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

JUN 30 1989

J7305

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA Reg. No.: 8340-17. Triphenyltin Hydroxide: Review of a subchronic (90 day) inhalation study in rats (RCC Study No.: 202353, dated February, 1989).

TOX CHEM No.: 896E
TOX PROJECT No.: 9-1039
Record No.: 241405
MRID. No.: 410177-01

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6/29/89
6/22/89

Background

The Hoechst Celanese Corporation has submitted a subchronic inhalation toxicity study with rats with the fungicide triphenyltin hydroxide (TPTH) in response to the data requirements set forth in the Registration Standard for this

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chemical. The study was reviewed by Toxicology Branch I (TB-I) and the following comments apply.

Toxicology Branch Comments

1. The study was reviewed and determined to be CORE GUIDELINE. The NOEL was set at 0.34 mg/m^3 and the LEL was 2 mg/m^3. At the LEL there were deaths.

The only target organ for TPTH recognized in this subchronic inhalation study was the lung and nasal cavity. The testing laboratory concluded that the rats died as a result of lung injury. The recovery aspect of this study indicated that some of the lesions persisted for the 28 day recovery period. Refer to the DER attached for additional details.

2. The protocol for this study was previously reviewed by TB-I (refer to review by J. Doherty dated April 19, 1988 for EPA Reg. No.: 8340-17). In this protocol review several deficiencies of the study design were noted and the registrant was asked to modify the protocol to include additional procedures and/or information. The Product Manager (Lois Rossi) sent the registrant a copy of TB's review of this study protocol on May 12, 1988.

The in-life phase of this study was started on February 17, 1988 and the main phase was terminated on May 18/19, 1988. Thus, the laboratory could not have had time to modify the protocol to include the comments made by TB-1.

In spite of the fact that the recommendations made by TB-I in the review of the protocol for this study were not followed, the study is considered acceptable and to define the potential subchronic inhalation toxicity in rats of TPTH. The recommendations made by TB-I concerned: i. method used to generate the test atmosphere containing a consistent and uniform particle size and concentration of TPTH; ii. analysis for TPTH and/or its metabolites in the blood or internal organs to demonstrate proof of absorption; and iii. special analyses to asses for potential immunotoxicity. The following discusses each of these issues separately.

i. Method for generation of the test atmosphere.

The study did not describe the apparatus used to generate TPTH into the test atmosphere as a dust. TB-I however, considers that sufficient analytical data on both the atmosphere concentration and particle size were presented to assure that the study was conducted in an acceptable manner.

The generating system was described only as a RGB-1000 aerosol generator (Pales, Germany). TB-I requests that the registrant provide a detailed description of this apparatus since TB personnel are not familiar with this particular system.

ii. Proof of absorption of TPTH.

No blood samples or internal organs were analyzed for TPTH and/or its metabolites. Therefore it is not possible to determine if TPTH was absorbed from the lung into the body. TB-I considers, however, that since the study defined the potential toxicity of TPTH by subchronic inhalation (i.e deaths by lung injury), it is not essential to demonstrate that the test material was systemically absorbed.

iii. Special assessments for immunotoxicity.

The bone marrow, lymphocyte, splenocyte and thymocyte assessments as requested by TB-I were not made. Inclusion of these parameters would have helped to detect any subtle effects of TPTH on the immune system. Spleen weights and immunoglobulin analyses were provided. Spleen weights were reduced for the high dose group but no effects were apparent on the immunoglobulin levels. The apparent effect on spleen weight was not considered a primary effect of TPTH. Overall there was no evidence that the immune system was affected in this study.

In the absence of the proof of absorption and the special analyses to assess for potential immunotoxicity, this study is considered by TB-I to be of limited usefulness in assessing for the potential immunotoxicity of TPTH.

3. This study is the third subchronic inhalation study submitted by the registrants for TPTH. The first study (refer to the TB Chapter for the Registration Standard for TPTH) was assigned RESERVED Classification with a request to the registrant to provide additional information. The study was conducted by the Cannon Laboratories which has since gone out of business. Since the registrant has not provided the requested information, the study is considered INVALID by TB.

The second study was also determined to be INVALID (refer to J. Doherty dated August 21, 1987 for EPA Reg. No.: 8340-17) because the TPTH was generated into the atmosphere as a mixture with talcum powder. A preliminary study submitted as a dose range finding study in which the TPTH was not generated into the atmosphere with talcum powder indicated that 60% of the rats dosed at 10 mg/m^3 died after a few exposures. This observation is consistent with the mortality observed in the most recent study which occurs at 2 mg/m^3. TPTH has been demonstrated to

have an acute inhalation LC_{50} of 0.06 mg/l (refer to the TB Chapter for the Registration Standard for TPTH).

REGULATORY IMPLICATIONS

The study provides sufficient data to indicate that deaths and lung pathological changes result from exposure to low dose levels (2 mg/m^3) of TPTH in the air. Respiratory/inhalation exposure to TPTH should be evaluated for existing and proposed uses of TPTH to determine actual and potential hazards to humans.

Reviewed By: John Doherty John Doherty 6/20/89
Section I, Toxicology Branch I - IRS (H7509C)
Secondary Reviewer: Robert Zendzian
Section I, Toxicology Branch I - IRS (H7509C) 6/20/89

DATA EVALUATION REPORT

Study Type: 82-4 - Subchronic (90 day) Inhalation, Rats

MRID No.: 410177-01 TOX CHEM No.: 896E

Test Material: Triphenyltin hydroxide (96.2% purity)

Synonyms: Fentinhydroxid and also known by Code #HOE 029664 OF ZD97 0004.

Test Animals: Wistar outbred rats, KFOR Kleinteirfarm, Nadoerin, AG, Switzerland.

Study Number: 202353

Sponsor: Hoechst Aktiengesellishaft, Federal Republic of Germany. Study submitted by Hoechst Celanese Corp. Somerville, New Jersey.

Testing Facility: Research Consulting Company, (Inlife Phase)
RCC Unweltchemie (Analytical Aspects)
PATCO (Pathology)
ANAWA Laboratories AG (Immunoglobulins)

All laboratories located in Switzerland.

Title of Report: "Fentinhydroxid (TPTH) Technical Grade Subchronic (90-Day) Repeated Dose Inhalation Toxicity Study in Rats."

Author(s): F. Duchosal, Ph. Thevenaz, H. Luetkemeier, O. Vogel, G. Pappritz, P. Miadenovic, and Ch. Terrier.

Report Issued: February 1989

Conclusions: The NOEL is set at 0.34 mg/m^3. At the LEL (2.0 mg/m^3) there are deaths (especially among the males), due to effects of TPTH in the lung as indicated by labored breathing, rales, pathological indications of inflammatory response in the lung and nasal cavity, increase in lung weight (males).

Classification: GUIDELINE

Special Review Criteria (40 CFR 154.7): The low NOEL (.034 mg/m^3) for this study and deaths at the LEL (2 mg/m^3) may indicate a potential serious inhalation hazard from subchronic inhalation exposure.

Quality Assurance Statement:

A statement signed (signature illegible) by a representative for the Manager of the Quality Assurance Unit (K. Schneider) attested that the study was inspected or audited on 10 different dates and that 9 reports were prepared. The Quality Assurance reports were not provided with the study.

Review:

The basic design of this study consisted of exposing four groups of rats (Wistar, outbred, KFOR Kleintierfarm, Nadoerin AG, Switzerland) to atmospheres containing triphenyltin hydroxide (TPTH). The rats were 10 weeks old at pretest. The four groups consisted of a control (exposed to air only) and high test group with 20 males and females in each group. Of these 20, 10 of each sex were scheduled for sacrifice after the 90/91 day exposure period and the remaining 10 of each sex were scheduled for sacrifice following a recovery period of 28 days. During the 90/91 day exposure period, there were 65 or 66 exposures, 6 hours/day for 5 days per week.

The test material used was TPTH and was 96.2% pure. It was obtained from Hoechst AG and identified by Code HOE 029664 OF ZD97 0004. A certificate of analysis was cited.

The test atmospheres were generated as a dust into the exposure chambers by means of an RBG-1000 aerosol generator (Pales, Germany). The system was stated as being designed to achieve a mass median aerodynamic diameter of 3 um or less. No further description of this apparatus was provided in the sstudy report.

The test chamber was of a flow-past nose-only design (refer to diagram attached).

The test atmospheres were reported as being sampled at the area of the rats snout. The analytical concentration of the atmospheres was determined by collecting the sample atmospheres through filters which were subsequently extracted with methanol and analyzed by liquid chromatography. The gravimetric concentration was determined by assessing the weight changes in the filters. These analyses revealed the exposures as follows:

	Analytical	Gravimetric
Group 1 Control	-	0.072* ± 0.007
Group 2 (Low Dose)	0.014 ± 0.007	0.086 ± 0.048
Group 3 (Mid Dose)	0.338 ± 0.054	0.454 ± 0.116
Group 4 (High Dose)	1.997 ± 0.334	1.950 ± 0.347

*Mean variation in filter weight.

Gravimetric measurements of the atmospheric concentrations were made for each exposure (66 determinations), but analytical determinations were made on 13 exposure days, for each level. For the low-dose group, the analytical concentrations were an average of 18.0 ± 13.9 percent of the gravimetric concentrations. The mid-dose group was 77.9 ± 14.5 percent and the high-dose

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group was 97.1 ± 9.7 percent of the gravimetric concentration.

The particle size of the test atmospheres was determined using a Mercer 7 stage cascade impactor (Model 02-1300, In Tox Products, Albuquerque, New Mexico). In this model, the test atmosphere was impacted on stainless steel slips which were weighted before and after sampling. This analysis revealed that 100 percent of the particles were < 4.6 um in diameter and that 60.8 percent and 38.6 percent of the particles were < 1.06 um in diameter for the mid- and high-dose test groups, respectively. The particle size was determined 30 and 35 times for the mid- and high-dose test groups, respectively. Although the mass mean aerodynamic diameter and its standard deviation were not reported, the data indicated that > 25 percent of the particles were < the 1 um diameter recommended in the current inhalation toxicity guidelines. The particle size of the atmospheres for the low-dose group could not be determined because an insufficient amount of material was trapped on the cascade impactor.

Results:

1. Mortality - There were no deaths in either the control, low or mid-dose groups. There were a total of 13 deaths in the high-dose exposure group: 11 males and 2 females. Among the females, one died during week 10 and the other during the first recovery week. Among the males, two deaths occurred during weeks 2, 5, 9, and 11 and single deaths occurred during weeks 7, 13, and 14 (recovery period). The cause of death is discussed below.

   NOEL (for deaths) = 0.50 mg/m^3, LEL = 2.00 mg/m^3.

2. Clinical Signs - Compound-related signs were reported as being evident in the high-dose test group only. These included labored respiration and rales and transitory signs of "somnolence, apathy; hunched posture and ruffled fur." There were no specific signs reported in the rats preceding deaths.

   NOEL (for clinical signs) = 0.50 mg/m^3, LEL = 2.00 mg/m^3.

3. Ophthalmoscopic Examinations - No treatment-related effects were evident.

4. Body Weight and Food Consumption - No definite effects of exposure were evident in body weight gain. There was a transient decrease in food consumption during weeks 2 to 3 in the high dose group which is not regarded by TB-I as being of toxicological

significance.

NOEL (body weight) > 2.00 mg/m^3.

[Note for parts 5 (hematology) and 6 (clinical chemistry) below, blood samples were taken from the retro-orbital plexus while the rat was under light ether anesthesia during the day (6:30 a.m. to 9 "p.m.". The reference to "p.m." is likely a misprint since it should be "a.m." to minimize circadian variations). The rats were fasted for 18 hours prior to blood sampling.]

5. Hematology - The parameters investigated included erythrocyte count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin and concentration, platelet count, nucleated erythrocytes, Heinz bodies, total leukocyte count, differential leukocyte count, cell classification, red cell morphology, coagulation (thromboplastin time and partial thromboplastin time). Note: There were 20, 10, 10, and 9 males available for assessment at 13 weeks for the control, low-, mid- and high-dose groups, respectively, and 10 and 6 males for the controls and high dose groups available at 17 weeks.

   The study report maintains that the hematological data indicated "no change of toxicological significance at the end of the treatment." There were, however, reported some "slight" variations that were statistically significant in hematological parameters as follows.

   a. In females dosed with 2.0 mg/m^3 only:

      - erythrocyte count (-3.6%)
      - hemoglobin concentration (-4.1%)
      - hematocrit (-4%)
      - platelets (+13.3%)

   These findings are not considered toxicologically relevant by TB-I.

   b. leukocyte counts. The following table illustrates the data reported for leukocyte counts:

Group	Males	Females
Control	9.4	7.0
0.05 mg/m^3	7.3*(-22%)	6.3(-10%)
0.50 mg/m^3	8.7^{ns}(-7%)	4.8*(-31%)
2.00 mg/m^3	6.6*(-30%)	4.5*(-35%)

* statistically significant, $P < 0.05$.

The above table implies that WBCs are decreased at dose levels as low as 0.05 mg/m^3.

Differential WBC count among the male groups indicated <u>increases</u> in segmented neutrophils (+27 to 47%) and decreases in lymphocytes (to -9.5%).

After the recovery phase, the only parameter demonstrating a statistical difference was platelet count among males which was 13 percent decreased.

If the data from this study were taken alone, it would be easier to accept the study report conclusion that no changes of toxicological significance were indicated by hematology data. TPTH, however, is being investigated for its possible effects on the immune system of which the WBCs are a component. The early indications of this were the decreases in WBCs noted in sub-chronic rat and guinea pig studies (refer to the TPTH Registration Standard, Toxicology Branch Chapter). In this study, there are noted effects on the WBCs but the effect is most evident in the <u>females</u>. The males also indicate effects but there is not a clear dose response with the low and high doses being statistically decreased, but the mid-dose level decreased but not significantly lower. The rat 90 day subchronic feeding study also indicated decreases in WBCs (refer to J. Doherty review dated July 15, 1986 for EPA Reg. No.: 8340-17).

NOEL (for hematology): Equivocal. The decreases in WBC counts including a decrease in the males in the low dose group are acknowledged. Refer to study conclusions for assignment of NOEL for this study.

6. <u>Clinical Biochemistry</u> - The parameters investigated included: glucose, urea, creatinine, total bilirubin, total cholesterol, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, creatine kinase, alkaline phosphatase, glutamyl (gamma)-transferase, calcium, phosphorous, Na^+, K^+. Cl^-, albumin, total protein, globulin, albumin/globulin ratio, immunoglobulins G, G_1, G_{2a}, G_{2b}, G_{2c}, A, and M.

The testing laboratory concluded that the variations noted were "considered to have no biological relevance."

Inspection of the data showed that there were some statistical differences which indicated possible dose-related effects of TPTH exposure. These are discussed as follows:

Ca^{++}: The males were -2, -5, and - 10 percent decreased for the low-, mid- and high-dose test groups. The mid and high dose groups were statistically significant $p < 05$.

The females were statistically significant at all dose levels and were -5, -7, and -10 percent for the low-, mid-, and high-dose groups.

Phosphorous: - All male groups were 8 to 11 percent decreased but only the mid-dose group (-11%) was statistically significant.

There was a dose-related decrease among the females with the progression being -19, -22, and -28 percent. The phosphorous levels were still decreased (-18%) in the high-dose group after the recovery period.

Glucose: The female mid- (+17.2%) and high- (+19.4%) dose groups were elevated.

The findings regarding Ca++, phosphorous and glucose from this study are considered equivocal. In the absence of similar findings from oral studies (rat 90 subchronic and 2 year feeding study), TB-I notes the variations as above but decides not to conclude that they are related to TPTH exposure.

There were also some statistically significant differences noted in creatinine, total protein, gamma-glutamyl transferase, K^+, Cl^-, albumin, and globulin but these did not indicate a dose response and are not considered to be related to TPTH exposure by TB-I.

Special assessment of immunoglobulins - TPTH is considered as being immunotoxic and other studies have indicated decreases in various immunoglobulins. In this study, the several immunoglobulin classes were assessed using antisera with laser nephelometry, PEG enhanced. Using these methods, there were no decreases in immunoglobulins noted. The occasional increases included IgM (33 to 40%, for males in the mid and high dose groups and 28% for females in the mid dose group),

$Ig2_b$ (60 to 85% for males in the low and mid dose groups and IgG 30% for females in the high dose group). These changes are not considered by TB-I to be definitely compound-related.

Overall, the NOEL is > 2.0 mg/m^3. The effects noted are considered equivocal and there are no supporting pathological changes.

7. Organ Weights and Organ Weight Ratio - The organs weighed were brain, heart, lungs, liver, thymus, kidneys, adrenals, spleen, and testes. There were only three males available for organ weight analysis at 13 weeks and six at 17 weeks for the high dose group. The following statistically significant changes in organ weights were reported.

   a. Spleen - Males in the high-dose group were -25 percent decreased. Following recovery the spleen to body weight was elevated +23 percent and spleen to brain weight was elevated +21.7 percent. TB-I considers that at worst there is an indirect effect of TPTH on the spleen.

   b. Lungs - Males in the high-dose group were +32.5 percent increased for the lung to body weight and +20.3 percent for lung to brain and weight. Elevations were still evident after recovery with the lung to body weight ratio being +11 percent.

      Female lung weights at 13 weeks were, however, lower than controls (-12%) for the low- and mid-dose groups. The high dose female group was equivalent to the control. The study is not considered by TB-I to demonstrate an effect on female lung weight.

   c. Thymus - Mid-dose group females were decreased (-26%) absolute and -23 percent for the body weight ratio and -24 percent for the brain ratio.

   d. Brain - Males after the recovery period - The study report indicates that the brain weight for males in the recovery group (-3%).

e. Ovaries - The ovary weight to body weight was elevated +21 percent for the high dose group after the recovery period.

Of these organs, TB-I considers that the lungs and spleen of males are affected by TPTH exposure.

NOEL (for organ weight changes) = 0.5 mg/m^3, LEL = 2.0 mg/m^3.

8. Gross Pathology - The only remarkable finding reported at gross necropsy was the presence of "multiple red foci in the parenchyma" of the lung in the decedent rats.

9. Microscopic Findings - Microscopic assessment was performed on a comprehensive list of tissues/organs plus all gross lesions. All rats in the control and high-dose groups were examined for all tissues/organs. Only the brain, kidneys, liver, lungs, anterior and posterior nasal cavity, trachea, spleen, thymus, and microscopic abnormalities were examined for the low- and mid-dose groups.

The following lesions dose related lesions were reported in this study. They indicate that TPTH exposure results in inflammatory responses in the lung and respiratory passage. Refer to the Table attached (pages 11-12).

a. Nasal Cavity (Anterior) - Minimal to severe ulceration of the squamous epithelium in the ventral meatus (2 males and 4 females) in Group 4. Epithelial metaplasia in males (1 mid dose and 4 high dose males).

Nasal Cavity (Posterior) - Round cell infiltration (three high dose group males).

b. Trachea - Marked epithelial desquamation in one male, and severe subacute trachitis in one female, both in Group 4. (Not shown in Table on page 11-12).

c. Lungs - Three types of lesions were reported: fibrinous bronchopneumonia (8 males and 2 females in group 4, all of these 10 rats were spontaneous compound-related deaths); bronchitis (slight, in 6 rats total; all in Group 4); and multifocal hyperplasia of the bronchial epithelium (a single female in Group 4).

There was still some evidence of pathological changes

including the above lung lesions in the rats in the recovery group indicating that these lesions are slowly reversible (refer to second line under each lesion in Table on page 11-12). The recovery rats were reported as having epithelial metaplasia in the anterior nasal cavity (none in the controls but 5 in the males and 2 in the females) and alveolar macrophages in the lung (none in the controls but 2 in the males and 7 in the females).

The liver, kidney, and adrenal glands for the high dose group males were all reported to have six incidences of "congestion" at the 90 day sacrifice and the liver and kidney were reported to have three incidences each at the recovery sacrifice. None of the controls or low or mid dose rats and none of the females were reported as having this condition. This condition may have been related to the death of the rats since 4 of the 6 rats affected with this condition in the liver and adrenal glands and 3 of 6 rats affected with this condition in the lung had this condition. It would be more convincing if all of the rats with this condition were decedents to relate the condition with death moreover it was also present in the recovery rats. Because of the vague nature of this lesion, TB-I does not consider the presence of congestion to be a definite systemic response to TPTH.

In the spleen the mid and low dose groups for both males and females showed increased incidence of "incr. hemopoiesis". The high dose groups, however, were equivalent to the controls. The spleen (2 males affected) and thymus (6 males and 1 female affected) for the high dose group had "lymphoid depletion". This condition was also present in the recovery animals (spleens: 3 males, 1 female; thymus: 1 male and 1 female). None of the controls, low or mid dose rats were affected. These histopathological findings are not considered by TB-I to be a definite result of exposure to TPTH.

All other organs/tissues were reported as being within normal limits without indications of effects of TPTH exposure.

NOEL (for histopathology) = 0.5 mg/m^3, LEL = 2.0 mg/m^3, inflammatory lesions in the lung and nasal cavity.

Conclusion:

This study is CORE GUIDELINE. The NOEL is set at 0.34 mg/m^3. At the LEL (2.0 mg/m^3) there are deaths (especially among the males), due to effects of TPTH in the lung as indicated by labored breathing, rales, pathological indications of inflammatory response in the lung and nasal cavity and increase in lung weight (males).

Note: Possible but indefinite indications of immunotoxicity were implied by a spleen weight difference and an equivocal finding of decreased WBCs. Immunoglobulin counts were not definitely affected but some increases were noted. The study, however, is considered to be of limited usefulness for assessment of the potential immunotoxicity of TPTH because of the limited assessments made and because there was no proof of absorption of TPTH from the lung.

Table. Microscopic lesions in the nasal cavity (anterior or posterior) and lung showing indications of response to TPTH in the atmosphere.

	Males				Females			
	Con	Low	Mid	High	Con	Low	Mid	High
Nasal Cavity (n)* (anterior)	8	10	10	10	10	10	10	10
EPITHEL. METAPLASIA**	0	0	1	4	3	4	0	2
(Recovery)***	0	-	-	5	0	-	-	2
ULCERATION	0	0	0	2	0	0	0	4
(Recovery)	0	-	-	0	0	-	-	1
Round Cell Infilt.	0	0	0	0	0	0	0	1
Inflammation	0	5	4	0	1	1	3	0
Nasal Cavity (n) (posterior)	8	10	10	10	9	10	10	10
)UND CELL INFILT.	0	0	0	3	3	0	0	1
Lungs (n)	10	9	10	10	10	10	10	10
BRONCHITIS	0	0	0	5	0	0	0	1
(Recovery)			(none reported)					
BRONCHOPNEUMONIA	0	0	0	8	0	0	0	2
(Recovery)	0	0	0	2	0	0	0	1
ALVEOLAR EDEMA	0	0	0	2	0	0	0	0
(Recovery)	0	-	-	3	0	-	-	1
Vasc. Mineralization	1	1	0	0	1	0	1	4
(Recovery)	2	-	-	2	0	-	-	1

(Table continued on next page)

(Table continued on next page)

Fibrosis	0	0	0	0	0	0	0	2
Alveolar macrophages	1	1	2	0	1	0	2	1
(Recovery)	0	-	-	2	0	-	-	7
Interstit pneumonia	0	0	0	1	0	0	0	0
(Recovery)	0	-	-	0	1	-	-	2
Epithel. Hyperplasia	0	0	0	0	0	0	0	1

*n the number of rats assessed for the main group is presented in the first line, the number of rats assessed for the recovery group was usually 10 for the control but was at most 6 for the high dose group males and 8 for the females.

**Items in capitized letters are considered to be a response to exposure to TPTH.

***Data for the main study group, sacrificed after 90-92 days after the first exposure, are presented in the first line; the results of the rats in the recovery group are presented in the second line. If no line is presented for the recovery period, there were no lesion of this type reported or there were clearly not more in the test groups than in the controls.

- Tissue not evaluated.

TPTH

Page 18 is not included in this copy.

Pages _____ through _____ are not included in this copy.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

_____ Identity of product impurities.

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