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11908

FYI - 1198 - 1344

October 26, 1998

Document Control Officer
Information Management Division/OPPT
U.S. Environmental Protection Agency
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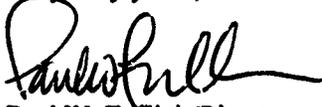
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98 NOV -2 PM 1:17

Dear Sirs:

Regarding the enclosed letters for WIN 9989 (aminoguanidine bicarbonate) and WTN 59250 (alkoxylated diamine), a former Sanofi Occupational Toxicologist submitted their substance toxicity data under "8(c) Allegations." I have reviewed this matter recently and concluded that this documentation should have been appropriately classified as FYI submissions rather than 8(c) Allegations.

Thank you in advance for your assistance in this matter and reclassifying these documents as FYI submissions.

Very truly yours,



Paul W. Frilici, Director
Environment, Health and Safety



FYI-98-001344

PWF/ac

Enclosure

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84990000005

Sanofi Pharmaceuticals Inc.

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OCT-23-1998 FRI 08:06 AM

FAX NO.

P. 01

8c

Sterling Winthrop Inc.
1250 South Collegedale Road
P.O. Box 7000
Collegedale, PA 19426-0900

PAUL FRALLICI
212-551-4924



93 JUL 26 PM 2:47

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Attn: 8(c) Allegations/
Document Processing Center (TS-790)
Room L-100, Office of Toxic Substances
Environmental Protection Agency
401 M St., Washington, DC 20460

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ORIGINAL

Dear Sir or Madam:

I have attached documentation summarizing the genetic toxicity data for Aminoguanidine bicarbonate, which is also known by the synonym Aminoguanidine hydrogen carbonate. The internal Sterling Winthrop registry number for purified Aminoguanidine bicarbonate is WIN 9989 and is referred to as such in the attached documentation. I can be contacted at (610) 983-6535 if further information is required.

Yours Sincerely

Leslie M.G. Wilson, Ph.D.
Occupational Toxicologist,
Health Safety and
Environmental Affairs.



82940000001

93 JUL 18 PM 1:26

Sterling Winthrop Inc.
1279 South Collegeville Road
P.O. Box 7000
Collegeville, PA 19326-0000



Aminoguanidine Bicarbonate

The purpose of this memo is to provide information on the genetic toxicological effects observed for WIN 9989 (aminoguanidine bicarbonate).

WIN 9989 - Genetic toxicity data.

In the Chromosome Aberration Assay, Chinese hamster ovary (CHO) cell cultures were exposed for five hours to 1250, 3500 and 5000 μg WIN 9989 base/ml, in the presence and absence of an exogenous rat liver (S9) metabolic activation system. (WIN 9989 is composed of 54.4% (w/w) unsolvated base; 183.3 mg WIN 9989 = 100 mg base.) Following 18 hours of post-treatment incubation, cells in metaphase were harvested and then microscopically evaluated for the presence of chromosome aberrations.

The results indicated that WIN 9989 in the absence of S9 induced a statistically significant trend in the proportion of cells with chromosome aberrations. A response of 9.55% aberrant cells was observed at the highest concentration tested, 5000 μg base/ml (-S9). The no-observed-effect-level (NOEL) was between 3500 - 5000 μg base/ml (-S9).

It is noteworthy to point out that although statistically significant, a level of 9.55% aberrant cells represents a weakly positive response. A contributing reason for judging the assay positive was at this concentration nearly 50% of the aberrant cells contained at least one complex aberration, a classification generally indicative of significant chromosome damage.

In the presence of S9, WIN 9989 was negative for inducing chromosome aberrations.

In the Ames Mutation Assay, WIN 9989 was negative for inducing revertant colonies in Salmonella strains TA98, TA100, TA1535, TA1537, TA1538, and E. coli strain WP2 *uvrA*. A concentration range between 100 - 5000 μg WIN 9989 base/plate was tested, with and without S9 activation. Despite the negative conclusion, the Ames data revealed the presence of pin-dot mutant colonies in several of the strains, with and without S9. Even though the pin-dot colonies were not consistently observed in repeat experiments, the decision was made to provide verification of the negative response by repeating the entire assay at a different contract facility.

Sterling Winthrop Inc.
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8c

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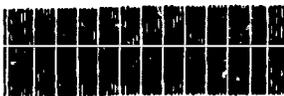
ORIGINAL

Dear Sir or Madam:

I have attached documentation summarizing preliminary developmental toxicity data for purified Alkoxylated diamine (CAS #: 11111-34-5) which is also known by the synonyms Tetronic 908; Poloxamine 908; T-908. Unpurified substance is purchased by Sterling Winthrop from BASF Corporation Chemicals Division, and purified by Sterling Winthrop for use in pharmaceutical research. The internal Sterling Winthrop registry number for purified Alkoxylated diamine is WIN 59250 and is referred to as such in the attached documentation. Study reports are not available as much of the data from the studies have not been critically evaluated and analyzed. If required, final reports on these studies can be forwarded to you when available.

Yours Sincerely

Leslie M.G. Wilson, Ph.D.
Occupational Toxicologist,
Health Safety and
Environmental Affairs.



8294888882

Sterling Winthrop Inc.
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Summary of Preliminary Developmental Toxicity Data for Purified Poloxamine 908.

The results presented below summarize the preliminary findings of exploratory subcutaneous teratogenicity studies in rats and rabbits with WIN 59250 (purified poloxamine 908). Examination of fetuses from these studies for skeletal abnormalities is in progress.

Exploratory Teratogenicity Study in Rats

WIN 59250 (3.5% aqueous solution) was administered to a group of 10 inseminated Sprague-Dawley rats by subcutaneous injection daily on days 6 through 17 of pregnancy at dosages of 35 and 105 mg/kg/day (1.0 and 3.0 ml/kg/day, respectively). A separate group of control rats was injected with saline using the same dosing regimen at a dosage of 3.0 ml/kg/day. Animals were terminated on day 20 of pregnancy and fetuses were examined for external and internal soft tissue abnormalities.

Cleft palate was observed in 2 of 109 fetuses (2.0%) from 2 of 9 litters (22%) in the 105 mg/kg/day WIN 59250 group. A significant reduction in live fetal weight was also observed for this group. Minimal, if any, maternal toxicity was observed for this group. Cleft palate was not observed in fetuses from the 35 mg/kg/day WIN 59250 group and there was no effect on live fetal weight. Cleft palate was also not observed in fetuses from the saline control group.

It should be noted that cleft palate is a very rare spontaneous developmental abnormality in this species. However, this abnormality can be induced in this species by a variety of chemicals as well as stress (i.e., maternal toxicity).

These results indicate that WIN 59250 is responsible for the induction of cleft palate in this species. The NOEL for this developmental abnormality is 35 mg/kg/day (1.0 ml/kg/day).

Exploratory Teratogenicity Study in Rabbits

WIN 59250 (3.5% aqueous solution) was administered to a group of 6 inseminated New Zealand White rabbits by subcutaneous injection daily on days 6 through 18 of pregnancy at a dosage of 105 mg/kg/day (3.0 ml/kg/day). A separate group of control rabbits was injected with saline using the same dosing regimen at a dosage of 3.0 ml/kg/day. Animals were terminated on day 29 of pregnancy and fetuses were examined for external and internal soft tissue abnormalities.

Treatment of pregnant rabbits with 105 mg/kg/day WIN 59250 resulted in abortions in seven out of eight animals. Abortions occurred on days 12, 18, 19, 20, 21 or 23 of pregnancy. Only one of eight rabbits in the saline control group aborted. Minimal, if any, maternal toxicity was observed in the WIN 59250-treated animals. Necropsy results of those animals terminated on day 29 of pregnancy revealed no fetal abnormalities (external and visceral evaluation) but an increased incidence of resorptions in the animals treated with WIN 59250 which did not abort.

These data indicate that WIN 59250 is capable of terminating pregnancy in the rabbit at a dosage of 105 mg/kg/day. A NOEL for this effect has not been established.

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