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Room 6428
Attention: 8(e) Coordinator
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency, ICC Building
1201 Constitution Ave., NW
Washington, DC 20004

Dear 8(e) Coordinator:

1,1,1,2-Tetrafluoroethane (CAS Number 811-97-2)
8EHQ-10-17991

DuPont received information from a third party on the above-referenced substance. DuPont has reviewed the information for reportability under TSCA §8(e) and provides below a summary of the information that has been determined to meet EPA's TSCA §8(e) criteria for reporting. It is unknown whether the information reported below has been previously reported to EPA by any third party or is otherwise considered known to the Administrator under TSCA §8(e) guidance.

Test substance: 1,1,1,2-Tetrafluoroethane (CAS number 811-97-2) – also referred to as HFC-134a or Fluorocarbon 134a

- Pituitary Assessment of Rats during Inhalation Exposure

Five male and five female Wistar rats were exposed by whole body inhalation for 1 hour/day, 7 days/week, for 2 weeks to a nominal concentration of 100,000 ppm. The mean measured concentration was 99,800 ppm. The pituitary gonadotropin and prolactin secretion was monitored on day 1 and day 14, by performing a LHRH (Luteinizing Hormone Releasing Hormone) test. On day 10, the response of serum prolactin was measured using a TRH (Thyrotropin Releasing Hormone) test. At the end of the treatment period (24 hours after the last inhalation), animals were killed for autopsy and the pituitary glands were removed for hormone assay. The test group animals showed stupor and staggering gait during the exposure period. The symptoms were reversible after exposure. No deaths occurred during the study. Marked changes in the hormone content of the pituitary were noted both in male and female rats after 14 days of exposure. The pituitary content of LH and FSH (Follicle Stimulating Hormone) was significantly reduced and the pituitary prolactin content was significantly increased. The serum

concentrations of LH showed no changes on the last day of the study period (day 14). However, there was an increase in pituitary FSH responsiveness at the end of the study. The response of FSH to the LHRH test dose was nearly four fold in treated male rats and was doubled in the treated females. There was no change in serum prolactin after test injection of thyrotropin releasing hormone (TRH) on day 10 of the study.

- Pituitary-Gonadal Assessment of Rats during Fluorocarbon Inhalation Exposure

Ten male and ten female Sprague Dawley rats were exposed by whole body inhalation for 6 hour/day, 7 days/week, for 2 weeks to a nominal concentration of 50,000 ppm. The mean measured concentration was 47,900 ppm. On Day 14, exposure was reduced to 2.5 hours. The pituitary response was monitored on day 14, by performing a dynamic function (buserelin stimulation) test. On day 10, the response of serum prolactin was measured using a MIT (Mono-Iodo-Tryosine) test. Immediately after the last exposure, animals were killed for autopsy and the pituitary glands were removed for hormone assay. The tissue content of testosterone in the testis was also determined and, for comparison, the related content of estradiol and progesterone in the ovaries. During necropsy the animals were examined for macroscopically visible abnormalities, the main organs weighed and the organ to body weight ratios calculated. Behavior and general health condition of the animals remained unaffected by exposure to the test substance. No deaths occurred during the study. In male rats, the prolactin response was reduced by 30% in the treated animals on day 10. On day 14, the stimulation of serum LH (Luteinizing Hormone) and FSH (Follicle Stimulating Hormone) showed no significant changes, although there was a slightly reduced response of LH after the buserelin test injection. There were no changes in pituitary LH, FSH and PRL (Prolactin) content. The testicular testosterone content was reduced by almost 50%. After the last exposure of the test substance, basal serum testosterone was slightly increased and the testosterone response after buserelin was markedly impaired. In female rats, there was no change in serum prolactin after the test injection of MIT on day 10. Marked changes were found in the pituitary hormone content of FSH and PRL after 14 days of inhaling the test substance. Pituitary FSH declined after treatment and pituitary prolactin content was slightly reduced. LH content was unaffected. The ovarian estradiol content increased slightly (not significant) while the progesterone content showed no changes.

- *In vitro* Studies on the Effects of Fluorocarbon 134a and Certain Potential Metabolites of Fluorocarbon 134a in Test Cultures

The effects of Fluorocarbon 134a and its metabolites TFA (Trifluoroacetic acid), TFAA (Trifluoroacetaldehyde) and TFEth (Trifluoroethanol) on testicular cell function were studied in cultures of Leydig cells (LCC) and Sertoli cells (SCC) and Sertoli-germ cell co-cultures (S-GCC) derived from Sprague-Dawley rats. Vapor concentrations of 750,000 ppm HFC-134a (3,130,000 mg/m3), either exposed directly or by 24-hour pre-treatment, were found to be non-cytotoxic to LCC, SCC and S-GCC. In addition, HFC-134a had no biologically significant effects on basal or hormone stimulated testosterone production in LCC, no effects on the morphology or on basal or dibutyryl cyclic AMP-stimulated (dbcAMP-stimulated) lactate and pyruvate production in SCC, and no effects on the morphology, cell loss, lactate dehydrogenase-X (LDHX) leakage and lactate and pyruvate production in SCC or on testosterone production in S-GCC. Trifluoroacetaldehyde (TFAA) was found not to be cytotoxic to LCC concentration of 50 mmol/l. At concentrations above 5 mmol/l, TFAA caused a dose-dependent reduction in basal

testosterone production and, at concentrations > 0.5 mmol/l, caused a dose-dependent reduction in hormonally-stimulated testosterone production in LCC. TFAA was found to be cytotoxic to SCC at concentrations > 0.75 mmol/l. Exposure of SCC to 0.75 mmol/l TFAA for 24 hours led to marked vacuolation and condensed, darkly staining nuclei. Concentrations of TFA > 0.05/0.1 mmol/l caused dose-dependent decreases in basal and dbcAMP-stimulated lactate and pyruvate production in SCCs. TFAA was also found to be cytotoxic to S-GCC at concentrations > 0.75 mmol/l. Exposure of S-GCC to 0.75 mmol/l TFAA for 24 hours resulted in the loss of most germ cells and to marked vacuolation of the Sertoli cells. Concentrations of TFAA > 0.01 mmol/l caused a dose-dependent increase in LDHX leakage from S-GCC. Concentrations of 0.75 mmol/l TFAA caused marginal decreases in basal and dbcAMP stimulated lactate production by S-GCC but had no significant effect on pyruvate levels. Trifluoroacetic acid (TFA) was found to be cytotoxic to LCC at concentrations above 20 mmol/l. At concentrations > 5 mmol/l, TFAA, at non-cytotoxic concentrations, had no effect on basal testosterone production and equivocal effects on hormonally-stimulated testosterone production in LCC. TFA was found to be cytotoxic to SCC at concentrations > 15 mmol/l. Exposure of SCC to 15 mmol/l TFA for 24 hours had no effect on their morphology. Concentrations > 15 mmol/l TFA had no significant effects on basal lactate and both basal and dbcAMP-stimulated pyruvate production in SCCs but did cause a dose-dependent enhancement of dbcAMP-stimulated lactate production. TFA was also found to be cytotoxic to S-GCC at concentrations > 15 mmol/l. Exposure of S-GCC to concentrations of TFA up to 15 mmol/l for 24 hours had no effect on their morphology, had no effect on LDHX leakage and no significant effects on basal and dbcAMP-stimulated lactate and pyruvate production. TFEth was found not to be cytotoxic to LCC at concentrations up to 100 mmol/l. At a concentration of 50 mmol/l, TFEth had no effect on basal testosterone production and equivocal effects on hormonally-stimulated testosterone production in LCC. TFEth was found to be cytotoxic to SCC at concentrations > 20 mmol/l. Exposure of SCC to 20 mmol/l TFEth for 24 hours had no significant effects on both basal and dbcAMP-stimulated lactate or pyruvate production. TFEth was found not to be cytotoxic to S-GCC at concentrations up to 50 mmol/l. Exposure of S-GCC to 20 mmol/l TFEth for 24 hours had no effect on their morphology or cell loss, no effect on LDHX leakage and no significant effects on basal and dbcAMP-stimulated lactate and pyruvate production.

- <u>Neurological Assessment of Rats During Inhalation Exposure</u>

Alpk:ApfSD Wistar-derived rats (5/sex/group) were exposed to HFC-134a at target concentrations of 0, 150,000 or 200,000 ppm (0, 625,000, 834,000 mg/m3) for 1 to 2 hours. Further groups of 5 male or female rats were pre-treated with ethanol and were subsequently exposed to air or 150,000 ppm (1.0 g ethanol/kgbw) or 200,000 ppm (5.0 g ethanol/kgbw) HFC-134a for 1 to 2 hours. A neurological examination was conducted on each rat before treatment and a quantitative assessment of sensory perception (tail flick test) was performed on each animal approximately 1 hour after the initiation of exposure. No evidence of neurological dysfunction was observed in any of the treated groups, with or without pre-treatment with ethanol. Female rats exposed to 200,000 ppm HFC-134a showed a small but statistically significant increase in tail flick time. This effect was not seen in male rats exposed to HFC-134a, with or without ethanol pre-treatment, nor in pre-treated female rats. The study showed that there

were no significant additive or synergistic effects between ethanol and HFC-134a on the neurological system in the rat.

Sincerely,

A. Michael Kaplan (dwd)

A. Michael Kaplan, Ph.D.
Director - Regulatory Affairs

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