

CALIFORNIA DEPARTMENT OF FOOD AND AGRICULTURE

SUMMARY OF TOXICOLOGY DATA

ASULAM

SB # 950-219, Tolerance # 360

December 4, 1986

Revised 08/26/87, 03/10/88

I. DATA GAP STATUS

Combined, rat:	No data gap, possible adverse effect
Chronic toxicity, dog:	Data gap, inadequate study, possible adverse effect indicated
Oncogenicity, mouse:	Data gap, inadequate study, possible adverse effect indicated
Reproduction, rat:	Data gap, inadequate study, possible adverse effect indicated
Teratology, rat:	Data gap, inadequate studies, no adverse effect indicated
Teratology, rabbit:	Data gap, inadequate studies, no adverse effect indicated
Gene mutation:	Data gap, inadequate studies, no adverse effect indicated
Chromosome:	Data gap, inadequate studies, no adverse effect indicated
DNA:	Data gap, inadequate studies, no adverse effect indicated

Neurotoxicity:

Not required at this time

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Toxicology one-liners are attached.

\*\* indicates an acceptable study.

**Bold face** indicates a possible adverse effect.

File name: SB219ASU.WC3

Revised by Stanton Morris, 03/10/88

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

COMBINED, RAT

**\*\*011 24966 to 24969** "Asulam toxicity and tumorigenicity in prolonged dietary administration in rats" (Huntingdon Research Centre, 6/25/81) Asulam (sodium salt, 99.9 and 97.5% by nitrite titration) was administered to sprague-Dawley rats (65/sex/dose) in the diet at 0, 1000, 5000, and 25000 ppm for 108 weeks; at 18 mos 15/sex/dose sacrificed for pathology exam. Adverse effects noted as combined adrenal medullary hyperplasia and pheochromocytoma in males; increased susceptibility to infection; proliferative lesions in thyroid of males. Intake of Asulam for respective groups (males/females) given as 36/47; 180/243; 953/1280 mg/kg/day; NOEL = 1000 ppm. Initial review (Christopher, 6/85) found study unacceptable but upgradeable (test substance purity, diet analysis). Data submitted (360-030 54142), allowing study to be upgraded to acceptable. (Harnois, 8/4/87)

EPA one-liner: Minimum

030 54142 Supplementary data for 011 24966-9. Analytical chemistry results for the batch and diet. Batch purity (2 lots) given as 99.9 and 97.5%. Diet analyses indicate nominal value approximated. (Harnois, 7/30/87)

029 36025 "Tumor Profile-- Untreated Sprague-Dawley Rats (1978-79) Obtained From Charles River" (Huntingdon Research Centre, 6/25/81) Christopher, 6/85, Schreider, 7/24/86. Historical control data as addendum to Record # 24969, Document # 360-011

029, 36023-36024 " Worst Case Risk Assessment for Asulam" (Huntingdon Research Centre, 6/25/81) Schreider, 4/21/86; not a "mandatory health effect" study; Addendum to Record # 24969, Document # 360-011

CHRONIC TOXICITY, DOG

**360-010, 950172:** "ASULAM: Six Month Oral Toxicity Study in Beagles;" May and Baker Ltd. (England), 4/18/80 (QA signoff date); asulam, 98-100%, by oral gavage at 1500, 300, 60, or 0 mg/kg/day to 6/sex/level for 26 weeks; **POSSIBLE ADVERSE EFFECTS:** decreased testes weights at 1500 mg/kg, increased thyroid weight at 1500 and 300 mg/kg, no microscopic changes; emesis at 1500 mg/kg verifies MTD; sporadic leukopenia with no differential change; decreased erythroid parameters at 1500 mg/kg. Prior review (JPC, 6/10/85): Insufficient information for assessment - incomplete and unacceptable, insufficient treatment duration, poor husbandry, no dosing suspension analysis; **No change in acceptability status** with second review, still **UNACCEPTABLE AND NOT UPGRADABLE** for original reasons. Tentative NOEL (thyroid weight)=60 mg/kg. HGM/FM, 3/7/88.

EPA one-liner: Guideline. NOEL = 60 mg/kg; LEL = 300 mg/kg (thyroid and body weights increased)

#### ONCOGENICITY, MOUSE

**023 to 025, 35354 to 35356** "18-Month Carcinogenicity Study of Asulam Technical in Mice", (Rhodia Inc., 7/31/78) JG, 10/21/85 Asulam (99.2%) tested at 0, 1500 and 5000 ppm in the diet in a 18-month carcinogenicity study in Charles River Carworth CF-1 mice; 60 mice/sex/group; intestinal calcifications; spleen enlargement; questionable incidence of skin and subcutaneous undifferentiated sarcoma in 5000 ppm males; possible adverse effect; systemic NOEL=1500 ppm; incomplete; unacceptable (justification of dose selection, only 2 doses, no hematology or cholinesterase measurements, incomplete data on ophthalmic exam, GLP compliance).

EPA one-liner: Guideline. Carcinogenic NOEL > 5000 ppm (HDT); Systemic NOEL < 1500 ppm Dose related decrease in weight of thyroid and increase in weights of kidney and heart

The Registrant has indicated (030, rebuttal cover letter) that a new study will need to be done.

#### REPRODUCTION, RAT

010 25257 "Asulam: two generation reproduction study in the rat" (May & Baker Ltd., 4/30/81). Asulam (98-99%) was administered in the diet at 0, 1000, 5000 and 25000 ppm to Charles River Sprague Dawley CD rats in a two generation reproduction study (males/females bred: F0, 12/24; F1, 16/32).

F0 fed for ~100 days prior to mating, F1 fed for 120 days post-weaning prior to mating. F1 parents provided 14-17 litters. Noted decreased body weight gain in pre-mating F1 females at 25000 ppm; increased thyroid weight both sexes at 25000 ppm. **Adverse effects:** decrease in live births/litter (F1 pups in 5000 and 25000 groups; F2 pups in 5000 group). Parental NOEL (body weight, thyroid) = 5000; reproductive NOEL (# live births)= 1000 ppm. Initial review (Christopher, 6/85) found study unacceptable (several points); review of data and material submitted by Registrant (360-030) finds status unacceptable, not upgradeable (too few litters for examination, too few animals underwent necropsy, extent of post-mortem examination inadequate, and maximum dose not justified). (Harnois, 8/4/87)

EPA one-liner: Minimum. Reproductive NOEL = 1000 ppm; Possible systemic effects were noted at 25000 ppm (HDT); The reproductive effect noted at the 5000 and 25000 ppm doses was decreased mean number of live births per litter

030 54477 "Asulam content of fortified rat diets used in a reproduction study" (May & Baker Ltd., England, 10/80). Suppl. data for 010 25257. Analytical chemistry results for the batch and diet. Batch purity (technical grade, 2 lots) for both given as 99.9%. Diet analyses indicate nominal value approximated. (Harnois, 7/30/87)

#### TERATOLOGY, RAT

029 36027 "'Asulox'-Study of Effects on the Rat Foetus" (May and Baker Ltd. 8/70) Schreider, 7/24/86. Asulox (60% Asulum in aqueous solution); oral-gavage; 0, 8 or 40 mg/kg; 21 dams per group; NOEL=40mg/kg; unacceptable; not upgradeable (insufficient information, two dose levels, no MTD)

EPA one-liner: Unacceptable. NOEL > 40 mg/kg (HDT)

010 25254 "Asulam: teratogenicity study by the oral route in the rat" (May & Baker, Ltd., 2/81). Asulam (98-99%) in 0.25% gum tragacanth at 0, 500, 1000 and 1500 mg/kg was administered by gavage (5 ml/kg) to mated female Sprague-Dawley CD rats (28/group) on gestation days 5-17 (Day 1 = evidence of mating). Report states no significant findings for dams or fetuses. Initial review (Christopher, 6/85) questioned dose, analytical methods, dose schedule, historical controls; found insufficient information for evaluation of adverse effects. Information supplied on test substance (360-030). Review of data for CDFA response to comments (360-030) found that there was an unacceptably wide variation in litter mean body weights within groups. Apparent NOEL (both maternal and developmental  $\geq 1500$  mg/kg. Unacceptable (clinical and post-mortem individual data on dams not supplied, fetal exam data not linked to individual fetuses, no historical controls, unacceptable amount of variation in litter mean body weight). Not upgradeable. (Harnois, 8/26/87)

EPA one-liner: Minimum. Terata NOEL  $\geq 1500$  mg/kg (HDT); maternal toxicity  $>1500$  mg/kg (HTD)

## TERATOLOGY, RABBIT

029 36026 "'Asulox'-Study of Effects on the Rabbit Foetus" (May and Baker Ltd. 11/70) Schreider, 7/24/86. Asulox (60% Asulum in aqueous solution); by oral capsule at 0, 8 or 40 mg/kg; 18 per group; NOEL=40 mg/kg; incomplete; unacceptable; not upgradeable (insufficient information, only 2 dose levels, no MTD)

028 35364 "Asulam-Test for Teratogenicity in the Rabbit" (May and Baker Ltd. 7/72) JAP, 10/21/85. Asulam (sodium salt, 40% w/v in solution) tested at 2, 4, 8 and 40 mg/kg by oral capsule on Days 4-18 of gestation in New Zealand white rabbits; no maternal or fetal toxicity; no evidence of teratogenicity; incomplete; unacceptable (no data on clinical observations, necropsy, individual litter, dose prep/analysis, justification of dose levels, quality control statement)

EPA one-liner: NOEL  $> 40$  mg/kg (highest level tested)

010 25258 (May and Baker, 4/30/81) JPC, 6/10/85; Asulam (98-99%) tested at 0, 150, 300, 750 and 1500 mg/kg/day in 0.25% w/v gum tragacanth (5ml/kg) by oral gavage on Days 5-20 of

gestation in New Zealand white rabbit; 8-28 females/dose group; 7/8 died with excess body weight loss at 1500 mg/kg/day; excessive mortality (29 deaths) mainly due to gavage errors, a few to infection; Inconclusive evidence of dose-related pre- and post- implantation loss; low incidence of malformations at 300 and 750 mg/kg/day can not be evaluated without historical data; insufficient information for assessment; NOEL = 750 mg/kg/day; incomplete; unacceptable (too many technical errors, questionable chemistry, inappropriate statistical treatment, no historical data, too many deaths)

EPA one-liner: Minimum. No teratogenic effects was noted up to 750 mg/kg

A possible maternal toxic effect of decreased weight gain was noted in the 750 mg/kg dose animals

The Registrant has indicated (030, rebuttal cover letter) that a new study will need to be done.

#### GENE MUTATION

027 35362 "Asulam: mutagenicity evaluation of Asulam (technical) in the Ames/Σαλμονελλα/microsome plate test--preincubation method" (Litton Bionetics, Netherlands, 10/83). Asulam (Lot PN85, technical) in DMSO at 0, 0.9, 8.7, 50, 87, 500, 1000, and 2000 ug/plate with and without activation was tested in triplicate cultures of TA1535, TA1537, TA1538, TA98 and TA100.

A 20 minute pre-incubation period was used; revertant colonies were counted after 2 days. Toxicity noted with  $\geq 500$ ug. No adverse effect reported. Initial review (JG,10/21/85) found study unacceptable ( no repeat trial). Review of data and Registrant's comments (360-030) leaves status unchanged. (Harnois, 8/5/87)

010 25256 (Inveresk Research Int'l, 7/77) JPC, 6/7/85. Asulam (purity unspecified) tested at 0, 10, 33, 100, 300 and 1000 ug/plate with and without S9 activation in the Ames Σαλμονελλα τυπιμουριου test in five strains (TA98, TA100, TA1535, TA1537 and TA1538); 3 plates/dose; no evidence of mutagenicity but insufficient information for assessment; (purity of test compound, weak positive control with S9 and no positive control without S9)

EPA one-liner: Acceptable. No indication of mutagenicity in 5 strains

## CHROMOSOME

027 35363 "Mutagenicity evaluation of asulam technical (dried) in an in vitro cytogenetic assay measuring chromosome aberration frequencies in human lymphocytes" (Litton Bionetics, Kensington, 10/84). Asulam (PN 85, Technical) at 0, and 1-2.5 mg/ml with activation for 1 hr; 0, and 0.125-1.0 mg/ml without activation for 48 hrs. Added to PHA stimulated human lymphocytes 24 hrs post PHA; cultures harvested approx. 50 hrs after start of treatment. Cytotoxicity and cell cycle delay at 1 mg/ml with 49 hr exposure (no activation) and 2 hrs recovery; no toxicity or cycle delay reported for 1 hr exposure (with activation) followed by 49 hrs recovery period. Initial review (JG 10/21/85) found study unacceptable (missing cell source data) with no adverse effects reported. Review of study data and Registrant's comments (360-030) showed that there was inadequate information for assessment and leaves status as unacceptable, not upgradeable (inadequate sampling). (Harnois, 7/31/87).

EPA one-liner: None available

027 35358 "Dominant Lethal Study of Asulam in Mice" (Rhodia, Inc. 8/29/75). Asulam (purity unspecified) tested at 0, 1500 and 5000 ppm in the diet for 45 days in Charles River Carworth CF-1 males and CD-1 females mice; 15 males and 60 females/dose group; mated 1 male:2 females for 2 weeks. Initial review (JG, 10/18/85) found no adverse effect; incomplete; unacceptable (purity of the test compound, only 2 doses and dose level justification, no individual data, GLP compliance); review of Registrant's response (030) leaves status unchanged. (Harnois, 8/17/87)

EPA one-liner: NOEL > 5000 ppm (HLT)

## DNA

027 35361 "Asulam: Test to Determine the Ability of Asulam to Induce Unscheduled DNA Synthesis of HeLa Cells" (May and Baker/Microtest

Research, 5/82) JG, 10/21/85. Asulam (purity unspecified) tested at 0.0025, 0.125, 0.025, 0.125 and 0.25 mg/ml in HeLa S3 cells; 2 hours exposure to confluent cultures; dpm of tritiated thymidine/ug DNA from triplicate cultures were measured; no adverse effect reported; incomplete; unacceptable; upgradeable (purity of compound, dose justification, cytotoxicity data, individual values for triplicate cultures, DNA concentration determinaton, CPM to DPM conversion procedure, GLP compliance).  
EPA one-liner: None available

010 25255 "C3H/10T<sub>1/2</sub> cell transformation assay" ( EG&G Mason Research Inst., 10/5/79). Asulam (98.8%) was tested at 0, 256, 512, 1024 and 2048 ug/ml (12 plates/level); >75% cytotoxicity at 2048 ug/ml in pilot; 200 cells/ plate in toxicity test; 1000 cells/plate in transformation assay. Initial review (JPC 6/7/85) noted no evidence of cell transformation but insufficient information for assessment (no trial with activation); unacceptable (no purity of test compound, no quality assurance statement, no trial with activation). Review of data and information supplied with Registrant's response (360-030) shows that data on purity supplied, but study status is still unacceptable (no trial with activation). (Harnois, 8/19/87)