

8EHQ-0296-13573

The Goodyear Tire & Rubber Company

Akron, Ohio 44316-0001

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February 5, 1996



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Attn: Section 8(e) Coordinator
Office of Pollution Prevention and Toxics (OPPT)
U S Environmental Protection Agency
401 M Street S W
Washington, DC 20460



88960000053

Dear Ladies/Gentlemen:

Contains No CBI

Subject: **TSCA Section 8(e) Notice**

This submittal does not contain Confidential Business Information.

The Goodyear Tire & Rubber Company is currently sponsoring a study at Research Triangle Institute (RTI) in Research Triangle Park, NC to examine the reproductive toxic potential of a rubber antioxidant in laboratory rats. The identity of the material is as follows:

Chemical Abstract Name: 1,4 Benzendiamine, N,N'-mixed Ph and Tolyl derivs

Chemical Abstract Number: 68953-84-4*

Preliminary results from the pilot phase of this study were recently communicated to Goodyear by the study director, Dr R Tyl. These early findings indicated a toxic effect at a high dose level that may represent a substantial risk. Consequently, under the requirements of TSCA Section 8(e), The Goodyear Tire & Rubber Company is providing EPA with the attached copy of RTI's report (dated January 25, 1996).

In this pilot study, the test chemical was administered in the diet to male and female rats for two weeks prior to mating, during a mating period up to two weeks, and throughout gestation. Pregnant females were allowed to deliver at term. Adult males and females in the parent generation (F₀) and their offsprings (F₁) were monitored for mortality and other signs of adverse effects.

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The results indicated that the high dose group of pregnant females experienced a high incidence of mortality at parturition (six of eight). In addition, parturition was delayed by ~two days at this dose level. This group also delivered a low number of litters with live pups (three of eight). Viability (to Day four postpartum) of pups born alive in this dose group was also low (three of six).

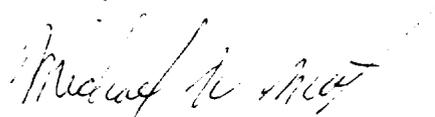
The mid-dose group displayed one possible compound-related finding. One of nine pregnant females delivered a large nonviable litter (15 pups).

No other findings attributable to the test material were reported. Because these findings are from the pilot phase which utilizes limited numbers of animals, it is not possible at this time to assign any significance to the results. A definitive two-generation reproduction study is scheduled to begin during the 2nd quarter of this year. Upon completion of the definitive study, final reports will be forwarded to the EPA.

My address and telephone number are as follows:

The Goodyear Tire & Rubber Company
Department 100D
1144 E Market Street
Akron, Ohio 44316-0001
Telephone Number: (216) 796-2362

Sincerely,



Michael W Smith

s6m2a1/wp61/rms

Section Manager, Chemical Information
Systems & Regulatory Affairs

Attachment

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Chemistry and Life Sciences
Center for Life Sciences and Toxicology

January 25, 1996

Dr. A. Philip Leber
Project Coordinator
Toxicology and Regulatory Compliance
The Goodyear Tire and Rubber Company
142 Goodyear Blvd.
Akron, Ohio 44305

RE: 65C-6429-200

Dear Dr. Leber:

We are currently performing the study entitled "Range-Finding Study for the Two-Generation Reproductive Toxicity Evaluation of Wingstay 100 Administered in the Feed to CD® (Sprague-Dawley) Rats" (RTI-548). As you recall, the study design included 10 rats/sex/group (10 weeks old at the start of exposure), designed the F0 generation, exposed to 0, 120, 1900 or 5700 ppm Wingstay 100 (CAS No: 68753-84-4) in the diet ad libitum for a two-week prebreed exposure period and a two-week mating period (F0 males will be necropsied at the end of the mating period). The date of evidence of mating will be designated gestational day (gd) 0. F0 females will continue exposure through the three-week gestation period and three-week lactation period. The date of delivery will be designated postnatal day (pnd) 0. Offspring, designated the F1 generation, will be culled to eight pups/litter (with as even a sex ratio as possible) on pnd 4 and will be weaned on pnd 21. At weaning, F0 dams will be sacrificed and 10 weanling pups/sex/group (from the maximal numbers of available litters) will be randomly selected for a two-week postwean exposure period (at the same dietary dose as their parents) and then sacrificed. Parental and offspring body weights, feed consumption and clinical observations will be documented throughout the study and a complete necropsy will be performed, including weights of a number of selected organs, on F0 parental animals and F1 selected postwean offspring.

At this point in time in the study, all mating, gestation and parturition (delivery) phases are completed, F0 males have been sacrificed at the end of the mating period, and we have just completed culling live litters on pnd 4. Although the study is not yet completed, and we have not entered, summarized or analyzed all of the data generated to date, I wanted to inform you of adverse reproductive findings at 5700 ppm (and possibly at 1900 ppm) summarized in the attached draft table.

There were no effects of treatment on mating or fertility indices (for either males or females). Of the 10 females paired at 5700 ppm, eight were pregnant. Of the eight pregnant, six (75.0%) died during delivery (one, no. 12, after delivering one live pup with 12 dead fetuses in utero). All of these females either delivered dead pups or had dead fetuses retained in utero. Of the three (out of eight, 37.5%) with live litters on pnd 0, one dam (no. 12, see above) died, one (no. 2) delivered four live pups, two of which are still alive as of pnd 4, and one delivered one live pup (which died prior to pnd 4) and 11 dead pups; *i.e.*, only one dam with a live litter is currently alive at this dose.

At 1900 ppm, there were no maternal deaths, but one dam (no. 18) delivered 15 dead pups. Since this observation is unusual in control CD® rats and is consistent with effects observed at 5700 ppm, we are tentatively assuming it is also treatment related.

Additional information (not yet collated) includes the following:

- (1) Nonpregnant females at 5700 and 1900 ppm (and at 120 and 0 ppm) appear normal and healthy.
- (2) Pregnant females at 5700 ppm appeared normal and healthy until just before expected parturition, when their eyes became very light and they became hypoactive. Parturition appeared delayed 1-2 days (we usually see littering beginning on gd 21, with most litters born on gd 22), with most deliveries occurring on gd 24. There was no evidence of external bleeding and deliveries were not apparently accompanied by excessive bleeding. The dead pups (and those fetuses retained in utero) appear full size and full term, with no apparent external or visceral malformations in the dead pups.
- (3) At my request, the Animal Research Veterinarian, Dr. D. B. Feldman, DVM, ACLAM examined the dams at 5700 ppm during their deliveries. He and I concur that the symptoms appear to be consistent with a maternal anemia.

The study is continuing with one dam with a surviving litter (dam no. 2), two apparent nonpregnant females, and one female (no. 58) who lost her litter at 5700 ppm, eight dams with live litters, one apparently nonpregnant female and one dam who delivered a dead litter (no. 19) at 1900 ppm, seven dams with live litters and three nonpregnant females at 120 ppm, eight dams with live litters, one dam who lost her litter (no. 80, with only one pup to begin with) after pnd 4, and one apparently nonpregnant female at 0 ppm.

Please note that final verification of actual pregnancy status of all females must wait until the dams are sacrificed on pnd 21 and the uteri are examined for implantation/resorption sites.

I will keep you informed of the study's progress. If you have any questions, do not hesitate to call me.

Sincerely,



Rochelle W. Tyl, Ph.D., DABT
Study Director/Research Director
Center for Life Sciences and Toxicology

RWT:ng
Enclosure

cc: Ms. C. B. Myers
Mr. D. L. Brodish, QA
Dr. D. B. Feldman, ARF
Ms. S. M. Taulbee, QA (lo)
Ms. C. S. Parker, Contracts (lo)

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Summary of the F₀ Reproductive Indexes

	Wingstay 100 (ppm in feed)			
	0	120	1900	5700
No. Animals Started on Study				
Males	10	10	10	10
Females	10	10	10	10
No. Females Paired	10	10	10	10
No. of Females that Mated	10	9	10	9
Mating Index (no. females that mated/no. females paired)	100.0	90.0	100.0	90.0
No. of Pregnant Females	9	7	9	8
Fertility Index (no. pregnant females/no. females that mated)	90.0	77.8	90.0	88.9
No. Females with Live Litters (pnd 0)	9	7	8 ^a	3 ^b
Gestational Index (no. females with live litters (pnd 0)/no. females pregnant)	100.0	100.0	88.9	37.5
No. (%) Pregnant Females that Died during Delivery	0 (0.0)	0 (0.0)	0 (0.0)	6 ^c (75.0)
No. Males Paired	10	10	10	10
No. Males that Mated	10	9	10	9
Mating Index (no. males that mated/no. males paired)	100.0	90.0	100.0	90.0
No. Males Siring Litters	9	7	9	8
Fertility Index (no. males siring litters/no. males that mated)	90.0	77.8	90.0	88.9

^aDam 18 delivered 15 dead pups.

^bDam 2 delivered 4 live pups, 2 of which were still alive on pnd 4. Dam 12 delivered 1 live pup prior to dying. Dam 58 delivered 11 dead pups and 1 live pup which died prior to pnd 4.

^cDam 12 delivered 1 live pup prior to dying and had 12 dead fetuses in utero. Dam 38 delivered 12 dead pups prior to dying. Dam 42 delivered 2 dead pups prior to dying and had 13 dead fetuses in utero. Dams 56 and 68 died and each had 13 dead fetuses in utero. Dam 74 died that had 14 dead fetuses in utero.