

elf atochem

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King of Prussia, PA 19406-0018

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Contains No CBI

September 10, 1992

CERTIFIED MAIL

RETURN RECEIPT REQUESTED

SEHQ-92-12697

50420010876

INIT

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 four-hour aerosol toxicity in rats study to the EPA. This study does not involve effects in humans.

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

The enclosed study provides information on the chemical tributyltin oxide. Its exact chemical name is hexabutyldistannoxane and its CAS number is 56-35-9.

The title of the enclosed study is Systemic Toxicity Testing of ZK 21,955 as a Liquid Aerosol in Rats (M + F), as a Single Dose by Inhalation Over a Period of 4 Hours (LC₅₀). The following is a summary of the adverse effects observed in this study.

Groups of five rats of both sexes were exposed to aerosols of tributyltin oxide for four hours. The inhalation LC₅₀ was calculated to be 0.064 ml/m³.

mm
2/9/95

TSCA CAP
Tributyltin Oxide
September 10, 1992
Page Two

To our knowledge, Atochem has not previously submitted any TSCA Section 8(e) notices or premanufacture notifications on the subject chemical.

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

Sincerely,

A handwritten signature in cursive script, appearing to read "C.H. Farr".

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

Enclosures

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Trial Design.

(1) Animals, exposure period and period of observation.

25 male and 25 female rats, 150 - 210 g in weight (m) or 130 - 180 g (f), of the Sprague Dawley strain and SPF quality, bred by Gassner, were fed on standard diet (Altromin R) and tap water ad libitum and maintained under standard conditions in Type II Macrolon cages with perforated floor (1 rat per cage) in an air-conditioned room (room temperature about 22° C, relative humidity about 65%), under controlled lighting conditions (12 hour day/night rhythm). They were randomly sub-divided into 5 groups each of 5 m and 5 f rats, and marked on the ears for identification.

The period of acclimatisation before the beginning of the trial was 14 days. The animals' feed was withdrawn 15 hours before beginning the inhalation. The period of observation was up to Day 22 (Day 1 = day of exposure).

The 5 groups received stepwise concentrations of ZK 21,955 liquid, as a single exposure for 4 hours to an aerosol.

(2) Inhalation system

Key to diagram: Luftfuhrung = air passage
 Aerosolfuhrung = aerosol passage.

The dynamically driven inhalation system (v. Fig 1) consists of the actual inhalation unit for producing and delivering the aerosol (1.1.) and the surveillance unit for the quantitative and qualitative control of the aerosol (1.2.)

(2.1.) Operation of the Inhalation Unit.

The air pressure in the domestic system was brought to a constant pressure of 5.2 bars in a binary nozzle (C) after passing through a fine dust filter, and pressure stabiliser and a volume meter (A). In the nozzle the mixture was made with the liquid to be aerosoled, via a perfusion pump which could be regulated in steps (B). The inhalation chamber (60 l content) consisted of an upper aerosol distribution chamber and a

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lower animal chamber with restriction apparatus (E). The arrangement of the restrictors was such that the rat's nose was forcibly held into the aerosol stream.

The exit of aerosol and air from the chamber was measured and regulated (A').

The temperature and relative humidity in the chamber were supervised (D).

(2.2.) Qualitative and Quantitative Control of the Aerosol.

Qualitative control.

An optical particle counter (F) (Partoskop A, Messrs Kratel), with 280 or 2800 cm³/minute samples, was placed at the nose of the animal. Coincidence losses (release of only one impulse by several particles) was balanced automatically by the apparatus. The particle counter was coupled to a 200-channel storing oscillograph (Messrs Wenzel, PAM 202) (6). The distribution curve shown on the oscillograph screen (particle frequency/channel) was transformed to a particle size distribution curve using the standard curve of the Partoskop. As a result of the usual techniques of aerosol formation, this particle size distribution curve is of the normal logarithmic type.

In order more easily to orientate the work and to obtain a direct answer to the question as to how many particles (%) were present in each order of magnitude, the aerosol particle size distribution curve was made linear. This was done by plotting the summated values for the particle sizes on to a logarithmic probability grid (Fig 2, Curve A).

Since the assessment of inhalational toxicity is made from the data of concentration (LC₅₀ in ml compound/m³ inhaled air), it is informative to convert the particle size distribution, as a further step, to mass distribution. Under the conditions here applying, of a log normal distribution, this is done using the Hatch-Choate equation:

$$\log \text{MMD} = \log \text{CMD} + 6.9 \log^2 \epsilon g$$

where MMD (mass median diameter) represents the 50% level of the weight distribution curve (Fig 2, Curve B), CMD (count median

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diameter) the 50% level and σ_g of the rise ($\sigma_g = 84.3\%$, diameter/CMD) in the particle size distribution curve (Fig 2, Curve A). It can be seen that the weight of aerosoled substance (r^3 !) is principally that of the large particles.

Quantitative Control.

Samples were taken at the nasal position of the rat, at a flow rate of 1.3 l/minute, through a glass tube (ϕ 7 mm) into two wash bottles, connected in series, and covered with ice-cooled absolute alcohol (Fig 1, H). The contents of these wash flasks were investigated for their ZK 21,955 level by titration. The indicator used was 1% bromphenol blue in ethanol, and titration was carried out with n/100 HCl.

Analytical procedure: After the air sample had been taken the quantity of alcohol was measured and samples (5 ml) titrated with n/100 HCl against bromphenol blue from blue to yellow. Consumption, plotted on a previously established standard curve, showed the percentage concentration of the solution. By calculation with reference to the amount of air passed through, the (actual) air content of TBTO was determined.

Formula:

$$\frac{\% \text{ of wash flask solution} \times \text{ml solution. content} \times 100}{100 \times \text{amount of air passing out (l)}}$$

The aerosol concentrations, determined by titration, are described as actual concentrations, while those calculated from the consumed air and liquid levels are nominal concentrations.

Experience shows that the actual concentration is much lower than the nominal concentration, since it can only show the airborne particles taken up in the sample. The nominal concentration includes all the losses due to precipitation.

(3) Investigation of animals.

The rats were observed continuously during the four-hour period of exposure and daily during the 22 days post-exposure observation period.

FILED: CN 981-85

Schering Aktiengesellschaft
Postfach 15 40
D-4619 Bergkamen 1

TR 91-281
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Pharma-Forschung
Pharmaceutical Research

Pharma Forschungsbericht Pharma Research Report Fachbereich IV III	Bericht Nr./Report No. IC	Seite/Page 1
	Datum/Date 6.6.1977/k8	Umfang, Seiten Total No. of pages

Titel des Berichtes/Title of Report ✓ Systemic toxicity testing of ZK 21,955 as a liquid aerosol in rats ✓ (M + F), as a single dose by inhalation over a period of 4 hours ✓ (LC ₅₀). Protocol No 124/76 T-139		
Klinische Prüfphase Clinical trial phase	Die Prüfungen wurden durchgeführt/The trials were carried out von/from bis/to	Prüf-Nr./Trial No.
Fachbereich IV Leiter/Head III Dr R. Kopp	Themengruppe/Subject group IC	
Unterschrift/Signature		ZK-Nr./ZK No. 21,955
Department/ Sektion Department/ Section Dr P. Glünzel Leiter/Head	Generic name Tri-n-butyl-tin oxide	
Unterschrift/Signature		SH-Nr./SH No.
Berichter/Author N. Schmidt		Kennzeichnung der biol. Wirkung/Characteristic biological effect Unknown
Unterschrift/Signature		

Problemstellung/Purpose of Study

In the course of toxicity testing of compound ZK 21,955 it was desired to investigate its systemic toxicity in rats given a single dose as an inhalation over a period of 4 hours. For this purpose it was proposed to determine that concentration of the substance in air which resulted in the death of about 50% of the animals within the period of observation (LC₅₀)

CAS 56-35-9

Deckblatt 2/Fly Sheet 2	Bericht Nr./Report No.	Seite/Page 2
<input type="checkbox"/> Fachbereich II <input checked="" type="checkbox"/> Fachbereich III <input type="checkbox"/> Fachbereich IV	IC	

Kurzfassung des Berichtes/Summary of Report

Five groups each of 5 m and 5 f albino rats were made to inhale a continuously freshly made aerosol in a "nose only position" over a period of 4 hours. The post-exposure observation period was 22 days.

The aerosol prepared from the ZK 21,955 liquid was analysed qualitatively and quantitatively.

For the purposes of the LC₅₀ it was determined that 50% of all the aerosol particles were $\leq 0.52 \mu\text{m}$. It was calculated from this that 50% of the total aerosol particle content was $\leq 4.2 \mu\text{m}$.

In the clinical picture the dominant signs were dyspnoea and apathy, up to the fifth day of the period of observation.

Animals dying (up to day 7 of the period of observation) showed macroscopic signs of pulmonary oedema and congestive hyperaemia in the lesser circulation, and evidence of enteritis.

Animals sacrificed on the 23rd day showed no pathological changes on macroscopic examination.

The LC₅₀ of the ZK 21,955 liquid used is:

Schlußfolgerung/Conclusion

Actual LC₅₀ (measured) = 0.064 ml/m³ (limits of confidence 0.041-0.160)
 " LC₅ " = 0.037 ml/m³
 " LC₉₅ " = 0.114 ml/m³
 Nominal LC₅₀ (calculated) = 0.250 ml/m³
 LC₅₀ based on particle size $\leq 10 \mu\text{m}$ = 0.054 ml/m³

Conclusion:

The ZK liquid aerosol tested shows high toxicity. However, this toxicity does not quantify the inhalation risk of the compound in practice.

Since in practice ZK 21,955 is not made into an aerosol, there is

only the possible occurrence of air contamination by gaseous ZK 21,955.

The inhalation risk of gaseous ZK 21,955 in practice will be investigated in a separate trial, with due regard to the vapour pressure curve of TBTO.

Deckblatt 3/Fly Sheet 3	Bericht Nr./Report No.	Seite/Page	4
		<input type="checkbox"/> Fachbereich II <input checked="" type="checkbox"/> Fachbereich III <input type="checkbox"/> Fachbereich IV	
IC			

Angaben zu Prüfsubstanz(en) und -präparat(en)/Data on test substance(s) and formulation(s)

Chargen-Nr. der Prüfsubstanz(en) und/oder geprüften Formulierung(en)
Batch No. of test substance(s) and/or tested formulation(s)

EK 75-3544

Hersteller der Prüfsubstanz(en)/Manufacturer of test substance(s)

Schering AG

Hersteller der Formulierung der Prüfsubstanz(en)/Manufacturer of formulation of test substance(s)

Schering AG

Galenische Formulierung (bei Anwendung von SH-Formulierungen SH-Nr. angeben)
Formulation (if SH formulations are used, state SH No.)

Not necessary, since in aggregate it is "liquid"

The TBTO content of the liquid was determined as 97.1 - 97.4% by the Analytical Laboratory of Dept. Industrial Chemicals (see letter from Dr Plum, 20.1.1977).

Angaben zu Referenzsubstanz(en) bzw. Bezugspräparat(en)/Data on reference substance(s) or preparation(s)

Generic name und ZK-Nr. von Referenzsubstanz(en) bzw. Name von Bezugspräparat(en)/oder Handelspräparat(en)
Generic name and ZK No. of reference substance(s) or name of reference preparation(s)/or commercial preparation(s)

Hersteller der Referenzsubstanz(en)/Manufacturer of reference substance(s)

Hersteller der Formulierung der Referenzsubstanz(en)/Manufacturer of formulation of reference substance(s)

Galenische Formulierung/Formulation

Deckblatt 4/Fly Sheet 4	Bericht Nr./Report No. IC	Seite 4/Page 5
		<input type="checkbox"/> Fachbereich II <input checked="" type="checkbox"/> Fachbereich III <input type="checkbox"/> Fachbereich IV

Strukturformel ab ZK 28.000 vom Department Zentrale Dokumentation anfordern
Upwards of ZK 28,000 structural formula request from Department of Central Documentation

Chem. Bez./Chemical name (Iupac)

Tri-n-butyl tin oxide
Generic name

ZK-Nr./ZK No.
21.955

Chem. Bez./Chemical name (Iupac)

Generic name

ZK-Nr./ZK No.

Chem. Bez./Chemical name (Iupac)

Generic name

ZK-Nr./ZK No.

Chem. Bez./Chemical name (Iupac)

Generic name

ZK-Nr./ZK No.

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At the end of the trial the rats were sacrificed under CO₂, autopsied and examined macroscopically.

Results.

The conditions of exposure, including the concentrations of the compound in the aerosol, are shown in Table 1:

Group	Exp time	Exposure conditions and concentrations				
		Air from nozzle	Supply by perf pump	Air exit from chamber as measured	Nom. conc in chamber ZK 21955 soln 97.1-97.4% (ml/m ³)	Actual conc in chamber ZK 21955 soln 97.1-97.4% (ml/m ³)
	(h)	(l/h)	(ml/h)	(l/h)		
1 (5 M, 5 F)	4	600	0.380	ca 250	0.633	0.173
2 "	4	600	0.180	ca 250	0.300	0.072
3 "	4	600	0.110	ca 250	0.183	0.053
4 "	4	600	0.047	ca 250	0.078	0.020
5 "	4	600	0.0105	ca 250	0.018	0.012

The relative humidity measured in the chamber was 10% and the temperature 20 - 21° C.

Fig 2 shows the results of qualitative analysis of the aerosol.

Key to Fig 2:

- A: CMD size distribution
- B: MMD mass distribution

It can be seen from the diagram that 50% of the aerosol particles were $\leq 0.52 \mu\text{m}$ (A). 50% of the ZK 21,955 substance mass presented was in the form of particles of diameter $\leq 4.2 \mu\text{m}$ (B). Aerosols of particle size up to about 10 μm can be described as inhalable through the nose and mouth (deposition in the nasopharynx and thence lower down as far as the alveoli depends on particle size).

Action profile and toxicity.

No abnormal symptoms were detected during the four-hour period of inhalation. At the end of the period of exposure to the two highest

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concentrations there were severe dyspnoea, apathy and the adoption of the prone position. In the animals which died these symptoms persisted until death. In the surviving animals there were slight to moderate degrees of apathy, dyspnoea, nasal discharge and roughness of the coat. Some rats showed inflamed eyes at all dose levels. The animals were symptom-free from Day 4 on average (see Table 2).

Table 2: Clinical symptoms during the 22-day period of observation

Group	Reaction	Appeared after end of exposure /no of rats	Duration (days)	Mortality	
				In the chamber (min)	During observation (days)
1	Prone, severe apathy severe dyspnoea scabbing of mouth & nose	Immed 2	Up to death	1/0 (240)	0/2 (1)
		Immed 7			
		Immed 9			
		from Day 2 5			
2	Prone, mod. apathy severe dyspnoea Nasal flow Rough coat	from D2 3	1	0/0	2/2 (2)
		Immed 10	4		
		From D2 6	4		
		From D2 5	1		
		From D2 8	4		
3	Mod. apathy Mod. dysp. Nasal flow Rough coat	Immed 10	3	0/0	2/0 (2)
		from D2 7	3		
		Immed 5	3		
		From D2 10	6		
4	Slight apathy Mod. dyspn. Rough coat	Immed 10	5	0/0	0/0
		From D2 3	1		
		From D2 7	5		
5	Sl. apathy	Immed 1	6	0/0	0/0

The surviving animals were symptom-free 23 days after exposure, and were sacrificed.

Post-mortem findings (only those definitely or probably due to or favoured by the compound):

Animals dying: Pulmonary oedema and congestive hyperaemia in lesser

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circulation, due to compound.

Macroscopic suggestions of enteritis

Sacrificed animals: Nil



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

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P.O. Box 1536
King of Prussia, Pennsylvania 19406-0018

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MAR 30 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

12697A



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Triage of 8(e) Submissions

Date sent to triage: MAY 10 1995

NON-CAP

CAP

Submission number: 12697A

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: 0 1 2 pages 112

pages 112, 4, 5

Notes:

Contractor reviewer: PAR

Date: 2/22/95

CECATS/TRIAGE TRACKING DBASE ENTRY FORM

CECATS DATA: Submission # 8EHQ-1092-12697 SEQ. A
 TYPE: INT. SUPP FLWP
 SUBMITTER NAME: Elf Atachem Noc
Aeriscor Inc.

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

SUB. DATE: 09/10/12 OTS DATE: 10/06/92 CSRAD DATE: 02/09/95
 CAS #: 56-35-9

CHEMICAL NAME: TBTO

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

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

USE:

TOXICOLOGICAL CONCERN:

TRIAGE DATA: NON-CBI INVENTORY

CAS SR: YES
 NO
 IN IT N MINI
 REF: R

SPECIES: RAT

LOW
 MED
 HIGH

ONGOING REVIEW
 YES (DROP/REFER)
 NO (CONTINUE)

10/12/12

> <ID NUMBER>
8(e)-12697A

> <TOX CONCERN>
H

> <COMMENT>
ACUTE INHALATION TOXICITY IN RATS IS HIGH CONCERN WITH AN LC50 OF 0.064 ML/M3 FOR A 4 HOUR EXPOSURE. 50 ANIMALS (5/SEX/GROUP) WERE EXPOSED TO 0.173, 0.072, 0.053, 0.020 AND 0.012 ML/M3. 1 MORTALITY OCCURRED AT THE 0.173 ML/M3 DOSE LEVEL (1/5 M, 0/5 F). CLINICAL OBSERVATIONS INCLUDED PRONE, SLIGHT TO SEVERE APATHY, MODERATE TO SEVERE DYSPNOEA, SCABBING OF MOUTH AND NOSE, NASAL FLOW, AND ROUGH COAT. PATHOLOGIC EXAM REVEALED PULMONARY EDEMA, CONGESTIVE HYPERANEMIA IN LESSER CIRCULATION (DUE TO COMPOUND), AND ENTERITIS.