

CALIFORNIA DEPARTMENT OF FOOD AND AGRICULTURE  
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

ISOFENPHOS

SB 950-not assigned, Tolerance # 387

Date September 8, 1988, revised April 28, 1989

I. DATA GAP STATUS

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

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Toxicology one-liners are attached.

\*\* indicates an acceptable study.

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

File name: T890428

Toxicology index and summary prepared by H. Green and G. Patterson, revised by A. K. Klein.

## II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

Combined (chronic + onco), Rat

002 985209, "SRA 12869, Chronic Toxicity Study on Rats (Two-year feeding experiment)", (Bayer AG, #54182, 9/1/77), combined-835-rat, SRA 12869 technical grade, batch 1603/73, stated purity on receipt = 85.6%, 50% premix prepared with Wessalon S, administered in the diet for 24 months to 100/sex/group at 0 ppm and to 55/sex/group at 1, 10, and 100 ppm. **NO ADVERSE EFFECTS** indicated. Somatic effects NOEL = 10 ppm (body weight gain reduced in females). Cholinesterase (ChE) inhibition NOEL = 1 ppm (dose-related inhibition of RBC and plasma ChE at 10 and 100 ppm). Also transient clinical signs of depression during first week of study at 100 ppm, and slight brain ChE inhibition detected at terminal sacrifice. **UNACCEPTABLE**, not upgradeable (required tissues not examined microscopically, no routine microscopic examinations of tissues of animals dying on study, no ophthalmological exams; other deficiencies listed in 4/01/88 review). (A. Apostolou, 6/27/85; C. Aldous, 4/01/88)

Chronic Toxicity, Rat

No study on file.

Chronic Toxicity, Dog

**002 985210**, "SRA 12869, Chronic Toxicity Study on Dogs (Two-year feeding experiment)", (Bayer AG, # 54410, 10/25/77), SRA 12869, 89.3% purity, used as a 50% premix with Wessalon S, administered originally in the diet at 0, 3, 15 (= average intake of a.i. about 0.45 or 0.53 mg/kg/day for M and F, respectively), and 75 ppm (average intake of a.i. about 2.6 mg/kg/day) with 4/sex/group. The following dosing level changes occurred: 3 ppm males decreased to 2 ppm from week 84, 75 ppm groups (M & F) increased to 150 ppm from week 54 and to 300 ppm from week 100. Term of experiment was 104 weeks. The 6/25/85 review indicated **POSSIBLE (CHRONIC) ADVERSE EFFECTS**, noting: depressed cholinesterase (ChE) activities, hind leg weakness and related effects, increased alkaline phosphatase, and decreased albumin/globulin quotient, and esophageal lesions. On re-evaluation (4/8/88), there is no change in study status, but findings have been placed into perspective, and deficiencies needing correction have been identified. The 4/8/88 review indicates that ChE inhibition was not progressive over the term of a chronic study, and other effects were mild in degree and/or have well-defined NOELs. The chronic effects NOEL is 15 ppm, based on erosion of esophageal mucosa at 150 to 300 ppm. **UNACCEPTABLE**, upgradeable; (additional information needed, especially on test article). (A. Apostolou, 6/28/85; C. Aldous, 4/8/88).

Oncogenicity, Rat

No study on file.

Oncogenicity, Mouse

005 985207, "SRA 12869, Chronic Toxicity Study on NMRI Mice (108-Week Feeding Experiment)", (Beratungsforum für Präventivmedizin und Umweltschutz GmbH, #67372, 11/30/78), SRA 12869 technical, batch 1603/73, 89.3% purity, premixed 1:1 with Wessalon S, administered in the diet for 108 weeks at 0, 1, 10, and 100 ppm with 40/sex/group allocated for oncogenicity study. **NO ADVERSE EFFECTS** reported. NOEL = 1 ppm (plasma ChE depression of 74-83% at 10 ppm). **UNACCEPTABLE**, not upgradeable (small initial group sizes, coupled with high mortality (esp. in F) often attributed to pulmonary "affection" (sic), inadequate histopathology-some recommended tissues not examined, not clear from tables what tissues were examined, other deficiencies noted in 7/1/85 review). (A. Apostolou, 7/1/85)

Reproduction, Rat

**002 985218**, "Effect of SRA 12869 on Reproductive Function of Multiple Generations in the Rat, Final Report", (Huntingdon Research Centre, # 52796, 2/21/77), SRA 12869, 50% active ingredient (balance of test article not defined), administered in the diet for 3 generations, 1 litter/generation at 0, 1, 10, and 100 ppm (nominal) with 20/sex/dose. **POSSIBLE ADVERSE EFFECTS** indicated [markedly reduced mating performance (attributed primarily to effects on females), markedly increased neonatal mortality, somewhat decreased pup weights among survivors, slightly decreased maternal weight gain during pregnancy and lactation, all at 100 ppm]. Parental NOEL = Reproductive NOEL = 10 ppm. Cholinesterase inhibition NOEL = 1 ppm (no cholinesterase inhibition-related clinical signs at any dose tested). **UNACCEPTABLE**, not upgradeable (No microscopic examinations of any animals, reproductive toxicity of test article not characterized). Other deficiencies noted in individual reviews. (A. Apostolou, 6/26/85, C. Aldous, 3/29/88).

Teratology, Rat

**011 985213**, "SRA 12869, Studies for Embryotoxic and Teratogenic Effects on Rats Following Oral Administration", (Bayer AG, # 35482, 10/25/72), SRA 12869 (isofenphos), batch 1601/71, Lo-No. 1067, purity 86.6%, administered in lutrol by gavage on gestation days 6-15 at 0, 0.3, 1.0, and 3.0 mg/kg/day with 23 or 24 inseminated rats/group. **POSSIBLE ADVERSE EFFECTS**: slightly (not statistically significantly) increased resorptions at 3.0 mg/kg/day. NOEL maternal = 3 mg/kg/day, developmental = 1.0 mg/kg/day. **UNACCEPTABLE**, possibly upgradeable with submission of dose analysis and justification (no maternal toxicity) and fetal data (live/dead and M/F ratios, skeletal anomalies, number of corpora lutea, and individual fetal bodyweights). (Apostolou 6/25/85; re-examined, no change in status, no new written review, C. Aldous, 3/25/88.)

032 36478, "Evaluation for Embryotoxic and Teratogenic Effects in Rats Following Dermal Application", (Bayer AG, report # 9801, 2/3/81), SRA 12869 (Isofenphos), batch no. 808716101, lot no. 2147, 92.4% purity, 5 hours/day exposure on gestation days 6-15 to shaved, intact, dorsal skin of 25 females/group at 0 (Lutrol), 0.3, 1.0, 3.0, and 10.0 mg/kg. **NO ADVERSE EFFECTS** reported. Apparent maternal NOEL = 3.0 mg/kg (reduced weight gain; clinical signs, esp. ruffled coat). Apparent developmental NOEL = 10.0 mg/kg. **UNACCEPTABLE**, upgradeable (additional information requested in section VI. A. of CDFA review). (Green/C. Aldous, 3/22/88)

032 36477, "Embryotoxicity and Teratogenicity Study with SRA 12869 in Rats", (Research and Consulting Co. Ltd, project 000066, July 1981), SRA 12869 (isofenphos), batch no. PT.808 016 131, 91.8% purity, administered, by gavage on days 6 through 15 of pregnancy at 0 (2% CMC), 0.3, 1.0, and 3.0 mg/kg/day to 25 mated females/group. No maternal toxicity reported at any dose. **NO ADVERSE** effects reported. NOEL = maternal & developmental = 3 mg/kg/day. **UNACCEPTABLE**, unlikely to be upgradeable (adequacy of high dose was not demonstrated). (Green/C. Aldous 3/21/88)

032 36479, "Study of Embryotoxic and Teratogenic Effects on Rats after Inhalation", (Bayer AG, report # 9808, 2/17/81), SRA 12869 (isofenphos), batch 808716101, 91.1% purity, 6 hours/day head-only inhalation exposure on gestation days 6-15 with 25 females/group at 0 (lutrol: ethanol, 1:1), 0.25, 0.75, and 3.1 mg/l(analytical). **NO ADVERSE** maternal nor embryo toxic effects reported. NOEL, maternal and developmental = 3.1 mg/l. **UNACCEPTABLE**, not upgradeable (adequacy of high dose was not demonstrated). (Green/C. Aldous, 3/22/88)

Summary: Since the rat teratology studies are evaluated collectively, the most appropriate one to upgrade appears to be the dermal study (032:36478), because: (1) no adverse effects are indicated and (2) it is the most complete with a relevant route of dose and the demonstration of an maternal MTD.

#### Teratology, Rabbit

011 985214 "SRA 12869 [Isofenphos]: Studies of embryotoxic and teratogenic effects on rabbits following oral administration". Bayer AG Institut fuer Toxikologie, 11/10/75. SRA 12869, Batch 16005/74 (not further characterized). 0, 1, 2, and 5 mg/kg/day on gestation days 6-13, by gavage in 0.5% Cremophor. 11-13 pregnant dams/group. **NO ADVERSE EFFECTS** indicated. Apparent maternal NOEL = 2 mg/kg/day (3 deaths, 2 attributed to treatment; diarrhea and emaciation reported-- all in 5 mg/kg/day group). No apparent developmental toxicity. **UNACCEPTABLE**. Upgradeable (see 3/28/88 review). A. Apostolou, 6/25/85; and C. Aldous, 3/28/88.

#### Mutagenicity Gene Mutation

002 32696, "SRA 12869, Mutagenicity Test on Bacterial Systems", (NITOKUNO Agricultural Chemicals Institute, #54125, 12/19/77), reversion assay-842-Salmonella typhimurium, SRA 12869 Technical grade, 87.5% purity, dissolved in DMSO, tested Salmonella typhimurium TA1535, TA1537, TA98, and TA100 with S9 activation (phenobarbitol induced rat and mouse liver) at 0, 0.1, 10.0, and 1000.0 mg/plate and without activation at 1000.0 µg/plate. AAF, AF-2, 9AA, NTG, AND DMNA as positive controls. Reported **negative for reversion**. **UNACCEPTABLE**, not upgradable (only one plate per dose level and only 1 concentration (1000.0 µg/plate) without activation, no justification of highest concentration with no cytotoxicity reported). (Apostolou 6/26/85 and Gee 3/18/88)

037 63445, "Isophenphos, Mutagenicity Test on Bacterial Systems", (Institute of Environmental Toxicology, #90887, 2/2/80), reversion assay-842, isofenphos, 92.4% purity, tested with Salmonella typhimurium (TA1535, TA1537, TA1538, TA98, TA100) and Escherichia coli WP2 hcr in duplicate with and without S9 (Aroclor 1254 induced SD male rat liver) activation at 0 (DMSO), 10, 50, 100, 500, 1000, or 5000 µg/plate. 2-AA, AF-2, 2 nitrofluorene, b-propiolactone, and 9-aminoacridine as positive controls. **No increase in reversion rate** reported. **UNACCEPTABLE**, not upgradable (no evidence of actual exposure through cytotoxicity and no repeat trial confirming the negative result). (Green, Gee 3/21/88)

022 985220, "Ames Test for Oftanol (isofenphos)", (Bayer AG, sponsor # 53954, 9/29/77), Oftanol (isofenphos, SRA 19, lot 16012/75, purity 93.2 %), tested with Salmonella typhimurium strains TA100, TA1537, and TA98 in duplicate with/without S9 (Aroclor 1254 induced male SD rat liver) activation at 0 (DMSO), 3.15, 10.0, 31.5, 100.0, 315.0, 1000.0, and 3150.0 nl/plate. Benzo(a)pyrene, 2-AA, 3-Methylcholanthrene, benzo(a)pyrene 4,5 oxide, and N-methyl-N'-nitro-N-nitrosoguanidine as positive controls. **No reverse mutation** reported. **UNACCEPTABLE**, not upgradable (strain TA1535 not tested). (Green, Gee 3/24/88)

Summary: Although no one study for gene mutation in Salmonella was found acceptable due to flaws in the design or reporting of data, CDFA believes that collectively they provide sufficient data to determine that isofenphos does not produce a positive response in the gene mutation assay. (Gee 9/88)

#### Mutagenicity Chromosome

032 36476, "Micronucleus Test on Mouse to Evaluate SRA 12869 (Isofenphos; Active Ingredient of Oftanol) for Mutagenic Potential," (Bayer Ag, report #10018, 6/30/81), SRA 12869 (isofenphos), batch 808016131, 91.8% purity, in 0.5% cremophor emulsion, 2 doses administered 24 hours apart by gavage at 0, 15, and 30 mg/kg with 5/sex/group. Single sacrifice at 6 hours after second dosing. Trenimon intraperitoneally as positive control. No evidence of an MTD or bone marrow cytotoxicity. **No adverse effects** reported. **UNACCEPTABLE**, not upgradable (no MTD, single sacrifice time). (Green, Gee 3/21/88)

022 985221, "SRA 12869, Dominant Lethal Test on the Male Mouse to Test for Mutagenic Effect", (Bayer AG, sponsor # 39567, 11/7/73), SRA 12869, no purity stated, single exposure by gavage at 0 (cremophor) and 15 mg/kg with 20 male mice/group. Mated 1 male:3 females weekly for 8 weeks. **No dominant lethal effects** reported. **UNACCEPTABLE**, not upgradable (no positive control, only 1 dose level with no justification and no toxic signs-no individual data, and no test article purity). (Green, Gee 3/24/88)

\*\* 045 073146 "Chromosome Aberrations in Chinese Hamster Ovary (CHO) Cells" (Microbiological Associates, Inc., Laboratory Study T8298.337, 2/6/89) Oftanol technical, isofenphos, CAS #2511-71-1, Batch #5030009, 91% pure, was tested with CHO cells with and without activation by arochlor-stimulated rat liver S-9 fraction, 2 flasks/dose/test condition, 1 trial, at 0 (DMSO), 0.02, 0.04, 0.08, 0.16 ul/ml for 2 hours with activation, 18 hours without activation; **no adverse effects** (no increase in chromosome aberrations); **acceptable**. (klein, 4/26/89)

#### Mutagenicity DNA

002 32697, "SRA 12869, Mutagenicity Test on Bacterial Systems", (NITOKUNO Agricultural Chemicals Institute, #54125, 12/19/77), Rec-assay-844-Bacillus subtilis, SRA 12869 Technical grade, 87.5% purity, dissolved in DMSO, tested with strains NIG45 (rec<sup>-</sup>) and NIG17 (rec<sup>+</sup>) at 3.0, 30.0, and 300.0 µg/disc without activation only with MC at 0.3 as positive control. **No DNA damage reported**. **UNACCEPTABLE**, not upgradable (brief summary only, single plates only, no activation, no cytotoxicity reported = no test). (Apostolou 6/26/85 and Gee 3/18/88)

037 63445, "Isophenphos, Mutagenicity Test on Bacterial Systems", (Institute of Environmental Toxicology, # 90887, 2/2/80), Rec-assay-844-Bacillus subtilis, isofenphos, 92.4% purity, tested with strains H-17, (rec<sup>-</sup>) and M-45, (rec<sup>-</sup>) at 0 (DMSO), 1, 5, 10, 50, or 100% v/v 20 µl per disk, single plate. Kanamycin as negative control and mitomycin C as positive control. **No DNA damage reported**. **UNACCEPTABLE** (no activation, no cytotoxicity with either strain = no test), not upgradable. (Green, Gee 3/21/88)

\*\* 045 073145 "Unscheduled DNA Synthesis in Rat Primary Hepatocytes" (Microbiological Associates, Inc., Laboratory Study T8298.380, 2/10/89) Oftanol technical, isofenphos, CAS # 25311-71-1, Batch # 5030009, 91% pure, was tested with primary rat hepatocytes in the presence of <sup>3</sup>H-thymidine, 3 plates/treatment, 1 trial, at 0 (DMSO), 0.001, 0.003, 0.01, 0.02, 0.03 ul/ml for 18-20 hours, 50 cells/slide, 150 cells/treatment scored; **no adverse effects noted** (no unscheduled DNA synthesis); **acceptable**. (klein 4/13/89)

#### Neurotoxicity, Hen

011 985195, "SRA 12869, Acute Neurotoxicity Studies on Hens", (Bayer AG, #34025, 3/20/72), isofenphos technical grade, purity not stated, single dose administered in Iutrol (polyethylene glycol 400) by gavage at 35, 40, 50, 70, 74, 75, and 100 mg/kg with protection (50 mg atropine sulphate/kg), 10 hens/group. TOCP positive control. No neurotoxicity reported. Insufficient information for adverse effect determination. **UNACCEPTABLE**, not upgradable (no repeat dosing, no negative control). (Apostolou 6/25/85)

011 985196, "Acute Delayed Neurotoxicity of Technical Isofenphos in Hens", (Mobay Chemical Corp., # 80678, 4/19/82), technical isofenphos, 91.9% purity, 30 hens received a single dose administered by gavage at 32 mg/kg with protection (intramuscular injection of 50 mg/kg atropine). 5 hens served as untreated controls, 5 received 500 mg/kg water, and 10 were positive controls with TOTP [TOCP] at 500 mg/kg. **NO ADVERSE EFFECTS** reported. **UNACCEPTABLE**, not upgradable (no repeat dosing at 21 days). (Apostolou 6/26/85)

011 985198, Supplemental to 985196.

026 2268, Supplemental to 985196 and 985198.

024 2267, "Acute Delayed Neurotoxicity of Isofenphos (AMAZE)", (Mobay Chemical Corp., # 86134, 12/21/83), Isofenphos Technical, 91.9% purity, batch 005281, 2 doses by gavage 21 days apart with protection (50 mg/kg atropine and 31 mg/kg 2-PAM 30 and 15 minutes post-dosing respectively) at 32 mg/kg with 20 or 15/group and 2 untreated controls of 5/group, 1 group with protection. TOCP as positive control at 500 mg/kg with 10 hens. Degeneration of digestion chamber, axons, and neurons; and accumulation of macrophages and lymphocytes reported in all groups. The delayed neuropathy seen in the TOCP group was not observed in the hens dosed with the test article. **UNACCEPTABLE**, possibly upgradable with submission of explanation of grading system used for histopathology determination. (Apostolou 6/25/85, Patterson 7/7/88). Rereviewed upon receipt of explanation of histopathology grading system used (387-044). **NO ADVERSE EFFECT** reported. **Status change to ACCEPTABLE**. (Patterson 8/23/88)

\*\*031, 027, 043 32788, 22071, 64608, "Study for Subchronic Neurotoxicity (90-day study with chickens)", (Bayer AG, #90231, 5/13/85), SRA 12869 (Oftanol technical), 92.5% isofenphos, batch #0005281, administered in a 2% v/v demineralized water/Cremophor EL solution by gavage for 90 days at 0.25, 1.00, and 2.00 mg/kg/day with 10 hens/group and with vehicle, negative, and TOCP positive control groups. NOEL = 0.25 mg/kg/day (reduced bodyweight (9-10%) and plasma ChE depression (50-60%) at 1.00 mg/kg/day). Histopathology: slight to moderate spinal cord degeneration reported in both the vehicle control and 2.00 mg/kg/day groups and severe degeneration seen in the TOCP group. Lesions reported in the control and 2.00 mg/kg/day group were not similar to the well defined delayed neuropathy seen in the TOCP group. **NO ADVERSE EFFECT. ACCEPTABLE**. (Green, Patterson 7/6/88)

Supplemental Information

032 36480, "Antidotes and Neuropathic Potential of Isofenphos", (CDFA and UC Davis, # 86433, journal article-Bull. Environ. Contam. Toxicol. 33:386-394, 1984), isofenphos technical grade, 92% purity, administered by gavage without protection to hens (4-6/group) at 0 (PEG 400), 1.5, 3.0, 4.5, 5.0, 6.75, 7.0, or 20.0 mg/kg and to rats (4-18/group) at 20.0, 25.0, 30.0, 35.0, 40.0, 45.0, 50.0, 55.0, or 80.0 mg/kg. With protection (repeated injections of atropine and 2-PAM) to hens (5/group) at 25.0, 50.0, 75.0, or 100.0 mg/kg and to rats (4-6/group) at 40.0, 45.0, 80.0, 90.0, or 135.0 mg/kg. TOCP as positive control. Reported LD50 is between 3.0 and 5.0 mg/kg for hens and ~ 40.0 mg/kg for male rats. Delayed neuropathy (based on ataxia, decreased brain NTE activity, and histopathology of ischiatic nerve and distal branches, spinal cord, and brain) was reported at 100.0 mg/kg in hens with protection. Supplemental information. (Green, Patterson 7/7/88)