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8EHQ-0893-12003
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August 18, 1993

Document Processing Center (TS-790)
Attn: 8(e) Coordinator
OPPT
U.S. EPA
401 M Street, S.W.
Washington, D.C. 20460

8EHQ 93 12003 init
88930000399

Dear 8(e) Coordinator:

is submitting this notice under Section 8(e) of the Toxic Substances Control Act.

is notifying the Agency of draft information obtained from an NTE (neurotoxic esterase) study of a series of tricresyl phosphate (TCP) substances. TCP substances have been previously reported in the literature and in other submissions to EPA to induce organophosphate induced delayed neurotoxicity (OPIDN) as evidenced by NTE inhibition, clinical signs of ataxia, and histopathological lesions.

In this study, each test substance was administered to hens (10 hens per group) by gavage at a dosage level of 2000 mg/kg for five consecutive days. Hens were sacrificed 24 hours after the final dose and brain NTE assays were performed. Thirty hens were administered corn oil as the negative control, and ten hens were dosed with TOCP (60 mg/kg) which served as the positive control. The criteria for a positive finding was a brain NTE inhibition of 70% or greater.

As shown on the attached draft laboratory data sheets, the TCP substances inhibited NTE more than 70%, and therefore, were considered positive in this assay.

We are planning to submit a copy of the final report to your office as soon as it is received by If you have any questions regarding this draft data, you may telephone me directly at

Sincerely,

MR

RECEIVED 9-8-93

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7 pgs

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Not Q.A. Reviewed

NEUROTOXICITY STUDY OF TCP SUBSTANCE) IN ADULT HENS

Neurotoxic Esterase (NTE) Activity (Mean ± Standard Deviation) and % Inhibition

	Negative Control Corn Oil	Positive Control TOCP, 60 mg/kg/day	TCP SUBSTANCE 2000 mg/kg/day
N	30	10	10
NTE Activity[a]	20 ± 4.8	0[c]	0[c]
% Inhibition	–[b]	100	100

[a]nmole/min/mg of protein
[b]Not applicable
[c]All esterase activity in the sample was non-specific (*i.e.*, non-NTE) or related to spontaneous hydrolysis.

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NEUROTOXICITY STUDY OF TCP SUBSTANCE IN ADULT HENS

Neurotoxic Esterase (NTE) Activity (Mean ± Standard Deviation) and % Inhibition

	Negative Control Corn Oil	Positive Control TOCP, 60 mg/kg/day	TCP SUBSTANCE 2000 mg/kg/day
N	30	10	10
NTE Activity[a]	20 ± 4.8	0[c]	0[c]
% Inhibition	--[b]	100	100

[a]nmole/min/mg of protein
[b]Not applicable
[c]All esterase activity in the sample was non-specific (*i.e.*, non-NTE) or related to spontaneous hydrolysis.

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Not Q.A. Reviewed

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NEUROTOXICITY STUDY OF TCP SUBSTANCE) IN ADULT HENS

Neurotoxic Esterase (NTE) Activity (Mean ± Standard Deviation) and % Inhibition

	Negative Control Corn Oil	Positive Control TOCP, 60 mg/kg/day	TCP SUBSTANCE 2000 mg/kg/day
N	30	10	10
NTE Activity[a]	20 ± 4.8	0[c]	2 ± 4.1
% Inhibition	--[b]	100	88

[a]nmole/min/mg of protein
[b]Not applicable
[c]All esterase activity in the sample was non-specific (*i.e.*, non-NTE) or related to spontaneous hydrolysis.

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NEUROTOXICITY STUDY OF TCP SUBSTANCE) IN ADULT HENS

Neurotoxic Esterase (NTE) Activity (Mean ± Standard Deviation) and % Inhibition

	Negative Control Corn Oil	Positive Control TOCP, 60 mg/kg/day	TCP SUBSTANCE 2000 mg/kg/day
N	30	10	10
NTE Activity[a]	20 ± 4.8	0[c]	5 ± 4.1
% Inhibition	--[b]	100	76

[a]nmole/min/mg of protein
[b]Not applicable
[c]All esterase activity in the sample was non-specific (*i.e.*, non-NTE) or related to spontaneous hydrolysis.

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NEUROTOXICITY STUDY OF: TCP SUBSTANCE IN ADULT HENS

Neurotoxic Esterase (NTE) Activity (Mean ± Standard Deviation) and % Inhibition

	Negative Control Corn Oil	Positive Control TOCP, 60 mg/kg/day	TCP SUBSTANCE 2000 mg/kg/day
N	30	10	10
NTE Activity[a]	20 ± 4.8	0[c]	2 ± 2.7
% Inhibition	--[b]	100	89

[a]nmole/min/mg of protein
[b]Not applicable
[c]All esterase activity in the sample was non-specific (*i.e.*, non-NTE) or related to spontaneous hydrolysis.

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Not Q.A. Reviewed

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NEUROTOXICITY STUDY OF TCP TYPE SUBSTANCE IN ADULT HENS

Neurotoxic Esterase (NTE) Activity (Mean ± Standard Deviation) and % Inhibition

	Negative Control Corn Oil	Positive Control TOCP, 60 mg/kg/day	TCP TYPE SUBSTANCE 2000 mg/kg/day
N	30	10	10
NTE Activity[a]	20 ± 4.8	0[c]	0[c]
% Inhibition	–[b]	100	100

[a]nmole/min/mg of protein
[b]Not applicable
[c]All esterase activity in the sample was non-specific (*i.e.*, non-NTE) or related to spontaneous hydrolysis.

Triage of 8(e) Submissions

Date sent to triage: 5/28/94 NON-CAP CAP

Submission number: 12003 A TSCA Inventory: Y N D

Study type (circle appropriate):

Group 1 - Gordon Cash (1 copy total)

ECO AQUATO

Group 2 - Ernie Falke (1 copy total)

ATOX SBTOX SEN w/NEUR

Group 3 -HERD (1 copy each)

STOX CTOX EPI RTOX GTOX

STOX/ONCO CTOX/ONCO IMMUNO CYTO NEUR

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

Notes:

- [x] This is the **original** 8(e) submission; refile after triage evaluation.
- [ ] This **original** submission has been **split**; rejoin after triage evaluation.
- [ ] Other:

Photocopies Needed for Triage Evaluation

entire document: 0 1 2 3

front section and CECATS: 0 1 2 3

Initials: JW **Date:** 5/23/96

CECATS\TRIAGE TRACKING DBASE ENTRY FORM

CECATS DATA:
Submission # 8EHQ- 0893-12003 (5) SEQ. A

TYPE: (INT) SUPP FLWP

SUBMITTER NAME: CONFIDENTIAL

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

DISPOSITION:
(0639) REFER TO CHEMICAL SCREENING
0678 CAP NOTICE

VOLUNTARY ACTIONS:
(0401) NO ACTION REPORTED
0402 STUDIES PLANNED/UNDERWAY
0403 NOTIFICATION OF WORKER/OTHERS
0404 LABEL/MSDS CHANGES
0405 PROCESS/HANDLING CHANGES
0406 APP./USE DISCONTINUED
0407 PRODUCTION DISCONTINUED
0408 CONFIDENTIAL

SUB. DATE: 08/18/93 OTS DATE: 08/19/93 CSRAD DATE: 09/08/93

CHEMICAL NAME:

CAS#
1330-78-5

INFORMATION TYPE:		P F C	INFORMATION TYPE:		P F C	INFORMATION TYPE:		P F C
0201	ONCO (HUMAN)	01 02 04	0216	EPI/CLIN	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~~	ECO/AQUA TOX	(01) 02 04	0245	CLASTO (ANIMAL)	01 02 04
0206	REPRO/TERATO (HUMAN)	01 02 04	0221	ENV. OCCC/REL/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			
X ~~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	ONGOING REVIEW	SPECIES	TOXICOLOGICAL CONCERN:	USE:	PRODUCTION:
	(YES) (CONTINUE)	YES (DROP/REFER)	CKN	(LOW)		
	NO (DROP)	NO (CONTINUE)		MED		
	DETERMINE	REFER:		HIGH		

COMMENTS: NONCAP Ten hens were orally gavaged with 2000 mg/kg of the test substance for 5 days. Corn oil was administered to 30 hens as the negative control and 60 mg/kg TOCP was administered to 10 hens as the positive control. Positive effects were considered NTE-inhibition of greater than 70%. Positive effects were found with the test substance and with TOCP.