

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

POTASSIUM DIMETHYLDITHIOCARBAMATE

Chemical Code # 001934, Tolerance # 52063

Original date: January 16, 2002, revised June 14, 2002 and August 14, 2002

I. DATA GAP STATUS

Chronic toxicity, rat:	Data gap, no study submitted.
Subchronic, rat:	No data gap, no adverse effect
Chronic toxicity, dog:	Data gap, no study submitted
Oncogenicity, rat:	Data gap, no study submitted.
Oncogenicity, mouse:	Data gap, no study submitted.
Reproduction, rat:	Data gap, no study submitted.
Teratology, rat:	No data gap, no adverse effect
Teratology, rabbit:	No data gap, possible adverse effect
Gene mutation:	No data gap, possible adverse effect.
Chromosome effects:	Data gap, inadequate study, no adverse effect indicated.
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	Not required at this time

Toxicology one-liners are attached.

All record numbers through 136929 were examined.

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

File name: T020814

Original: Kishiyama and Gee, 1/16/02, revised 6/14/02 and August 14, 2002.

The sodium (CC 548) and the potassium (CC 1934) salts of dimethyldithiocarbamate are grouped by US EPA (See the "Rainbow Report" of 1998.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

CHRONIC TOXICITY, RAT

No study submitted.

Subchronic:

** 152 - 031 130890 Siglin, J. C. "91-Day Dermal Toxicity Study in Rats with Busan 85". (Springborn Life Sciences, Inc., SLS Study No. 3138.15, August 12, 1988.) Busan 85 [50% potassium dimethyldithiocarbamate formulation] was administered dermally at doses of 0 (water), 75, 350 or 750 mg/kg/day, 6 hours/day, five days/week for 13 weeks, to 10 Sprague-Dawley rats/sex/group. Body weight and food consumption were reduced significantly for high-dose males, but only slightly for high-dose females. Erythrocyte counts were decreased and correlated with the increased incidence of splenic hemosiderosis for the high-dose group. The skin at the site of application was irritated for mid and high-dose groups with increases in the incidences of erythema, desquamation, eschar and discoloration. Microscopic examination confirmed acanthosis, epidermal exudate and ulcers. Dermal NOEL = 75 mg/kg/day. Systemic NOEL = 350 mg/kg/day (body weight, hematology). Evaluated as unacceptable, possibly upgradeable with verification of the preparation of the dosing material and doses of the active ingredient used. (Kishiyama and Gee, 7/19/01). Record 186644 (see below) in 52063 - 006 upgrades the study to ACCEPTABLE status. No worksheet. (Gee, 8/14/02).

52063 - 001 136923 Duplicate of 152 - 031 but missing pages 90 - 120.

52063 - 006 186644 Supplement to record 130890, 91-day rat dermal study. The record contains a letter from J. C. Siglin, Springborn Laboratories, dated April 9, 2002, confirming that the active ingredient was potassium dimethyldithiocarbamate. The letter further describes how the dosing material was prepared, using a test article of 50% active ingredient. The Busan 85 was diluted to give 300 mg/ml w/v, 30%, without adjusting for actual content of the potassium dimethyldithiocarbamate. Therefore, actual doses of the ai need to be adjusted for dose preparation when determining a NOEL/LOEL for the study. This explanation upgrades record 130890 to acceptable status. No worksheet. (Gee, 8/14/02).

CHRONIC TOXICITY, DOG

No study submitted.

ONCOGENICITY, RAT

No study submitted.

ONCOGENICITY, MOUSE

No study submitted.

REPRODUCTION, RAT

No study submitted.

TERATOLOGY, RAT

** 52063 - 003 136925 Rodwell, D. E. "Teratology Study in Rats with Busan 85". (Springborn Life Sciences, Inc., SLS Study No. 3138.17, August 31, 1988.) Busan 85 (lot 7-0726, 50% a.i., 50% water) was given at doses of Busan 85 of 0, 0, 25, 150 or 400 mg/kg/day via gavage during gestation days 6 through 15 to 28 mated female Sprague-Dawley rats/group. The dosing material was not corrected for chemical purity, therefore the doses of potassium dimethyldithiocarbamate presumably would be approximately 50% of the nominal doses. Clinical signs of treatment were mostly confined to the mid and high dose groups, with dark material around the nose and mouth, rough coat, salivation being increased, among others. Dose-related lower body weight and food consumption were seen in the mid and high dose groups, especially days 6 - 9. Maternal NOEL = 25 mg/kg/day (clinical observations including salivation and dark material around mouth at 150 mg/kg, lower body weight at 400 mg/kg). Fetal effect of reduced weight was noted for the high dose group, although not statistically significant (3.3 g versus 3.7 g). Developmental NOEL = 150 mg/kg/day. There was no treatment-related increase in malformations/variations. No adverse effect. ACCEPTABLE. (Kishiyama and Gee, 1/10/02).

50282 - 14 074568: Same study as 052063-002 136925.

TERATOLOGY, RABBIT

** **52063 - 002 136924** Rodwell, D. E. "Teratology Study in Rabbits with Busan 85". (Springborn Life Sciences, Inc., SLS Study No. 3138.19, September 20, 1988.) Busan 85 (lot 7-0726, 50% a.i., 50% water) was given by gavage at doses of 0, 0, 25, 75 or 150 mg/kg/day during gestation days 6 through 18 to 20 artificially inseminated New Zealand White female rabbits/group. The dosing material was not adjusted for chemical purity, therefore, the actual doses of potassium dimethyldithiocarbamate were approximately 50% of the Busan 85 dose. One and two does died at 75 and 150 mg/kg/day, respectively; one and two does aborted at these same doses. These were considered to be related to treatment. Reduced bodyweight gain or weight loss were dose-related for mid and high dose groups. Live litter size was reduced for mid-dose (3.5) and the high dose (0.5**) groups compared with the two control groups (4.9 and 4.6). This was related to the increase in post-implantation loss. Early resorptions were increased, the means being 2.0** and 3.8** at the mid and high doses versus 0.4 and 1.7 for the two control groups. Although mean fetal weight was lower at the mid (41.1 g) and high (37.9 g) doses compared with controls (46.5 g and 47.6 g), the values were not statistically significant. The historical control data indicated a mean fetal weight of 41.6 g. The litter incidence of several malformations, especially skeletal, increased at 75 mg/kg/day (4* litters versus 0 and 3 in the control litters for *total* skeletal malformations). At the high dose, only 4 fetuses were evaluated and no meaningful data were collected. Skeletal variations were also increased in incidence in litters. These effects were seen in the presence of maternal toxicity (abortion, death, lower weight gain, post-implantation loss) and may be related to the maternal effects. Maternal and Developmental NOEL = 25mg/kg/day. Possible adverse effects. (early resorptions, total litter loss, increase in skeletal malformations/variations at 75 mg/kg with no preponderance of any specific finding). ACCEPTABLE (Kishiyama and Gee, 1/11/02).

50282-14 074567. Same study as 052063-002 136924.

GENE MUTATION

**** 52063 - 004, 007 136926, 186858** Young, R. R. "Mutagenicity Test on Busan 85 Lot Number 7-2020 in the CHO/HGPRT Forward Mutation Assay". (Hazleton Laboratories America, HLA Study No.: 10281-0-435, September 16, 1988.) Busan 85 (lot 7-2020, purity not given) was tested at concentrations ranging from 0.1 to 30 µg/ml without metabolic activation and from 1 to 25 µg/ml with rat liver metabolic activation for induction of forward mutations at the HGPRT locus in Chinese hamster ovary cells. Data were reported from two trials with activation and three trials without activation. At each concentration, there were duplicate cultures for mutation induction and three cultures for cytotoxicity. Exposure was for 4 hours. After 7 days for expression, each culture was plated in dishes for mutation frequency, for a total of 12 dishes, with 6-thioguanine for selection and in three dishes for cloning efficiency. Mutant frequency was increased above the normal background level with Busan 85 only at toxic concentrations, both with and without metabolic activation. Evaluated as unacceptable, upgradeable with purity of the test article. (Kishiyama and Gee, 1/9/02). Purity of lot 7-2020 was 52.2%. Additional information upgraded the study to ACCEPTABLE status. No new worksheet. (Gee, 6/13/02)

**** 52063-004, 007 136929, 186859** Jagannath, D. R. "Mutagenicity Test on Busan 85 in the Ames *Salmonella*/Microsome Reverse Mutation Assay". (Hazleton Laboratories America, Inc., Laboratory Project ID HLA Study No.: 9970-0-401, October 30, 1987.) Busan 85 (lot 7-0726, 50% a.i.) was evaluated for mutagenic activity at concentrations ranging from 0.01 to 5.0 µl/plate using *Salmonella typhimurium* strains TA 98, TA100, TA1535, TA1537 and TA1538. There were triplicate plates per concentration with and without rat liver activation. The assay was repeated with strains TA100 and TA1535. The author states that there were an increased number of revertants with *Salmonella* strains TA 100 and TA1535 with and without S9 Mix. The repeat trial confirmed results of the initial trial. An independent evaluation could not be conducted because all the pages containing data were not included (pages 21 onward). Evaluated as unacceptable. Upgradeable with submission of missing pages. (Kishiyama and Gee, 1/9/02) Record number 186859 contains pages 21 through 34. Review of the data confirm the increase in revertants in strains TA1535 and TA100. A possible adverse effect. ACCEPTABLE. (Gee, 6/13/02).

CHROMOSOME EFFECTS

52063 - 004, 007 136927, 186860 Murli, H. "Mutagenicity Test on Busan 85 in an *In Vitro* Cytogenetic Assay Measuring Sister Chromatid Exchange Frequencies in Chinese Hamster Ovary (CHO) Cells". (Hazleton Laboratories America, Laboratory Project ID HLA Study No.: 9970-0-438, August 6, 1987) Busan 85 (lot 7-0726, 50% a.i., 50% water) was tested at concentrations ranging from 0.005 through 0.033 µg/ml without metabolic activation for 25 hours and from 0.5 through 50.0 µg/ml with rat liver S9 Mix for 2 hours followed by 23 additional hours of incubation before harvest by mitotic shake-off. There was a single culture per concentration and 50 cells per concentration were scored for sister chromatid exchanges. Toxicity was evaluated by percent confluent by visual examination and by mitotic cells/dead cells. There was no increase in the number of SCEs with Busan 85 treatment. UNACCEPTABLE (single culture per concentration), not upgradeable. (Kishiyama and Gee, 1/9/02). Record 186860 contains a letter from H. Murli of Covance, dated April 15, 2002, justifying the use of a single culture based on the lack of OECD guidelines for SCE assays. The letter also cites a publication by Soper and

Galloway, *Mutation Res.* 312: 139 - 149 (1994) regarding the need for duplicate flasks for chromosome aberration assays. These statements are not relevant. Guidelines were available in 1983 from USEPA requiring duplicate cultures. UNACCEPTABLE. No new worksheet. NOTE: The potassium and sodium salts of dimethyldithiocarbamate are grouped for toxicological effects. See the combined Summary of Toxicology Data. (Gee, 6/13/02)

DNA DAMAGE

** 52063 - 004, 007 136928, 186861 Cifone, M. A. "Mutagenicity Test on Busan 85 In the Rat Primary Hepatocyte Unscheduled DNA Synthesis Assay." (Hazleton Laboratories America, Inc., Laboratory Project ID HLA Study No.: 9970-0-447, November 11, 1987.) Busan 85 (lot 7-0726, 50% a.i.) was tested at concentrations from 2.5 to 2000 µg/ml. Concentrations from 2.5 to 100 µg/ml were evaluated for the ability to induce UDS in rat primary hepatocytes. Higher concentrations were too toxic for evaluation and a precipitate formed by the end of the incubation period at 500 µg/ml. Cytotoxicity was determined by trypan blue dye exclusion. Busan 85 did not induce UDS in primary rat hepatocytes at concentrations from 2.5 to 100 µg/ml with survival ranging from 108 to 77%. Evaluated as unacceptable but upgradeable with additional data on individual cultures including nuclear counts and cytoplasmic grain counts. (Kishiyama and Gee, 1/9/02) Record 186861 contains the results for each of the three replicate cultures, as requested, upgrading the study to ACCEPTABLE status with no adverse effect. No new worksheet. (Gee, 6/13/02).

NEUROTOXICITY

Not required at this time.