

ORIGINAL

TSCA NON-CONFIDENTIAL BUSINESS INFORMATION

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8EHQ-06-16478	89130000232	1/9/13

COMMENTS: 8EFU

DOES NOT CONTAIN CBI

MR#350977



DuPont Haskell Global Centers
for Health and Environmental Sciences
1090 Elkton Road, P.O. Box 50
Newark, DE 19714-0050

January 8, 2013

Via Federal Express

Document Processing Center (Mail Code 7407M)
Room 6428
Attention: 8(e) Coordinator
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
1201 Constitution Ave., NW
Washington, DC 20004



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OPPT CBIC
2013 JAN -9 AM 10:32

Dear 8(e) Coordinator:

8EHQ-06-16436/8EHQ-06-16478
2,3,3,3-tetrafluoro-2-(heptafluoropropoxy)propionic acid, ammonium salt
CAS # 62037-80-3

This letter is to inform you of the preliminary results of a 2 year rat oral gavage study with the above referenced test substance. This test substance is subject to a Consent Order, P-08-509.

A 2-year oral gavage study was conducted in CrI:CD(SD) rats (80/sex/concentration) with the test substance at doses of 0, 0.1 (males only), 1, 50, and 500 (females only) mg/kg bw/day. The rats were evaluated for mortality, clinical signs, body weight and weight gain, food consumption, and food efficiency, and received an ophthalmology examination pretest and after 1 and 2 years of dosing. Ten rats/sex/dose were designated for evaluation of chronic toxicity. These rats were evaluated for clinical pathology at 3, 6, and 12 months, and for anatomic pathology (organ weights, gross and microscopic pathology) at the end of 12 months. The remaining rats (70 rats/sex/dose; main study rats) were dosed for up to 23 (females) or 24 (males) months. Females were sacrificed at week 100 due to poor overall survival, although survival was comparable among all dose groups. Clinical pathology (WBC differential counts) was evaluated at 12, 18, and 24 months in all surviving main study rats. All animals received a gross pathology evaluation at necropsy, and organ weights were collected in animals surviving to terminal sacrifice. Microscopic examination of tissues was conducted in animals that survived to scheduled sacrifice (12 month and end of study), and in all animals that died prior to scheduled sacrifice.

No test substance-related differences in survival or in clinical or ophthalmological signs were observed in any dose group. No adverse effects on overall body weight and nutritional parameters were observed in any dose group, although these parameters were transiently lower than control (statistically significant) in high-dose males (50 mg/kg/day) and females (500 mg/kg/day) over some weekly/biweekly intervals, particularly during the middle of the study. In 500 mg/kg/day females, the body weight over the first year of the study was statistically significantly lower than in control, although the difference was not statistically significant at the end of two years. Test substance-related, adverse or potentially adverse findings were observed in some clinical and anatomic pathology parameters in females at 500 mg/kg/day and in males at 50 mg/kg/day parameters, as discussed below.

Clinical pathology: The following statistically significant differences were considered adverse:

500 mg/kg/day (females only):

- ↓ red blood cell mass parameters (RBC, HGB, HCT, most time points), with ↑ MCV and reduced MCHC at the 12 month time point.
- ↑P (12 month), ↑ BUN (12 month), ↑A/G ratio (all time points), ↓globulin (all time points),

CONTAINS NO CBI

- urine: ↑urine volume and pH, ↓specific gravity (6, 12 month)

50 mg/kg/day:

- ↑ALP (male all time points), ↑ALT (male 12 month), ↑albumin (male all time points), ↑A/G ratio (male all time points)

Anatomic pathology: Increases in the following microscopic pathology findings were considered adverse:

500 mg/kg/day (females):

- Liver: adenoma, hypertrophy (also ↑ at one year), degeneration and necrosis; ↑ liver weight (at one and two year)
- Kidney: papillary necrosis and edema, chronic progressive nephropathy (also ↑ at one year), dilated tubules,
- Stomach: non-glandular mucosal hyperplasia
- Tongue: mucosal hyperplasia/inflammation

50 mg/kg/day:

- Liver: ↑ liver weight (males at one year only), hypertrophy, degeneration and necrosis (also ↑ in males at one year), basophilic foci; (males only except hypertrophy)
- In males, marginal increases were observed in the following:
 - Pancreas: acinar cell tumors; equivocal acinar cell hyperplasia (both sexes)
 - Testes: interstitial cell tumors and hyperplasia

All other statistically significant changes in clinical and anatomic pathology parameters were considered spurious and/or nonadverse based on absence of a dose response, the transient occurrence of the finding, the minimal nature or direction of the change, and/or the lack of correlative changes in related parameters. These included:

500 mg/kg/day (females only)

- ↑ Cl (6 month), ↑albumin (3 month), ↓bilirubin (all time points), ↓total protein (3 month), ↓ cholesterol (6 month), ↓APTT (12 month)
- Uterus: stromal polyps (not significant by Fisher's exact test and within historical control range)
- Lung: histiocytosis (within historical control range)
- Adrenal: benign pheochromocytoma (not significant by Fisher's exact test, within historical control range and not associated with correlative increase in hyperplasia)

50 mg/kg/day:

- ↓red blood cell mass parameters (RBC, HGB, HCT) at all time points in males; ↓RBC in females (12 month)
- ↓APTT (12 month; female))
- ↑ Ca (male 12 month), ↑P (male 3 month), ↑A/G ratio (female 3 and 6 month), ↓globulin (female 6 month)
- Urine: ↓urine volume (male 12 month) and pH (male 6 and 12 month)

1 mg/kg/day:

- ↓HGB (female 3 month), ↑ALP (male 12 month), ↑ BUN (male 12 month), ↑albumin (male 12 month), ↑A/G ratio (male all time points), ↑Cl (female 6 month)
- Urine: ↑urine volume (male 12 month) and pH (male 6 and 12 month; female 6 month)

0.1 mg/kg/day (males only):

- ↑P (3 month)
- Urine: ↓urine volume and ↓ pH (both 12 month)

Under the conditions of this study, the no-observed-adverse-effect level (NOAEL) was considered to be 1 mg/kg/day in male and female rats. Test substance-related neoplastic changes were observed at the high dose (500 mg/kg/day in females; 50 mg/kg/day in males) and included hepatocellular tumors in females and, in males, equivocal increases in pancreatic acinar cell tumors and testicular interstitial cell tumors. These tumor findings are typical of those previously reported in rats following exposure to other PPAR α agonists. Based on the high dose threshold for these tumor responses in this study, the lack of genotoxicity of the test material across a battery of *in vitro* and *in vivo* tests, and the known responses of the rat versus other species, including humans, to these PPAR α -associated tumor responses, these tumor findings are not considered relevant for human risk assessment.

This information is submitted in accordance with current guidance issued by EPA indicating EPA's interpretation of Section 8(e) of the Toxic Substances Control Act or, where it is not clear that reporting criteria have been met, it is submitted as a precautionary measure and because it is information in which EPA may have an interest.

Sincerely,

A handwritten signature in black ink, appearing to read 'S. Satheesh Anand', with a stylized flourish at the end.

S. Satheesh Anand, Ph.D., DABT
Senior Research Toxicologist

SSA/SAM: jhh
(302) 366-5314

FedEx Express **NEW Package**
US Airbill

FedEx
Tracking
Number

8759 3684 8285

RECIPIENT: PEEL HERE

1 From This portion can be removed for Recipient's records.

Date 11/8/13 FedEx
Tracking Number

875936848285

Sender's
Name

Phone

Company DUPONT / CRED / STINE HASKEL

Address 1090 ELTON RD

Dept./Floor/Suite/Room

City NEWARK

State

DE

ZIP

19711-3507

2 Your Internal Billing Reference

3 To

Recipient's
Name

Phone

Company

Address

We cannot deliver to P.O. boxes or P.O. ZIP codes.

Dept./Floor/Suite/Room

Address

Use this line for the HOLD location address or for continuation of your shipping address.

City

State

ZIP

HOLD Weekday

FedEx location address
REQUIRED NOT available for
FedEx First Overnight.



HOLD Saturday

FedEx location address
REQUIRED Available ONLY for
FedEx Priority Overnight and
FedEx 2Day to select locations.



0438872855



8759 3684 8285

0215

Recipient's Copy

4 Express Package Service

* To most locations.
NOTE: Service order has changed. Please select carefully.

Packages up to 150 lbs.
For packages over 150 lbs., use the new
FedEx Express Freight US Airbill.

Next Business Day

- ☐ **FedEx First Overnight**
Earliest next business morning delivery to select locations. Friday shipments will be delivered on Monday unless SATURDAY Delivery is selected.
- ☐ **FedEx Priority Overnight**
Next business morning.* Friday shipments will be delivered on Monday unless SATURDAY Delivery is selected.
- ☒ **FedEx Standard Overnight**
Next business afternoon.* Saturday Delivery NOT available.

2 or 3 Business Days

- ☐ **NEW FedEx 2Day A.M.**
Second business morning.* Saturday Delivery NOT available.
- ☐ **FedEx 2Day**
Second business afternoon.* Thursday shipments will be delivered on Monday unless SATURDAY Delivery is selected.
- ☐ **FedEx Express Saver**
Third business day.* Saturday Delivery NOT available.

5 Packaging

* Declared value limit \$500.

- ☐ FedEx Envelope* ☐ FedEx Pak* ☐ FedEx Box ☐ FedEx Tube ☐ Other

6 Special Handling and Delivery Signature Options

- ☐ **SATURDAY Delivery**
NOT available for FedEx Standard Overnight, FedEx 2Day A.M., or FedEx Express Saver.
- ☐ **No Signature Required**
Package may be left without obtaining a signature for delivery.
- ☐ **Direct Signature**
Someone at recipient's address may sign for delivery. **Fee applies.**
- ☐ **Indirect Signature**
If no one is available at recipient's address, someone at a neighboring address may sign for delivery. For residential deliveries only. **Fee applies.**

Does this shipment contain dangerous goods?

- One box must be checked.
- ☒ **No** ☐ **Yes** As per attached Shipper's Declaration. ☐ **Yes** Shipper's Declaration not required.
- ☐ **Dry Ice**
Dry Ice, 9 UN 1845 _____ x _____ kg
- ☐ **Cargo Aircraft Only**
- Dangerous goods (including dry ice) cannot be shipped in FedEx packaging or placed in a FedEx Express Drop Box.

7 Payment Bill to:

Enter FedEx Acct. No. or Credit Card No. below.

Obtain recip. Acct. No. ☐

☒ **Sender** Acct. No. in Section 1 will be billed. ☐ **Recipient** ☐ **Third Party** ☐ **Credit Card** ☐ **Cash/Check**

Total Packages _____ Total Weight _____ lbs. Credit Card Auth. _____

*Our liability is limited to \$100 unless you declare a higher value. See the current FedEx Service Guide for details.

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