONALE)

DISPOSITION:
0679 REFER TO CHEMICAL SCREENING
0678 CAP NOTICE

VOLUNTARY ACTIONS:
0401 NO ACTION REPORTED
0402 STUDIES PLANNED/IN PROGRESS
0403 NOTIFICATION OF WORKER HEALTH
0404 LABEL/MSDS CHANGES
0405 PROCESS/HANDLING CHANGES
0406 APP/USE DISCONTINUED
0407 PRODUCTION DISCONTINUED
0408 CONFIDENTIAL

SUB. DATE: 10/15/92 OTS DATE: 10/27/92 CSRAD DATE: 03/03/95

CHEMICAL NAME: _____

CASE
1100-88-5
4736-60-1

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INFORMATION TYPE:	P F C	INFORMATION TYPE:	P F C	INFORMATION TYPE:	P F C
0201 ONCO (HUMAN)	01 02 04	0216 EPICLIN	01 02 04	0241 IMMUNO (ANIMAL)	01 02 04
0202 ONCO (ANIMAL)	01 02 04	0217 HUMAN EXPOS (PROD CONTAM)	01 02 04	0242 IMMUNO (HUMAN)	01 02 04
0203 CELL TRANS (IN VITRO)	01 02 04	0218 HUMAN EXPOS (ACCIDENTAL)	01 02 04	0243 CHEM/PHYS PROP	01 02 04
0204 MUTA (IN VITRO)	01 02 04	0219 HUMAN EXPOS (MONITORING)	01 02 04	0244 CLASTO (IN VITRO)	01 02 04
0205 MUTA (IN VIVO)	01 02 04	0220 BCO/AQUA TOX	01 02 04	0245 CLASTO (ANIMAL)	01 02 04
0206 REPRO/TERATO (HUMAN)	01 02 04	0221 ENV. OCCUREL/FATE	01 02 04	0246 CLASTO (HUMAN)	01 02 04
0207 REPRO/TERATO (ANIMAL)	01 02 04	0222 EMER INCI OF ENV CONTAM	01 02 04	0247 DNA DAM/REPAIR	01 02 04
0208 NEURO (HUMAN)	01 02 04	0223 RESPONSE REQEST DELAY	01 02 04	0248 PROD/USE/PROC	01 02 04
0209 NEURO (ANIMAL)	01 02 04	0224 PROD/COMP/CHEM ID	01 02 04	0251 MSDS	01 02 04
0210 ACUTE TOX. (HUMAN)	01 02 04	0225 REPORTING RATIONALE	01 02 04	0299 OTHER	01 02 04
0211 CHR. TOX. (HUMAN)	01 02 04	0226 CONFIDENTIAL	01 02 04		
0212 ACUTE TOX. (ANIMAL)	01 02 04	0227 ALLERG (HUMAN)	01 02 04		
0213 SUB ACUTE TOX (ANIMAL)	01 02 04	0228 ALLERG (ANIMAL)	01 02 04		
0214 SUB CHRONIC TOX (ANIMAL)	01 02 04	0239 METAB/PHARMACO (ANIMAL)	01 02 04		
0215 CHRONIC TOX (ANIMAL)	01 02 04	0240 METAB/PHARMACO (HUMAN)	01 02 04		

TRIAGE DATA: NON-CBI INVENTORY

YES

CAS SR NO

IN TRAINING

ONGOING REVIEW

YES (DROP/REFER)

NO (CONTINUE)

REFER

SPECIES

RAT
RBT

TOXICOLOGICAL CONCERN:

LOW Dermal RBT (benzyltriphenylphos...)
MED Acute oral RAT (ethyltriphenylphos...)
HIGH Acute oral RAT (benzyltriphenylphos...)
Eye RBT (benzyl...)
Eye RBT (ethyl...)

USE:

PRODUCTION:

1099212

12339A

H

Acute oral toxicity of benzyltriphenylphosphonium chloride in the rats is of high concern based on an LD₅₀ of 43 mg/kg. Male albino rats (5/dose) received gavage doses of 10, 21.5, 46.4, 100 or 464 mg/kg. Deaths were as follows: 0/5, 1/5, 2/5, 5/5, and 5/5. Diarrhea occurred at all dose levels. At higher doses, clinical signs included depression, piloerection, depressed righting and placement reflexes, labored respiration, squinting, and salivation. At 100 mg/kg, animals also exhibited comatose appearance, pain reflexes, pale extremities, and hypothermia. Necropsy revealed changes in the adrenals and kidneys (congestion), gastrointestinal tract (irritation), and liver (pale) at 21.5 mg/kg; fluid-filled stomach at 46.4 mg/kg; changes in lungs (congestion) and liver (darkened) at 100 mg/kg; and whitened and thickened stomach at 464 mg/kg.

M

Acute oral toxicity of ethyltriphenylphosphonium iodide in the rats is of moderate concern based on an LD₅₀ of 79.4 mg/kg. Male albino rats (5/dose) received gavage doses of 21.5, 46.4, 100, 215, and 464 mg/kg. Deaths were as follows: 0/5, 0/5, 4/5, 5/5, and 5/5. Clinical signs seen at all doses included depression, depressed righting and placement reflexes, piloerection, squinting, diarrhea, and staining of fur; at 46.4 mg/kg and greater, salivation and mucoid diarrhea, and at 100 mg/kg and greater, hypothermia. Necropsy of animals at the three highest doses revealed congestion in lungs, adrenals, and kidneys, changes in the gastrointestinal tract (irritated, fluid-filled) and liver (pale, wrinkled and light autolysis). At the two highest doses, darkened liver and spleen and at 464 mg/kg, whitening and irritation of the stomach occurred.

L

Dermal irritation of benzyltriphenylphosphonium chloride and ethyltriphenylphosphonium iodide in rabbits is of low concern. Six albino rabbits received occluded applications of 0.5 g of either material to intact and abraded skin for 24 hours. No irritation was seen with either material to skin at 24 or 72 hours.

H

~~Eye irritation~~ ^{toxicity} of benzyltriphenylphosphonium chloride in the rabbit is of high concern based on death within 24 hours. Six albino rabbits received application of 0.1 g of material to an unwashed eye. Five of six animals died within 24 hours. In the surviving rabbit, severe swelling and opacity was seen in iris, cornea, and conjunctivae, with discharge, erythema, and blanching of the conjunctivae at 72 hours.

H

Eye irritation of ethyltriphenylphosphonium iodide in the rabbit is of high concern. Six albino rabbits received application of 0.1 g of material to unwashed eyes. Moderate to severe corneal opacity was evident in all animals with severe erythema, swelling, and discharge from the conjunctivae, and swollen iris. In two rabbits the nictitating membrane and conjunctivae became blanched.