

**ATOCHEM
NORTH AMERICA**

elf aquitaine

ATOCHEM NORTH AMERICA, INC.
900 First Avenue, P.O. Box 1536, King of Prussia, Pennsylvania 19406-0018, (215) 337-6500

Contains No CBI

A

8EHQ-92-12579

88920010763

INIT

October 23, 1992

CERTIFIED MAIL

RETURN RECEIPT REQUESTED

Document Processing Center (TS-790)
Office of Toxic Substances
U.S. Environmental Protection Agency
401 M St., S.W.
Washington, D.C. 20460

Attn: Section 8(e) Coordinator (CAP Agreement)

RE: Report Submitted Pursuant to the TSCA Section 8(e)
Compliance Audit Program

CAP Identification Number: 8ECAP-0026

Dear Sir/Madam:

Pursuant to the Toxic Substances Control Act (TSCA) Section 8(e) Compliance Audit Program and the Agreement for TSCA Section 8(e) Compliance Audit Program (CAP Agreement) executed by Elf Atochem North America Inc. (Atochem) and Environmental Protection Agency (EPA), Atochem is submitting the enclosed final report on three generation rat reproduction studies to the EPA. These studies do not involve effects in humans.

Nothing in this letter or the enclosed studies is considered confidential business information of Atochem.

The enclosed studies provide information on the chemicals dioctyltin bis(isooctylmercaptoacetate) and dioctyltin maleate. The exact chemical name of dioctyltin bis(isooctylmercaptoacetate) is acetic acid[(dioctylstannylene)dithio]di-bis(isooctyl) ester and its CAS number is 26401-97-8. The exact chemical name of dioctyltin maleate is 1,3,2-dioxastannanepin-4,7-dione, 2,2-dioctyl- and its CAS number is 16091-18-2.

The title of the enclosed study report is Three Generation Reproduction Study of Compounds 813 and 831. The following is a summary of the adverse effects observed in this study report.

mm
2/28/95

TSCA CAP
Dioctyltin Bis(Isooctylmercaptoacetate) and Dioctyltin Maleate
October 23, 1992
Page Two

Dietary administration of dioctyltin bis(isooctylmercaptoacetate) and dioctyltin maleate to male and female rats through the mating, gestation and lactations periods for 3 generations resulted in reductions in litter size and pup survival attributed to male fertility in some males with microscopic evidence of testicular degeneration.

Atochem previously submitted a TSCA 8(e) notice on dioctyltin bis(isooctylmercaptoacetate). The submission was made August 31, 1992; we have not been notified by EPA of the EPA Document Control Number for this submission.

Further questions regarding this submission may be directed to me at 215 337-6892.

Sincerely,



C.H. Farr, PhD, DABT
Manager, Product Safety
and Toxicology

Enclosures

PART II: THREE GENERATION REPRODUCTION STUDY OF
COMPOUNDS 813 AND 831

I. INTRODUCTION

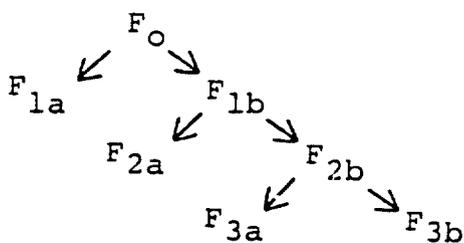
The purpose of the study was to determine the effects of 813 and 831 on reproduction in rats over three successive generations.

II. MATERIALS AND METHODS

A. Preparation of the Diets: Rats in this study received the same levels of 813 and 831 in the same lots of pelleted food as did rats in the two year feeding study.

B. Animals: Each treatment group consisted of ten male and twenty female Long-Evans rats, obtained as weanlings from the Simon-sen Laboratories. All animals received food and water ad libitum. Males were housed in groups of five in wire cages and females were housed individually in plastic cages.

C. Procedure: The weanling rats, designated F_0 , were mated on the 79th day of treatment when they were at least 100 days old. A period of two weeks was allowed for the mating of each female. Each female was exposed to two different males during that time. Males were always placed into female cages, with one female at a time. All pups from the first litter were discarded at weaning and the parent rats were mated again ten days later. Randomly selected pups, excluding runts, from the second litters were maintained on the same diets and mated in turn when 100 days old. This protocol was followed for three generations:



The number of pups in every litter was counted on the day of birth and on the fifth day. Litters greater than ten in number were reduced to ten on the fifth day by selecting runts where possible for discard. On the twenty-first day, the weanlings were counted and weighed and either sacrificed or saved for continuation on the diets. Parent rats were weighed, sacrificed and examined grossly when no longer needed. When the F_{3b} litters were twenty-one days old, ten male and ten female pups from each group were selected at random for autopsy. Individual body weights and brain, liver and kidney weights were recorded; sections of brain, heart, lung, liver, spleen, kidney and testes were preserved in formalin for histological examination.

A statistical analysis was made of numbers of pups born in each litter, percent survival in each group, weights of pups at twenty-one days, weights of parent rats at time of sacrifice, and organ/body weight ratios of F_{3b} weanlings. The Dunnett test was utilized for determining significant deviation of treated groups from control group values. The above statistical work was done at the computer center of the University of California Medical Center, San Francisco. Two sets of data, number of litters produced and number of litters where all pups died were analyzed by the chi square test.

In addition to the protocol just described, several supplementary studies were carried out. These are described in Section IV.

III. RESULTS

A. General Observations: The appearance and behavior of surviving rats in the experimental groups were indistinguishable from those of the control group in all generations. Thinning or absence of hair on the head, flanks or bellies occurred occasionally in most groups, including the control group.

B. Number and Size of Litters: Numbers of litters born and average numbers of pups per litter are summarized in Tables 1-6.

The number of litters produced in each group by the F_0 females at each of two matings varied from 18 to 20, which was better than expected frequency for Long-Evans rats. Fewer litters were produced by the F_{1b} females, but only one group, 831 middle, at the first mating, produced significantly fewer litters than the control group, a total of 10, as compared with 18 for the controls. Of the ten females which did not produce litters in this group, three died in late pregnancy. Among the F_{2b} females, three groups produced significantly fewer litters than the controls in both mating: twenty 813 middle females produced 4 and 5 litters in two mating, twenty 831 low females produced 7 and 12 litters, and nineteen 831 high females produced 5 and 9 litters, as compared with the twenty control females which produced 19 litters each time. The same females were not necessarily barren in both breedings.

In view of the low incidence of litter production among some of the groups, a number of F_{2b} females which had not produced litters at the second mating were held for ovulation and fertility tests.

The average number of pups born per litter in all groups varied from 9.1 to 12.2 in the first generation, from 8.5 to 10.6 in the

second generation, and from 8.7 to 11.1 in the third generation. None of the treated groups deviated significantly from the control group in this respect.

C. Mortality: The percent survival of pups at twenty-one days is presented in Tables 20-25.

The survival of pups at weaning in the first generation was comparable for all groups with the exception of 831 high, where the percent survival among F_{1a} litters was significantly less than in the control litters, 77% as compared with 97%. The 831 middle group also had a relatively low survival rate, 78%, but this value was not significant at the .05 probability level. However, both of these figures are within the expected range and significance resulted from the unusually high survival rate in the control group. In the second generation, the only group with a significantly lower survival rate than the control group was 831 middle, where 63% of F_{2b} pups survived at weaning as compared with 93% for the control group. In the third generation, the survival rate was comparable in all groups at weaning, in both matings. The high mortality in some of the groups was sometimes the result of all pups dying in a few litters. Application of the chi square test, however, revealed no significant differences in frequency of total litter mortality. In general, deaths were spread over most of the litters within a group.

In addition to the mortality which occurred between birth and weaning, a substantial number of pups which had been saved for continuation on the diets died shortly after weaning at age 22 to 29 days. Deaths occurred after a very brief interval of prostration and no abnormalities were noted upon autopsy. These post-weaning deaths

first occurred among F_{1b} litters and increased in frequency in F_{2b} litters. (F_{2a} litters were not retained after weaning). Groups most affected were the middle and high levels of both 813 and 831 although mortalities occurred in the low groups also. The control group was almost never affected in the basic study. In the supplemental study (Section IV) this condition reversed. In a few cases, most notably F_{2b} pups in the 831 middle and high groups, mortality was so high that fewer than twenty females per group survived for subsequent mating. In view of the peculiar mortality pattern in post-weaning pups, special tests were carried out on all F_{3a} pups and on unused F_{3b} pups, starting at weaning (see Section IV).

? *
An effect on pregnant or nursing mothers was seen also in several of the groups, starting with F_{1b} females at the birth of F_{2a} pups. At this mating, four females died in the 813 high group, three before and one after the birth of a litter, and three females in the 831 middle group died while pregnant. At the second mating of the F_{1b} females, two died in the 813 middle group and two more died in the 813 high group. After the first mating of F_{2b} females, one mother and litter died in the 813 high group. After the second mating of F_{2b} females, an additional mother with litter died in the 813 high group and one mother with litter died in the 831 middle group.

D. Weights of Weanlings: The average weights of surviving pups in each group at twenty-one days are presented in Tables 1-6. The average weights of F_{1a} and F_{1b} weanlings ranged from 34.5 to 40.8 grams, that of F_{2a} and F_{2b} weanlings from 35.0 to 43.3 grams, and that of F_{3a} and F_{3b} weanlings from 34.1 to 41.1 grams. In no case did the weights of weanlings in the experimental groups differ

significantly from control group weights.

E. Weights and Gross Examination of Parent Rats: The average weights of parent rats in each group at the time of sacrifice are presented in Tables 26 and 27. There were no deviations from control values in either males or females in any experimental group. Gross examination of sacrificed animals revealed no abnormalities other than isolated kidney lesions and occasional pathology of other organs which could not be related to treatment. Only one death occurred among adult males during the entire series: this was an F_{2b} male in the 831 high group which developed a large subcutaneous tumor and died after mating. Of the females mentioned earlier, which died during pregnancy or nursing, most underwent post-mortem changes and the cause of death could not be determined. In three, however, lung pathology was noted: two had mottling over the surface of the lobes and one had bright orange lungs. There were some post-mortem changes here too and the possibility of artifacts could not be ruled out.

F. Gross Examination of F_{3b} Weanlings and Organ/Body Weight Ratios: The average organ/body weight ratios of randomly selected F_{3b} pups at twenty-one days are presented in Tables 28 and 29. The liver and kidney ratios for both males and females in all experimental groups were comparable to the control group values. The brain ratios, however, in the 831 middle and high groups of males were significantly less than the control group ratio. The reduced values in these two groups probably occurred because the weanlings selected for autopsy had somewhat higher average body weights than did the controls. The average brain weights themselves, for the control, 831 middle and 831 high groups were almost identical.

Gross inspection of the weanling tissues revealed no abnormalities.

G. Micropathology of F_{3b} Weanling Tissues: All tissues of F_{3b} weanlings submitted for histological examination were normal for both males and females in all groups.

IV. SUPPLEMENTARY STUDIES AND DISCUSSION

In order to investigate the post-weaning mortality pattern, which first became apparent among F_{1b} litters and continued in F_{2b} litters, a cross-feeding experiment was set up using all F_{3a} pups which appeared healthy at weaning. These pups were distributed among eleven groups as follows, using 9 to 20 males and 15 to 20 females per group:

	<u>Source</u>	<u>Diet (subsequent to weaning)</u>
1.	Control	Control
2.	813 high	Control
3.	831 high	Control
4.	Control	Control for 7 days, then 813 low
5.	813 high	Control for 7 days, then 813 low
6.	Control	Control for 7 days, then 831 low
7.	831 high	Control for 7 days, then 831 low
8.	Control	813 high
9.	813 high	813 high
10.	Control	831 high
11.	831 high	831 high

Weanlings were transferred to the new diets when 21 days old and were maintained on them for four weeks. Approximate food consumption was measured for the duration and rats were weighed weekly. Cages were checked daily for dead pups and at the end of four weeks the percent mortality was calculated for each group.

The results are presented in Table 30. There were no differences in food consumption or weight gain. At least 80% of the rats in each group survived. All deaths occurred during the first week post-weaning (i.e. between the 22nd and 29th days of age). It is clear that the deaths were randomly distributed without regard to group or sex. The highest mortality occurred in a control group. (See the fourth group listed in the table; the deaths occurred before the switch-over to 813 low diet). It had been postulated earlier that the post-weaning deaths occurred as the result of the sudden change from a milk diet to a diet high in 813 or 831. This assumption was proved false by the low mortality in the two groups that went from control diet to 813 high or 831 high diets.

The rats were all housed as litters, 2 to 10 in a cage, and it was noted that where deaths occurred, usually more than one pup in a litter was involved, and sometimes all the pups in a single cage died. This pattern of mortality strongly suggests the presence of an extraneous infection.

After the final mating all F_{3b} weanlings not selected for histological examination were retained in their original feeding groups for observation and determination of percent mortality. The results are presented in Table 31. Here again, all the deaths occurred within the first week after weaning, although the pups were kept under observation for four weeks. In the control group and in all three of the 813 groups only two or three deaths occurred per group and only one litter was affected in each case. In the 831 low group, 7 deaths occurred involving 3 litters; in the 831 middle group, 3 deaths occurred involving 2 litters; in the 831 high group, 1 death occurred in one

litter. It must be concluded that here again, deaths occurred in a random fashion and probably resulted from an infection. The assumption of an infection in the colony is strengthened by the fact that mortalities occurred only among rats presumably in a state of lowered resistance, that is, among pregnant or lactating females, and among young rats immediately after weaning.

In an attempt to determine fertility in the F_{2b} females, those rats in the 813 middle, 831 low and 831 high groups which did not produce litters in the second mating, were held for ovulation tests. In many cases, these females had not produced litters in the first mating either. A number of normal F_{2b} controls were also held. A vaginal smear was taken from each rat on five successive days and checked microscopically for evidence of an estrus cycle which would indicate ovulation and fertility. A total of 25 experimental rats were checked, plus several controls. One female in the 831 low group had a vaginal tumor which was undoubtedly the cause of barrenness. Two females, one in the 813 middle group and one in the 831 high group, showed no evidence of ovulation. The remaining 22 rats all went through an estrus cycle and were thus presumed fertile. As an additional test, five females from each group plus five from the control group were mated with normal (control) adult males. One female from the 831 middle group which had been barren in two matings was also included.

The results are presented in Table 32. All groups did equally well, considering it was the first litter for most of the experimental females and the third litter for the control females. At least four out of five females in each experimental group produced litters

(and the single female from the 831 middle group produced a li
This demonstration of fertility in the experimental females mated
with normal males suggests that it was the F_{2b} males which were re-
sponsible for the low incidence of births. A review of the indivi-
dual matings of the F_{2b} animals showed that only a small proportion
of males had been effective in fathering litters. In the 813 middle
group, 3 of 10 males fathered 4 F_{3a} litters and 3 males fathered 5
 F_{3b} litters. In the 831 low group, 4 of 10 males fathered 7 F_{3a} lit-
* tters and 6 males fathered 12 F_{3b} litters. In the 831 high group, 4
of 10 males fathered 5 F_{3a} litters and 5 males fathered 9 F_{3b} litters.
The same males were probably effective in both matings, but this could
not be determined for sure.

Considering the high rate of mortality among F_{2b} weanlings re-
served for subsequent breeding and the possibility of an infection
present in the colony, it was thought that some of the surviving
males had experienced sub-lethal attacks of an infection which had,
however, left them sterile. If this were the case, the females which
had not had litters on either trial, but which were later shown to be
ovulating, had probably been paired with infertile males. On the
other hand, some males, known to be fertile, were unsuccessful in
fathering litters when rotated to other females which were later shown
to be fertile. The reasons for this are unknown. Apparently, a
number of factors were involved in producing this peculiar pattern
of litter production.

V. SUMMARY

Interpretation of the reproductive studies was rendered difficult because of several changes in the mortality pattern. This first occurred among pregnant and nursing females and 3-4 week old weanlings in the groups receiving the two highest levels of each compound. However, unexpected mortality in later matings occurred as well in the control group. If an extraneous infection was in fact present in the colony, it is possible that those rats receiving higher levels of the compound would have been the first to succumb, due to the extra stress. On this basis, 125 ppm of 813 and 50 ppm of 831 might be considered effect levels in that possibly resistance to infection was lowered in both mother rats and weanlings. The low production of litters in several of the groups in later generations was attributed to sterility in some of the males which also may have resulted from the same infection. There were no differences among the groups in adult weights, weanling weights, organ/body weight ratios in weanlings or pathology.

See pp 1-2

THE HINE LABORATORIES, INC.

RESEARCH AND DEVELOPMENT

1099 FOLSOM STREET

SAN FRANCISCO, CALIFORNIA 94103

PHONE 861-5494

TOXICOLOGICAL STUDIES OF COMPOUNDS 813 AND 831

Report No. 43

Addendum to Part II: Reproduction Study

Confidential Report
Prepared for

M & T Chemicals Inc.
Rahway, New Jersey

The Hine Laboratories, Inc.
1099 Folsom Street
San Francisco, California 94103

March 1968

SUMMARY AND CONCLUSIONS

Continuation of the reproduction study further confirmed that the difficulty encountered in the F₂ and F₃ generations was attributable to male rats. Litter production by the F_{3b} rats was below normal in all test groups at the first mating, but the majority of females which failed to produce F_{4a} litters were successful in producing F_{4b} litters when mated with normal males. Most males which had been ineffective in producing F_{4a} litters were ineffective also when mated with normal females. Microscopic examination of the testes of all F_{3b} males revealed degenerative pathology in those males known to be non-fertile. The etiology of this degenerative change is not clear, but it does not appear to be treatment related. See Table 6

The addition of Brewers' yeast to the diets had no significant effect on fecundity of the F_{3b} rats or survival of their litters: litter production (F_{4c}'s) was not improved over that seen prior to receiving the fortified diets and mortality was actually higher among F_{4c}'s than among F_{4a}'s. It should be noted that the F_{3b} groups had been on the pelletized non-fortified diet until just prior to breeding for F_{4c} litters and the degenerative pathology was apparently already present. Only the F_{4c} groups were entirely on a fortified powdered diet. Among the F_{4c} rats used for subsequent breeding, however, there was no evidence of reduced fertility or increased mortality in any of the groups, and the F_{5a} and F_{5b} litters were all within normal limits.

In conclusion, the continued study of the infertility pattern noted in the earlier portion of the reproduction study revealed a reversal in the trend, with normal fecundity achieved by the fifth generation. There was correlation between testicular pathology and lack of fertility in F_{3b} males.

I. INTRODUCTION

The results of the three generation study of compounds 813 and 831 were included in the final report (No. 43), Toxicological Studies of Compounds 813 and 831, and covered the reproduction study through weaning of the F_{3b} litters with additional data on fertility of adult rats and mortality of weanlings.

Due to the unusual mortality patterns observed and the sterility of some of the adult males, it was considered advisable to carry the study further through subsequent generations. Surplus rats from the F_{3b} litters were used. This report presents the results obtained from the time of mating of the F_{3b} rats to weaning of F_{5b} litters.

II. RESULTS

F_{3b} rats from the control, 813 middle, 831 low and 831 high groups were mated when 100 days old to obtain F_{4a} litters which were observed and discarded when 21 days old. Results of this mating are presented in Table 1. Litter production in all groups except the control was below normal: about 65% in the 831 groups and only one litter out of four in the 813 middle group. All groups were normal however in size of litters, weights of weanlings and percent survival.

Approximately ten days after weaning of the F_{4a} litters, the F_{3b} females in all groups were mated to a group of normal males which had been receiving control food but were not of the original control group. The results of this mating (litters designated F_{4b}) are presented in Table 2. With only one exception (a female in 831 Low) all females which had failed to produce an F_{4a} litter did

produce a litter after mating with normal males (one female in 831 high which did not produce an F_{4a} litter died before the second mating). The numbers, weights, and percent survival of the F_{4b} litters were within normal limits although the mortality among pups in the 831 groups was somewhat higher than in the other groups.

After weaning of the F_{4b} litters, the odd numbered F_{3b} control females (known to be productive) were mated with those F_{3b} males which failed to father litters in two separate attempts. Each control female was exposed to one male only. After ten days, vaginal smears were examined daily to establish pregnancy and these data were correlated with litter production. Results are presented in Table 3. Of the nine males tested, only three were successful in fathering litters; one of these was a male which had previously fathered one litter in two attempts.

In order to rule out the possibility of the males being ineffective due to too frequent breeding, two normal males were exposed to four control females each, a week apart. Results are presented in Table 4. Since one male fathered four litters in four attempts and the other fathered three litters in four attempts, the frequency of mating does not appear to be a factor in male ineffectiveness.

Following the foregoing tests, all F_{3b} rats were switched to powdered diets containing 1% Brewers' yeast in addition to the usual concentration of 813 and 831. The Brewers' yeast was added to compensate for any vitamin loss which may have occurred in the pelletized food as a result of high temperatures during production.

The fortified powdered diets were used throughout the remainder of the study. Sixteen to thirty days following the addition of Brewers' yeast to the diets, the F_{3b} rats were mated to produce an F_{4c} generation which was maintained for further study. The F_{3b} females were examined grossly and discarded after weaning of the F_{4c} litters and the F_{3b} males were sacrificed, examined grossly, with weights recorded for testes, adrenals and seminal vesicles. These organs plus brain and thyroid were preserved for microscopic examination. Results are presented in Tables 5 to 7. Examination of the F_{3b} females revealed resorption sites in some of the rats which had failed to produce litters or had produced very small litters: one control female, and two 831 low females had such resorbing fetuses. In addition, one control female and one 831 low female died immediately after giving birth. One 831 high female died before giving birth and was noted to have term fetuses. Ovarian cysts were noted in one control and one 831 high female, but these rats had normal litters. Organ weights and ratios of the F_{3b} males varied considerably as did body weights. Ratios for seminal vesicles were comparable in all of the groups but organ weights and ratios of testes and adrenals were less in the 813 and 831 groups than in the controls. Those rats which were ineffective in fathering litters had reduced testes weights which lowered the average for the groups. Reduced adrenal weights were not related to sterility, however. In general, the same male rats which had not fathered F_{4a} litters were ineffective in fathering F_{4b} and F_{4c} litters. Histopathological findings showed very good correlation with inability to father litters; every male which

had failed to father litters in both the F_{4a} and F_{4c} generations had testicular pathology including degeneration of seminiferous epithelium with or without fibrosis, or lobular degeneration. No testicular pathology was seen in fertile males and no other organs showed pathology in any of the males.

Although the numbers of F_{4c} litters produced were less in the 813 and 831 groups than in the control group, size and weights of litters were comparable for all groups. Mortality was somewhat higher in the 831 groups than in the control. The one litter produced in the 813 middle group was normal but this group was not continued because of insufficient numbers. The F_{4c} weanlings from the control, 831 low and 831 high groups, however, were maintained on the diets and mated when 120 days old.

Results obtained in two matings of the F_{4c} rats are presented in Tables 8 and 9. Both F_{5a} and F_{5b} litters were normal in number, size, weight and percent survival in all groups. Parent rats were comparable at sacrifice and no abnormalities were noted at autopsy in either parents or pups. No tissues were taken for histology and the study was terminated at this point.

Table 1: Average Numbers, Weights and Percent Survival of F_{4a} Litters

	Control	815 Middle	831 Low	831 High
Number of Litters Produced	18/20	1/4	13/19	13/20
Average Number (a) Pups per Litter				
Day 1	9.9	11	10.0	7.3
Day 5	9.5	11	9.0	7.2
Day 21	8.5	10	7.8	7.4
Average Weight of Weanlings at 21 Days (gm)	33.9	25.5	40.2	37.4
Number of Litters Where All Died	1/18	0/1	0/13	2/13
% Survival at 21 Days	87.8	100	86.4	85.3

(a) Litters greater than 10 in number are routinely reduced to 10 after counting on the 5th day

Table 2: Average Numbers, Weights and Percent Survival of F_{4b} Litters (a)

	Control	813 Middle	831 Low	831 High
Number of Litters Produced	19/19	4/4	16/19	19/19
Average Number Pups per Litter				
Day 1	9.2	9.0	0.3	8.8
Day 5	8.9	8.5	9.3	8.9
Day 21	7.7	8.2	7.6	7.2
Average Weight of Weanlings at 21 Days (gm)	39.2	37.5	45.6	43.0
Number of Litters Where All Died	1/19	0/4	2/16	5/19
% Survival at 21 Days	88.5	97.1	76.8	64.3
Average Weight of Mother at Weaning	353	349	353	335

(a) From F_{3b} females X normal males

Table 3: Mating of Ineffective F_{3b} Males with Control Females

Control Female No.	Male No.	Pregnancy (according to vaginal smear)	Production of Normal Litter
1	813M-1	-	-
3	813M-2	-	-
7	813M-3	+	+
9	831L-1	-	-
11	831L-3	-	-
13	831L-8	+	+
15	831H-4 (a)	-	-
17	831H-5	-	-
19	831H-8 (b)	+	+

(a) was originally mated to female who later died and was noted to have inflammed uterus; male may not have been at fault

(b) produced only one F_{4a} litter out of two chances

Table 4: Mating of Normal Males with Four F_{3b} Control Females a Week Apart

Control Female Number	Male Number	Production of Normal Litter
2	A	+
4	A	+
6	A	+
8	A	+
10	B	+
12	B	-
14	B	+
16	B	+

Table 5: Average Organ Weights and Organ/Body Weight Ratios of F_{3b} Adult Males

Group	Body Weight (gm)	Testes		Adrenals		Sem. Vesicles	
		Wt (gm)	Ratio	Wt (gm)	Ratio	Wt (gm)	Ratio
Control	623	3.8	.62	.041	.0066	.88	.14
813 Middle	552	2.3	.41	.030	.0052	.70	.13
831 Low	642	3.0	.47	.030	.0048	.88	.14
831 High	618	3.3	.55	.029	.0047	.72	.12

Table 6: Correlation of Sterility in F_{3b} Males with Histo-
pathology of Testis

Group	No.	No. of Litters Produced		Microscopic Findings in Testis
		F _{4a}	F _{4c}	
813 Middle	1	0	0	focal degeneration of seminiferous epithelium
	2	0	0	marked degeneration of seminiferous epithelium
	4	1	0	normal
831 Low	1	0	0	degeneration of seminiferous epithelium, fibrosis
	3	0	0	focal loss of seminiferous epithelium, fibrosis
	8	0	3	normal
	9	1	0	atrophy, degeneration of seminiferous epithelium, fibrosis
831 High	4	0	0	marked lobular degeneration
	5	0	0	marked lobular degeneration
	8	1	0	normal

Table 7: Average Numbers, Weights and Percent Survival of F_{4c} Litters

	Control	813 Middle	831 Low	831 High
Number of Litters Produced	16/19	1/4	14/19	10/18
Average Number Pups per Litter				
Day 1	9.2	8.0	8.3	7.2
Day 5	8.0	7.0	8.3	5.4
Day 21	7.5	7.0	7.5	4.8
Average Weight of Weanlings at 21 Days (gm)	39.0	36.3	40.0	46.1
Number of Litters Where All Died	1/16	0/1	4/14	2/10
% Survival at 21 Days	81.3	87.5	66.4	52.8
Average Weight of Mother at Weaning	354	377	383	371

Table 8: Average Numbers, Weights and Percent Survival of F_{5a} Litters

	Control	831 Low	831 High
Number of Litters Produced	20/20	19/20	17/18
Average Number Pups per Litter			
Day 1	10.3	9.3	9.8
Day 5	9.5	8.7	8.9
Day 21	8.1	7.7	7.8
Average Weight of Weanlings at 21 Days (gm)	33.0	35.8	34.9
Number of Litters Where All Died	1/20	0/19	0/17
% Survival at 21 Days	82.8	85.4	84.1

Table 9: Average Numbers, Weights and Percent Survival of F5b Litters

	Control	831 Low	831 High
Number of Litters Produced	17/20	18/20	18/18
Average Number Pups per Litter			
Day 1	9.4	9.6	10.4
Day 5	7.8	9.3	10.1
Day 21	7.0	7.6	7.9
Average Weight of Weanlings at 21 Days (gm)	39.2	36.4	37.5
Number of Litters Where All Died	0/17	0/18	0/18
% Survival at 21 Days	81.0	88.4	81.1
Average Weight Mother at Weaning	336	342	341
Average Weight Father After Mating	475	473	504



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

C. H. Farr, PhD, DABT
Manager, Product Safety and Toxicology
Atochem North America, Inc.
900 First Avenue
P.O. Box 1536
King of Prussia, Pennsylvania 19406-0018

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

APR 24 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

12579A



Recycled/Recyclable
Printed with Soy/Canola Ink on paper that
contains at least 50% recycled fiber

Triage of 8(e) Submissions

Date sent to triage: 12/14/95

NON-CAP

CAP

Submission number: 12579A

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:

THIS IS THE ORIGINAL 8(e) SUBMISSION; PLEASE REFILE AFTER TRIAGE DATABASE ENTRY

For Contractor Use Only	
entire document: <u>0</u> 1 2 pages <u>1,2</u>	pages <u>1,2, tabs</u>
Notes:	
Contractor reviewer : <u>LPS</u>	Date: <u>4/14/95</u>

CECATS/TRIAGE TRACKING DBASE ENTRY FORM

CECATS DATA:
Submission # BEHQ-1092-12579 SEQ. A

TYPE: INT SUPP FLWP

SUBMITTER NAME: EIF Abchem North America, Inc

INFORMATION REQUESTED: FLWP DATE:
0501 NO INFO REQUESTED
0502 INFO REQUESTED (TECH)
0503 INFO REQUESTED (VOL ACTIONS)
0504 INFO REQUESTED (REPORTING RATIONALE)
DISPOSITION:
063 REFER TO CHEMICAL SCREENING
0678 CAP NOTICE

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

SUB. DATE: 10/23/92 OTS DATE: 10/30/92 CSRAD DATE: 02/28/95

CHEMICAL NAME:

CASE

16091-18-2

26401-97-8

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. OCC/REL/FATE	01 02 04	0246 CLASTO (HUMAN)	01 02 04
<u>0207</u> 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	ONGOING REVIEW	SPECIES	TOXICOLOGICAL CONCERN:	USE:	PRODUCTION:
	<u>YES</u>	YES (DROP/REFER)	<u>RAT</u>	LOW	unable to	
CAS SR	NO	NO (CONTINUE)		MED	assess	
	IN TRAINING	REFER		HIGH		

COMMENTS
3-gen Repro
Dietary administration
levels not indicated -
only the same as 2yr feeding study

Only indication of doses is
on pg. 39-A i.e., 125ppm for
chemical 813 and 50ppm for chemical
831 considered effect levels.